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Manual of Clinical Problems in Pediatrics

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PREFACE

WHY DO YOU NEED THIS MANUAL? There are other small texts, of course, and there is Medline. So why is this *Manual* unique and useful? Mainly because the text is brief and compact, so you don't need to wade through lengthy chapters, and the references have been carefully selected and are annotated, so you don't have to spend hours with Medline trying to identify which articles are worth your time. That's the overview; here are some details:

1. Basic material is included in the text; sources of more advanced or detailed information are listed in the annotated references at the end of each chapter.
2. General principles of treatment are provided in the text, but specifics are not. (Consult the annotated references or The Children's Hospital of Boston *Manual of Pediatric Therapeutics* in the Lippincott Williams & Wilkins Spiral Manual series.)
3. The references are categorized, progressing from general reviews to specific issues. Frequently, though, the best discussion of a specific issue is provided in an article or collection listed with the general reviews. Therefore, check the beginning section of the references first.
4. In selecting references, preference was given to those most easily accessible and to reviews, both editorial and comprehensive, with good bibliographies. These criteria permitted the number of references to be limited to 20 to 30 per chapter. We could not resist sneaking in additional references, however, for a total of well over 3,000.

The contributing authors have been most gracious in accepting editorial comments. I am grateful to them, to medical librarian-extraordinaire, Leslie Mackler for her expertise and generous, helpful assistance, and to Ellen Roberts, who helped put this Manual together just as she has kept me together for more than 30 years.

Enjoy!

Kenneth B. Roberts, M.D.

SIGNS AND SYMPTOMS

For a discussion of the following signs and symptoms, see the chapters at right.

1. CARDIOPULMONARY ARREST AND RESUSCITATION

Olakunle B. Akintemi

Cardiopulmonary arrest in a child is the most dramatic and tragic emergency that practitioners confront. Cardiac arrest in children is due to respiratory arrest, failure, and shock rather than sudden dysrhythmia or ventricular fibrillation, as in adults. Primary cardiac dysrhythmia may occur, however, in adolescents and in patients with myocarditis and underlying cardiac disease. Survival rates for out-of-hospital cardiac arrest are much lower in children (5%) than in adults.

Cardiopulmonary resuscitation (CPR) is an “attempt to restore spontaneous effective ventilation and circulation,” and is subclassified as basic and advanced. Basic CPR involves application of noninvasive methods such as external chest compressions and mouth-to-mouth or mouth-to-mask ventilation to restore effective ventilation and circulation. Advanced CPR is the application of invasive methods (bag-and-mask ventilation, endotracheal intubation, intravenous medication) to restore effective ventilation and circulation.

Cardiac arrest is defined as the cessation of cardiac mechanical activity, determined by unresponsiveness, apnea, and the absence of a central pulse. Respiratory arrest is the absence of respiration with the presence of a palpable pulse, and therefore has a higher survival rate than cardiac arrest.

Because pediatric cardiopulmonary arrest is an uncommon event, studies of pediatric CPR have mainly been retrospective and have been plagued by inconsistent or lack of standard definitions, small sample size, and incomplete or invalid outcome measures. Guidelines have been published to improve uniform reporting, case definitions, and outcome measures for pediatric CPR research. The rate of bradycardiaasystole (bradyasystole) in pediatric cardiac arrest victims is 90%, while ventricular tachycardia ventricular/fibrillation (VT/VF) accounts for the remainder of cases. Survival after cardiac arrest is poor, especially in children younger than 1 year, in unwitnessed out-of-hospital arrests, and in children presenting with bradyasystole. Other predictors of poor survival include CPR duration of more than 30 min and administration of more than 2 doses of epinephrine. Children younger than 1 year, who account for about half of pediatric cardiopulmonary arrest victims, have a higher rate of asystole and therefore a lower survival rate. The most common causes of arrest in infants are injuries, sudden infant death syndrome (SIDS), respiratory disorders, airway obstruction, submersion, and sepsis.

The mainstay in the management of cardiopulmonary arrest is a rapid, methodical assessment of **A***irway*, **B***reathing*, and **C***irculation* by applying the techniques of basic and advanced life support. It is essential to establish and maintain a patent airway and support adequate ventilation. Unique anatomic differences between pediatric and adult airways must be considered in the management of the pediatric airway. These differences include a large occiput with excessive “sniffing position”; a relatively large tongue; a large, omega-shaped, soft epiglottis; vocal cords with a lower attachment anteriorly than posteriorly; and larynx located higher in the neck (C3–C4) than in adults (C4–C5).

The **a***irway* is opened by the head tilt–chin lift maneuver. However, if neck injury is suspected, the jaw-thrust technique without head tilt is recommended. If these techniques fail to provide a clear, unobstructed airway, insertion of either an oropharyngeal or a nasopharyngeal airway should be considered. The nasopharyngeal airway (nasal trumpet) may be used in semiconscious and conscious victims, while the oropharyngeal airway should be used in unconscious victims.

B*reathing* is assessed by looking for chest and abdominal movement, listening for expired air at the mouth and nose, and feeling for exhaled air at the mouth. If the victim is breathing and there is no evidence of trauma, the child is placed in the “recovery position.” Rescue breaths should be given immediately if respiration is not spontaneous: 2–5 initial breaths (mouth–to–mouth-and-nose), each delivered slowly over 1–1.5 seconds, with force sufficient to make the chest rise. Subsequent breaths should be provided at 20/min for infants and young children, and 12/min for older children. It is important to minimize gastric distention since it may elevate the diaphragm and compromise lung volume; this is achieved by delivering rescue breaths slowly and applying cricoid pressure. If spontaneous respiration is inadequate (insufficient chest movement and breath sounds, or apnea), positive pressure ventilation should be given with a bag-valve-mask device with an oxygen reservoir and a flow rate of at least 10–15 L/min. In addition, the bag-valve-mask device should be without a pressure release valve. If the patient is unresponsive to bag-and-mask ventilation, the trachea should be intubated. Pulse oximetry and the end-tidal carbon dioxide detector (capnography) are noninvasive techniques used to monitor adequacy of oxygenation and ventilation.

The next step is assessment of **c***irculation* by checking for the presence of a pulse in the central arteries. Palpation of the brachial pulse is recommended in infants younger than 1 year. In older children, the carotid pulse should be palpated. If the pulse is not felt or is present but the rate is less than 60/min (with poor skin perfusion), external chest compression (ECC) should be initiated. In both infants and children, compressions should be performed over the lower third of the sternum (because the heart lies under the lower third) at a depth of approximately one third of the chest, at a rate of 100/min, with a compression-to-ventilation ratio of 5:1. The exact technique used for ECC depends on the size and age of the patient. In infants, the sternum is compressed with two or three fingers. In children, however, the heel of the hand should be used. Compressions should be smooth and should occupy 50% of the circulatory cycle.

The essential objective of cardiac resuscitation is to reestablish or improve myocardial blood flow, restore spontaneous circulation, and maintain cerebral perfusion. There are conflicting data from experimental and clinical studies about the exact mechanism of blood flow during CPR. Initial studies suggested that compression of the heart results in ejection of blood into circulation (“cardiac pump mechanism”). However, later studies concluded that blood flow is due primarily to increased intrathoracic pressure (“thoracic pump mechanism”). The current consensus is that both mechanisms contribute to myocardial blood flow during ECC. Alternative methods of chest compression include interposed abdominal compression, vest CPR, active chest compression–decompression, and phased chest and abdominal compression–decompression. However, there are limited data about the efficacy of these methods in children.

Because ECC alone is insufficient to sustain “myocardial viability,” vascular access must be obtained for rapid delivery of resuscitation drugs to central circulation. The largest, most accessible (central or peripheral) vein that does not hinder CPR is preferred. Failure to obtain reliable vascular access within 90 s or after 3 attempts (whichever comes first) is an indication for intraosseous cannulation (in children 6 years or younger), or percutaneous venous access or saphenous cutdown (in children 7 years and older). If vascular access is not established within 3–5 min, epinephrine and other resuscitation drugs can be administered by the endotracheal route.

Primary resuscitation drugs include epinephrine, atropine, bicarbonate, calcium, and glucose. Epinephrine is a potent endogenous catecholamine with both a- and b-adrenergic effects. a-Adrenergic actions (vasoconstriction) include elevation of systolic and diastolic blood pressure and coronary perfusion pressure, and enhancement of oxygen delivery to the heart. b-Adrenergic effects (myocardial contractility) include increased heart rate, improvement of myocardial contractile state, and stimulation of spontaneous contraction in asystole. Epinephrine is indicated in cardiac arrest due to asystole, pulseless electrical activity, ventricular fibrillation, symptomatic bradycardia unresponsive to ventilation, and hypotension not due to hypovolemia.

The initial dose of epinephrine (intravenous or intraosseus) is 0.1 ml/kg of 1:10,000 solution. If pulseless cardiac arrest persists, a second and subsequent doses should be changed to 0.1 mL/kg of 1:1000 solution. If there is no return of spontaneous circulation despite adequate and appropriate CPR, prognosis for recovery is bleak. High-dose epinephrine is associated with adverse neurological outcomes; its efficacy, at best, is marginal; and its role in CPR remains unclear.

Acidosis (metabolic and respiratory) develops during cardiopulmonary arrest. Ensuring a patent airway, and restoring effective ventilation and perfusion are the mainstays of management of acidosis. Sodium bicarbonate should be considered in severe metabolic acidosis associated with prolonged cardiac arrest. Side effects of bicarbonate therapy include paradoxical cerebrospinal fluid and intracellular acidosis.

Atropine is a competitive muscarinic antagonist at the postganglionic cholinergic (parasympathetic) nerve endings. By reducing vagal tone, atropine increases heart rate and enhances atrioventricular conduction. Atropine is used for bradycardia associated with poor perfusion (symptomatic bradycardia). The efficacy of atropine in asystolic or bradycardiac cardiac arrest is unknown. The recommended dose is 0.02 mg/kg, with a minimum of 0.1 mg (to avoid paradoxical bradycardia), and a

maximum single dose of 0.5 mg in children and 1 mg in adolescents.

Glucose must be administered as soon as access is obtained when hypoglycemia is suspected to be the primary or a complicating factor in resuscitation. A rapid bedside glucose test should be obtained early, especially in critically ill or injured infants and in children with cardiorespiratory instability. Hypoglycemia should be corrected with 0.5–1.0 g/kg dextrose.

Secondary drugs (lidocaine, bretylium, magnesium, adenosine) are used infrequently in pediatric resuscitation. However, after successful resuscitation, epinephrine, dopamine, dobutamine, and isoproterenol should be considered to maintain and support circulation. Calcium (given as calcium chloride) is no longer recommended for either asystole or pulseless electrical activity. It is, however, indicated for the treatment of documented hypocalcemia, hyperkalemia, and calcium channel blocker overdose.

Defibrillation, indicated for the treatment of ventricular fibrillation and pulseless ventricular tachycardia, must be performed as soon as the abnormal rhythm is recognized, up to 3 times as needed. Initial energy dose of 2 J/kg is recommended, increasing to 4 J/kg with second and third doses. Synchronized cardioversion (0.5 J/kg initially, 1.0 J/kg subsequently) is the treatment of choice for supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, and atrial flutter with evidence of cardiovascular compromise. Adenosine is, however, the drug of choice even in unstable patients with supraventricular tachycardia, provided vascular access is present or available immediately.

It is important to monitor the effectiveness of CPR and to detect signs of return of spontaneous circulation during cessation of chest compression. End-tidal carbon dioxide monitoring (capnography) is a valuable tool for monitoring patients during CPR. Use of automated external defibrillation (AED) is currently not recommended for children younger than 8 years. Noninvasive (transcutaneous) pacing is indicated for management of symptomatic bradycardia refractory to both basic and advanced life support, although experience is limited in children. Open chest cardiac massage is used in cardiac arrest secondary to penetrating chest trauma, after thoracotomy, and in patients with chest deformities that prevent chest compression. Finally, there are few case reports of emergency extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass used for cardiac arrest refractory to conventional pediatric advanced life support (PALS).

The decision to terminate resuscitation is an extremely anguishing one because it is a final and definite act. The problem is compounded by the fact that there are limited data to guide pediatricians, and there is often disagreement among “experts.” The outcome of pediatric cardiac arrest is poor despite PALS measures. Some factors that influence the outcome of CPR in children have been identified. These include whether an arrest is witnessed or unwitnessed, in-hospital or out-of-hospital, the time elapsed before initiating basic life support (BLS), the time elapsed before initiating PALS, and total duration of CPR (>30 min). Other factors include cardiac rhythm (asystole has a worse prognosis than VF/VT) and number of doses of epinephrine (>2 doses).

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2. BACTEREMIA AND SEPTICEMIA

Kenneth B. Roberts and Olakunle B. Akintemi

For bacteria to infect the bloodstream, they must first bypass the defenses of the skin and mucous membranes and then escape phagocytosis in the extravascular tissues; they travel via the lymphatics to regional lymph nodes and, if not contained by the nodes, gain access to the venous circulation. The liver and spleen play a major role in “filtering” bacteria from the blood; the spleen is predominant if there is no preexisting circulating antibody to the organism. This filtering process can be overwhelmed by a large inoculum of bacteria; residual organisms are phagocytized by white blood cells in the circulation, at alveolar capillary sites in the lungs, and in the tissues. Therefore, the following factors (with examples of disorders) predispose the host to bacteremia: (1) loss of integrity of the external defenses (e.g., major burns, gastrointestinal ulceration, intravenous catheter); (2) inadequate phagocytic or immune function (e.g., immunosuppressive drugs, neutropenia, immune deficiency disorders); (3) impaired reticuloendothelial function (e.g., splenectomy, sickle cell disease); and (4) an overwhelming inoculum (e.g., perforated intestine). Bacteremia is a dynamic process, a balance between multiplication, invasion, and clearance of organisms; in most patients, host defenses predominate, and bacteremia is a transient phenomenon.

Bacteremia and septicemia are not synonymous. Bacteremia refers only to the presence of organisms in the blood; septicemia adds the connotation of severe illness. The distinction was highlighted in the 1970s by studies demonstrating that more than 3% of febrile infants have bacteremia while not appearing “toxic.” (Rates as high as 13% were documented in “nonseptic-appearing” infants, with fever, leukocytosis, and no apparent focus of bacterial infection.) The causative organism in the majority of infants with “occult” bacteremia was and continues to be *Streptococcus pneumoniae* (the pneumococcus). *Haemophilus influenzae* type b (Hib) was the next most frequent, but is now rare since the introduction of vaccines that are effective in infants. *Neisseria meningitidis* (the meningococcus) and salmonellae can also circulate in the bloodstream without causing clinical septicemia. These organisms are capable of causing focal complications or sepsis; there is no way at present to determine whether septicemia or a serious focus of infection (e.g., meningitis) will develop in a given child with bacteremia.

The clinical signs of septicemia are nonspecific and difficult to define. Generally, the child has high fever and is quite ill; the words toxic and septic are often used to describe the child's appearance. The white blood cell count is usually elevated (or markedly decreased), and there may be vacuoles or “toxic granulations” in the polymorphonuclear leukocytes. In neonates and very young infants, the signs of septicemia may be considerably more subtle (see Chap. 48).

When septicemia is suspected, treatment must be instituted immediately, prior to bacteriologic confirmation. The age and condition of the patient provide reasonable guides to the pathogens most likely to be responsible for clinical disease. In newborns, group B streptococci and gram-negative bacilli are the most frequent bacteria, followed by staphylococci. In immunocompromised hosts, gram-negative bacilli predominate, particularly *Pseudomonas, Escherichia coli,* and *Klebsiella* strains; *Staphylococcus aureus* is also common. In children with inadequate splenic function (congenital or operative absence of the spleen, or “functional asplenia,” as in children with sickle cell disease), the pneumococcus is the usual cause of sepsis. Certain bacteria are associated with specific foci of infection, as discussed in later chapters: pneumonia (Chap. 64), meningitis (Chap. 3), infections of the bones and joints (Chap. 106), urinary tract infection (Chap. 77), and bacterial endocarditis (Chap. 57). Skin lesions suggest infection with specific organisms: petechiae/purpura (*N. meningitidis*), pustules (*S. aureus*), small lesions with necrotic centers (*Neisseria gonorrhoeae*, the gonococcus), ecthyma gangrenosum (*Pseudomonas*), and rose spots (*Salmonella typhosa*).

A gram-stained specimen of pus from any source or an aspirate from a skin lesion may demonstrate the organism. Rapid techniques, such as latex agglutination, may detect organism-specific antigen in body fluids such as urine or cerebrospinal fluid; these tests have not been rewarding when applied to specimens of blood or serum, however.

In practice, it is often necessary to administer broad-spectrum antibiotic coverage until the bacterium is identified. The combination of vancomycin and a third generation cephalosporin (e.g., cefotaxime or ceftriaxone) may be used to treat invasive infections caused by the organisms that commonly colonize the skin or respiratory tract. Although the third generation cephalosporins are effective against many gram-negative organisms, an aminoglycoside is generally added to initial coverage if gram-negative sepsis is suspected. Once sensitivity testing is completed, the spectrum of antibiotic coverage can be narrowed. Penicillin is the drug of choice for sepsis resulting from meningococci or penicillin-sensitive pneumococci; a penicillinase-resistant penicillin (e.g., nafcillin, methicillin, oxacillin) for the staphylococcus; ceftriaxone or cefotaxime for b-lactamase–producing strains of *H. influenzae* (ampicillin can be used if the strain does not produce b-lactamase); and an aminoglycoside (e.g., gentamicin, tobramycin) for the commonly isolated gram-negative bacilli, excluding *Salmonella. Pseudomonas* infection, particularly if the host is immunosuppressed, is best treated with the synergistic combination of an aminoglycoside and a penicillin with anti- *Pseudomonas* activity (e.g., piperacillin). Current cephalosporins (e.g., ceftriaxone, cefotaxime) have been developed with characteristics that make them particularly attractive: excellent activity against the pneumococcus, Hib, and the meningococcus, even in the central nervous system, coupled with the safety characteristic of older cephalosporins. Ceftazidime is notable for its anti-*Pseudomonas* activity.

The most serious complication of bloodstream infection is the syndrome of septic shock, characterized by the hypoperfusion of vital organs. Metabolic acidosis and tissue starvation may be profound, resulting from an inadequate blood supply and mitochondrial injury. Endothelial cells are damaged, leading to edema and acting as a nidus for thrombus formation; platelets adhere to the damaged cells, fibrin is deposited, and a cycle is established that can lead to disseminated intravascular coagulation (DIC). In addition, both pathways of complement are activated, and there is potent stimulation for both vasodilatation and vasoconstriction, producing the characteristic findings of hypotension and poor peripheral circulation. Poor perfusion and DIC, in some cases complicated by adrenal hemorrhage, may result in the clinical state of purpura fulminans, with 40–80% mortality. The meningococcus is the most frequent cause of septic shock in normal hosts, but an identical syndrome may be caused by gram-negative bacilli and, particularly in patients with deficient splenic function, by the pneumococcus.

The high morbidity and mortality associated with septicemia and its complications are improved but by no means eliminated by early recognition and aggressive therapy. Antibiotic therapy must be initiated promptly; consideration is often given to the administration of corticosteroids along with (or just prior to) antibiotics, but clinical data to support steroid use are lacking. Supportive therapy is critical and includes the intravenous infusion of fluids, oxygen, and pressors, such as dopamine, when necessary. Respiratory failure is a major mode of death.

Approaches to prevention of bacteremia and septicemia include chemoprophylaxis and immunization. Rifampin chemoprophylaxis, for example, is generally prescribed for close contacts of patients with meningococcal disease, and is recommended for some contacts of patients with invasive *H. influenzae* disease; however, the ability of chemoprophylaxis to prevent septicemia on a large scale is obviously limited. Vaccination against Hib has been remarkably successful since the introduction of conjugate vaccines, i.e., those that couple the carbohydrate moiety of the organism to a protein; the protein permits the infantile immune system to “recognize” the antigen and develop protective antibodies. Since the introduction of the Hib vaccine, the incidence of Hib infection has declined by 95%. Similar technology has been applied to creating a pneumococcal vaccine for use during infancy; it is expected to be effective but may not be quite as successful as the vaccines against Hib because of the greater number of pneumococcal serotypes capable of producing invasive disease. Vaccines against meningococci (groups A, C, W-135, and Y) are available for children older than 2 years in high-risk groups, but these polysaccharide vaccines are of limited effectiveness in infants younger than 2 years. Immunization against *N. meningitidis* is further limited since there is no effective vaccine against certain strains, such as group B, that are common causes of meningococcal disease in the United States.

Fever and (Occult) Bacteremia

1. Baraff, L., et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. *Pediatrics* 92:1–12, 1993.
Definitely the place to start your reading. Includes the key references, a compilation of the findings, expert analysis, and recommendations. Note, however, that the prevalence of occult bacteremia in the post–Haemophilus influenzae type b (Hib) era is now about 1.6%. (See also Arch. Pediatr. Adolesc. Med. 152:624–628, 1998.)

2. Kramer, M., and Shapiro, E. Management of the young febrile child. A commentary on recent practice guidelines. *Pediatrics* 100:128–133, 1997.
A scholarly and thought-provoking commentary on the "practice guidelines" (Ref. 1 above). The authors question the utility of diagnostic testing (i.e., blood culture, bladder catheterization, suprapubic aspiration), and empiric antibiotic for febrile "nontoxic" children without a source of infection. See also pp. 133–138 for commentaries on the commentary.
3. Kuppermann, N. Occult bacteremia in young febrile children. *Pediatr. Clin. North Am.* 46:1073–1109, 1999.
A well-documented (230 references) review of the epidemiology, natural history and "basic science" of occult bacteremia. For a more basic and practical overview, see Contemp. Pediatr. 14:53–65, 1997.
4. Baraff, L., Oslund, S., and Prather, M. Effect of antibiotic therapy and etiologic microorganism on the risk of bacterial meningitis in children with occult bacteremia. *Pediatrics* 92:140–143, 1993.
The only failures of oral therapy were in children with Hib infection; no failures of ceftriaxone were identified in 139 children.
5. Harper, M., Bachur, R., and Fleisher, G. Effect of antibiotic therapy on the outcome of outpatients with unsuspected bacteremia. *Pediatr. Infect. Dis. J.* 14:760–767, 1995.
A retrospective study of 550 consecutive febrile children with unsuspected bacteremia to determine the efficacy of empiric antibiotic therapy. At follow-up, patients who received empiric antibiotic therapy (oral or parenteral) during the initial visit were afebrile; improved; and had fewer focal complications, persistent bacteremia, and admissions. (For a focus on meningococcal disease, see Arch. Pediatr. Adolesc. Med. 154:556–560, 2000.)
6. Rothrock, S., et al. Do oral antibiotics prevent meningitis and serious bacterial infections in children with *Streptococcus pneumoniae* occult bacteremia? A meta-analysis. *Pediatrics* 99:438–444, 1997.
This study confirms that, while oral antibiotics reduce the risk of serious bacterial infections in children with occult Streptococcus pneumoniae bacteremia, they do not prevent meningitis. (See also Acad. Emerg. Med. 5:599–606, 1998.)
7. Wittler, R., Cain, K., and Bass, J. A survey about management of febrile children without source by primary care physicians. *Pediatr. Infect. Dis. J.* 17:271–277, 1998.
A survey of primary care practitioners to determine their practice patterns since the publication of the 1993 practice guidelines. Most practitioners would admit the 3- and 7-week-old infants. But more pediatricians would use empiric outpatient antibiotics for the febrile 7-week-old infant. Clearly, the publication of guidelines on the management of febrile children has made little impact. See accompanying commentary, pp. 277–279. (For the result of the 1993 survey prior to the publication of the guidelines, see Pediatr. Infect. Dis. J. 12:179–183, 1993.)
8. McCarthy, P. Infants with fever. *N. Engl. J. Med.* 329:1493–1494, 1993.
A perspective editorial accompanying a report of outpatient management of febrile "low-risk" infants without antibiotics (p. 1437).
9. Baker, M., Bell, L., and Avner, J. The efficacy of routine outpatient management without antibiotics of fever in selected infants. *Pediatrics* 103:627–631, 1999.
The authors confirm the safety of the Philadelphia protocol for outpatient management (without antibiotics) of febrile infants 29–60 days at "low risk" for serious bacterial illness (SBI). (See also Clin. Pediatr. Emerg. Med. 7:102–108, 2000.)
10. Hoberman, A., et al. Prevalence of urinary tract infection in febrile infants. *J. Pediatr.* 123:17–23, 1993. And Shaw, K.N., et al. Prevalence of urinary tract infection in febrile young children in the emergency department. *Pediatrics* 102:e16, 1998. (Available at: http://www.pediatrics.org/cgi/content/full/102/2/e16.)
Just a reminder that bacteremia is not the only concern in febrile infants without apparent source of infection. White female infants have the highest prevalence of urinary tract infection. (Obtaining a chest x-ray in an infant with no respiratory signs and symptoms is unnecessary see Pediatrics 92:524, 199. But chest x-ray may be considered with a temperature of 39°C or higher and leukocytosis [WBC >20,000/mm^3] see Ann. Emerg. Med. 33:166–173, 1999.)

Laboratory Diagnosis

11. Rowley, A., and Wald, E. The incubation period necessary for detection of bacteremia in immunocompetent children. *Clin. Pediatr.* 25:485–489, 1986.
Of blood cultures containing any of the five most common pathogens, 98.5% were "positive" within 48 hours. (Rate is not as high when considering all pathogens, however. See Pediatr. Infect. Dis. 5:333, 1986.)
12. Saez-Llorens, X., and Lagrutta, F. The acute-phase host reaction during bacterial infection and its clinical impact in children. *Pediatr. Infect. Dis. J.* 12:83–87, 1993.
Insight into the "acute-phase reactants" that form the basis of nonspecific tests (e.g., white blood cell count, erythrocyte sedimentation rate) frequently performed to assess the risk of bacteremia.

Treatment of Presumed Sepsis

13. Klass, P., and Klein, J. Therapy of bacterial sepsis, meningitis and otitis media in infants and children: 1992 Poll of directors of programs in pediatric infectious diseases. *Pediatr. Infect. Dis. J.* 11:702–705, 1992.
In this periodic questionnaire regarding the treatment of presumed sepsis in 5-week-olds, 5-year-olds, and 12-year-olds, the favored treatment was the combination of ampicillin and a cephalosporin (cefotaxime) for 5-week-olds, and a cephalosporin (ceftriaxone, cefotaxime, or cefuroxime) alone in the older children.

Pneumococcus

14. Klein, J. The epidemiology of pneumococcal disease in infants and children. *Rev. Infect. Dis.* 3:246–253, 1981.
Part of a 200-page symposium on the pneumococcus. For more on the pneumococcal vaccine, see M.M.W.R. 64:1–19, 1997.
15. American Academy of Pediatrics Committee on Infectious Diseases. Therapy for children with invasive pneumococcal infections. *Pediatrics* 99:289–299, 1997.
Established therapy guidelines for both meningeal and nonmeningeal invasive pneumococcal infections.

***Haemophilus influenzae* Type b**

16. Centers for Disease Control and Prevention. Progress toward eliminating *Haemophilus influenzae* type b disease among infants and children. United States, 1987–1997. *M.M.W.R.* 47:993–998, 1998.
This report highlights the continuing decline in the incidence of Hib. Since 1988, when the Hib conjugate vaccines were first licensed for children aged 18–59 months, the number of cases of invasive Hib disease has declined by 99%. The end of Hib infection may be near. See Emerg. Infect. Dis. 4:229–237, 1998.
17. Wenger, J., et al. Day care characteristics associated with *Haemophilus influenzae* disease: *Haemophilus influenzae* Study Group. *Am. J. Public Health* 80:1455–1458, 1990.
The only characteristic associated with protection against Hib was the use of handerkerchiefs. (Our mothers were right!)

Meningococcus

18. Resenstein, N., et al. The changing epidemiology of meningococcal disease in the United States, 1992–1996. *J. Infect. Dis.* 180:1894–1901, 1999.
The recent epidemiology of meningococcal disease in the United States. The CDC estimates 2,400 cases annually, 22% of which are in children 2 years or younger. The highest age-specific incidence is in infants younger than 1 year, with a peak incidence in infants 4–5 months old. In 1996, 33% of cases were due to serotype Y. There have been increasing numbers of meningococcal infection outbreaks (mostly by serogroup C) (J.A.M.A. 273:383–389, 1995). For more on control and prevention of meningococcal disease, see M.M.W.R. 46:1–21, 1997.
19. Sullivan, T., and LaScolea, L. *Neisseria meningitidis* bacteremia in children: Quantitation of bacteremia and spontaneous clinical recovery without antibiotic therapy. *Pediatrics* 80:63–67, 1987.
Meningococcal bacteremia can be associated with meningitis, meningococcemia, occult bacteremia, or spontaneous recovery.
20. Towes, W., and Bass, J. Skin manifestations of meningococcal infection. *Am. J. Dis. Child.* 127:173–176, 1974.
No skin lesions in 14%; 75% with generalized maculopapular rash or petechiae; 11% with purpura. Meningitis was most frequent in the first group, and death in the third group.
21. Kirsch, E.A., et al. Pathophysiology, treatment and outcome of meningococcemia: A review and recent experience. *Pediatr. Infect. Dis. J.* 15:967–979, 1996.
A well documented review (131 references) of epidemiology, clinical features, pathophysiology, therapy, and prognosis of meningococcemia. For a more recent review of the pathophysiology of meningococcemia, see Eur. J. Pediatr. 157:869–880, 1998.

Salmonella

22. Torrey, S., Fleisher, G., and Jaffe, D. Incidence of *Salmonella* bacteremia in infants with *Salmonella* gastroenteritis. *J. Pediatr.* 108:718–721, 1986.
Estimates a 6% incidence.
23. St. Geme, J., et al. Consensus: Management of *Salmonella* infection in the first year of life. *Pediatr. Infect. Dis. J.* 7:615–621, 1988.
A group of experts give their opinions regarding how to manage infants with suspected Salmonella infection who are not "toxic" appearing and are well hydrated.

Septic Shock

24. Hayden, W. Sepsis terminology in pediatrics. *J. Pediatr.* 124:657–658, 1994.
The author proposes adoption of the system developed by the Society of Critical Care Medicine and the American College of Chest Physicians in the classification of sepsis in children.
25. Tapiero, B., and Lebel, M. Bacteremia, sepsis and septic shock. In:Jenson, H., and Baltimore, R. (eds.). *Pediatric Infectious Disease. Principles and Practice.* Norwalk, Connecticut: Appleton and Lange, 1995.
An excellent and comprehensive discussion of the definition, etiology, predisposing risk factors, clinical features, diagnosis, and treatment of bacteremia, sepsis, and septic shock. For a concise review of the definition, epidemiology, and prognosis of sepsis, see Pediatr. Emerg. Care 13:277–281, 1997. For a current overview of pediatric septic shock, see Pediatr. Rev. 20:303–308, 1999.

3. MENINGITIS

Kenneth B. Roberts and Olakunle B. Akintemi

As discussed in Chap. 2, bacteremia may be transient, cleared by host defenses, or may progress to clinical sepsis or to a localized focus of infection. The focal infection of greatest concern is meningitis. Until the recent introduction of vaccines against *Haemophilus influenzae* type b (Hib) that are effective during infancy, the epidemiology of meningitis was largely the epidemiology of Hib meningitis. *H. influenzae* type b was responsible for approximately 4 times as many cases as either of the other two bacteria commonly causing meningitis, i.e., *Neisseria meningitidis* and *Streptococcus pneumoniae.* Together, the three organisms accounted for 90% of cases of meningitis in infants and children beyond the neonatal period. The greatest risk for meningitis for all three organisms is between 6 and 12 months of age; 90% of cases occur before age 5 years. Because of the young age at which children developed Hib meningitis, it was hoped that a successful immunization program would reap benefits in a short period of time. In fact, the impact of vaccination against Hib has been truly remarkable, with a 95% reduction in the incidence of invasive diseases caused by Hib (e.g., meningitis, epiglottitis, septic arthritis). Pneumococcal meningitis occurs slightly more frequently than meningococcal meningitis overall, due to a high incidence in certain populations: It is 5–6 times more common in blacks than in whites, and children with sickle cell disease are at particular risk (36 times the risk for black children without sickle cell disease, 314 times the risk for whites); the rate in children with sickle cell disease under age 6 approaches 1% per year.

The signs and symptoms of meningitis are variable and depend on the age of the patient. In infants, whose cranial sutures are still open, fever, vomiting, irritability, lethargy, convulsions, and bulging of the fontanelle may be present; during the first 2 years of life in particular, the findings are often subtle or nonspecific. In older children, focal neurologic signs, such as a sixth nerve palsy, may be more prominent, and signs of meningeal irritation, such as nuchal rigidity, Kernig sign, or Brudzinski sign, are usually present.

Examination of the cerebrospinal fluid (CSF) is mandatory if there is clinical suspicion of meningitis. In most cases of bacterial meningitis, there is an increased number of white cells in the CSF, usually well over 100/µL, with a predominance of polymorphonuclear leukocytes. The glucose level in the CSF is reduced (hypoglycorrhachia), usually to below 40 mg/dL and less than half the concentration of the serum glucose; the protein level in the CSF is elevated. Organisms are visible in gram-stained specimens in the majority of cases. *S. pneumoniae* are lancet-shaped, gram-positive cocci that may appear in pairs with end-to-end orientation; *N. meningitidis* are bean-shaped, gram-negative diplococci that usually orient with the concave surfaces apposed; *H. influenzae* are gram-negative, pleomorphic coccobaccili. Bacterial products may be identified by rapid techniques; the most commonly performed test currently uses latex agglutination to detect organism-specific capsular polysaccharide. It is vital to recognize that none of the features described is a sine qua non for the diagnosis of bacterial meningitis: Any can be “normal” in a given patient, and on very rare occasions, meningitis is present in the absence of any of these changes. The definitive diagnosis is established bacteriologically.

Meningitis may be caused by agents other than pyogenic bacteria, including viruses, *Mycobacterium tuberculosis*, fungi, and neoplasms. These situations are generally associated with fewer, mostly mononuclear, cells in the CSF. Early in the course of viral meningitis, polymorphonuclear leukocytes may predominate; a specimen of CSF obtained 6–8 hours after the initial evaluation usually demonstrates the characteristic “shift” to mononuclear cells. The protein and glucose concentrations are usually normal, but meningitides caused by tuberculosis, mumps, and some enteroviruses are notable exceptions.

Treatment of bacterial meningitis must be instituted without delay, prior to bacteriologic confirmation. One of the cephalosporins, which penetrates well into the CSF and is effective against the usual causes of meningitis (e.g., ceftriaxone or cefotaxime), is administered parenterally in large doses until identification of the organism and antibiotic-susceptibility testing are complete; because of the possibility of resistant pneumococci, vancomycin is also administered. Laboratory studies have demonstrated that the chemical mediators of inflammation may be detrimental to the host, and clinical studies suggest that dexamethasone may have a protective effect against neurologic sequelae of Hib meningitis; the data regarding benefit in other forms of meningitis are scant. Supportive care is crucial and is aimed toward prevention and treatment of complications, the most important of which initially is increased intracranial pressure (see Chap. 9). Focal neurologic signs occured in approximately 10–15% of patients during the Hib era; sixth nerve palsies usually resolve in the first day or two of hospitalization, but gross focal neurologic signs are associated with sequelae still detectable after discharge from the hospital. Seizures occur in about one fourth of children, two thirds of whom have the seizures before treatment is instituted. Seizures beyond the third hospital day portend an unfavorable prognosis. Because of vomiting or decreased intake before the diagnosis of meningitis is established, many infants and children have some degree of dehydration and, as a consequence, appropriately high levels of antidiuretic hormone; rehydration should be aimed at normalizing circulating intravascular volume to promote adequate cerebral perfusion. The level of antidiuretic hormone can also be inappropriately high, due to central nervous system (CNS) inflammation, and can lead to hyponatremia, water intoxication, and seizures; these complications can be prevented by restricting the intake of fluids and electrolytes to the amount needed to maintain euvolemia. Intracranial inflammation may also cause cavernous sinus thrombosis, subdural effusions, or hydrocephalus. Other complications and sequelae include deafness, ataxia, and mental retardation. Because hearing loss may occur in children who have no apparent deficits and may be difficult to discern clinically (particularly when unilateral), infants and children who have had meningitis should have their hearing tested as part of routine follow-up care.

Mortality in bacterial meningitis has remained 5–10% despite prompt administration of antibiotics in appropriate doses and vigorous supportive therapy. The high mortality and morbidity underscore the importance of prevention of meningitis. As noted, the Hib vaccine has had outstanding success. It is expected that pneumococcal conjugate vaccine will also be effective, though concern remains about strains not included in the vaccine. Immunization against *N. meningitidis* is limited because it is carbohydrate based, and therefore not immunogenic in infants younger than 2 years; moreover, there is no effective vaccine against group B strains, which are common causes of meningococcal meningitis in the United States.

Reviews

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   A thorough review (29 pages, 205 references); a good place to start and to come back to.
2. Lipton, J., and Schafermeyer, R. Evolving concepts in pediatric bacterial meningitis. Part I: Pathophysiology and diagnosis. Part II: Current management and therapeutic research. *Ann. Emerg. Med.* 22:1602–1615, 1616–1629, 1993.
   A total of 27 pages, extensively referenced (Part I, 212 references; Part II, 172 references).
3. Saez-Llorens, X., and McCracken, G.H. Bacterial meningitis. In: Katz, S., Gershon, A., and Hotez, P. (eds.). *Krugman's Infectious Diseases of Children.* St. Louis, Missouri: Mosby, 1998.
   A brief review of the etiology, pathogenesis, pathophysiology, diagnosis, differential diagnosis, complications, treatment, and prognosis of bacterial meningitis. For a more recent review by the same authors, see Infect. Dis. Clin. North Am. 13:619–636, 1999. Also, the entire issue (240 pages) is on bacterial meningitis.
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   A basic, clinical review on meningitis from birth to age 21 years. For an in-depth review of infections of the central nervous system (CNS) (meningeal and parameningeal infections), see also Adv. Intern. Med. 43:403–447, 1998.

Epidemiology

5. Schoendorf, K., et al. National trends in *Haemophilus influenzae* meningitis mortality hospitalization among children, 1980 through 1991. *Pediatrics* 93:663–668, 1994.
   Hospitalization rates and mortality declined by nearly 50% for Haemophilus influenzae type b (Hib) meningitis but not for meningitis caused by Streptococcus pneumoniae or N. meningitidis.
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   This study reports the results of laboratory-based surveillance for bacterial meningitis in 1995, and what a difference a decade makes. Compared with 1986, the median age of persons with meningitis was 25 years in 1995; S. pneumoniae was the leading cause of bacterial meningitis (47%), followed by N. meningitidis (25%), and group B streptococcus (12%). Finally, there was a 94% reduction in the number of cases of H. influenzae meningitis. For additional review of epidemiology of bacterial meningitis, see Infect. Dis. Clin. North Am. 13:515–525, 1999.

Diagnosis

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   Tabulates from many series the abnormalities in meningitis; also provides a review of anatomic considerations, normal properties and composition, and evaluation of cerebrospinal fluid (CSF) contaminated by red blood cells ("traumatic tap"). (The author also provides values of CSF composition in infants younger than 8 weeks who did not have meningitis: Pediatr. Infect. Dis. J. 11:589–591, 1992. There were more white blood cells than in the CSF of older children but not more polymorphonuclear leukocytes.)
9. Ahmed, A., et al. Cerebrospinal fluid values in the term neonate. *Pediatr. Infect. Dis. J.* 15:298–303, 1996.
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12. Kaplan, S., et al. Association between preadmission oral antibiotic therapy and cerebrospinal fluid findings and sequelae caused by *Haemophilus influenzae* type b meningitis. *Pediatr. Infect. Dis. J.* 5:626–631,1986.
    Oral antibiotics do not alter CSF findings enough to obfuscate diagnosis in most cases; longer duration of illness prior to diagnosis increased likelihood of deafness.
13. Donald, P., Malan, C., and van der Walt, A. Simultaneous determination of cerebrospinal fluid glucose and blood glucose concentrations in the diagnosis of bacterial meningitis. *J. Pediatr.* 103:413–415, 1983.
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Antibiotic Treatment

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    An account of one hundred years of recommendations, including current guidelines. The author provides a valuable perspective: "Authority recommendations in fact have not been based on sufficient proof but instead have been derived from continuous experience, and they are accepted in the name of expediency."
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Pathophysiology and Nonantibiotic Management

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    A state-of-the art overview of the biology of cytokines and chemokines, and their role in bacterial, viral, fungal, and tuberculosis meningitis. See also Infect. Dis. Clin. North Am. 13: 527–548, 1999.
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    An extensive review (30 pages, 112 references), including pathophysiology, cerebral metabolism, cerebral blood flow, cerebral edema, cerebral perfusion pressure, autoregulation, and implications for treatment. For a shorter version of this article, see also Neurology 42:739–748, 1992.
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4. UPPER AIRWAY OBSTRUCTION

Kenneth B. Roberts and Conrad J. Clemens

Because of its size and structure, the upper airway in infants and children produces clinically apparent signs (such as stridor) with even a mild degree of obstruction. Resistance to air flow is proportional to the radius of the airway to the fourth power (r^4) if flow is laminar, to the fifth power (r^5) if flow is turbulent. Thus, a small amount of narrowing of an already small airway can greatly compromise flow. Moreover, the submucosa is “loose,” which is conducive to the accumulation of edema fluid, but the confines of the airway are rigid and cartilaginous; any accumulation, then, encroaches on the lumen of the airway. A final factor contributing to the vulnerability of the infant to upper airway obstruction is the short distance between the pharynx and the trachea; compromise that in an adult can be localized to a relatively short portion of the upper airway may appear more generalized in the very small infant.

Many ways of organizing a differential diagnosis of the several causes of upper airway obstruction have been proposed: by age of the patient, by relationship of the lesion to the airway (intrinsic-extrinsic), by the level of the lesion (supraglottic-glottic-subglottic), or by the pathophysiologic process producing upper airway obstruction (e.g., infectious, neoplastic). In practice, however, the clinician uses all these simultaneously to arrive at the most likely diagnosis, recognizing that all but a few causes are uncommon.

The most common cause of upper airway obstruction in infants is viral croup. The majority of cases occur between October and April, caused chiefly by parainfluenza viruses and also by respiratory syncytial virus and influenza viruses. The usual age group affected is infants, 3 months to 3 years of age; boys outnumber girls 2:1. The signs and symptoms of upper airway obstruction appear after several days of upper respiratory tract infection. The child has stridor and the characteristic barking, croupy cough; retractions and dyspnea, with increased efforts during inspiration, are present. Anxiety usually exacerbates the infant's difficulties, and there may be progression to fatigue, restlessness, and air hunger. The respiratory rate provides a good estimate of the Pao_2: As the respiratory rate increases from 20 to 45, the Pao_2 decreases linearly from 90 to 60 mm Hg. The respiratory rate does not reflect the Pco_2, which is usually normal despite the hypoxia; an explanation for the disproportionate hypoxia is that the marked inspiratory effort with upper airway obstruction creates sufficient intrathoracic negative pressure to cause pulmonary edema.

In general, viral croup is considered a benign, self-limited disease lasting between 1 and 14 days. Currently, with improved treatment regimens, tracheostomy or intubation occurs rarely and only in those children hospitalized in severe respiratory distress. Nebulized (racemic or l-) epinephrine causes topical vasoconstriction and decreases mucosal edema. The relief provided is rapid but transient, and repeated courses, frequently administered are sometimes required. However, the use of epinephrine has not been shown to shorten the duration of the illness or of hospitalization. Corticosteroids, through their anti-inflammatory action, are effective in improving outcomes and are generally provided. Antibiotics are not warranted in the usual uncomplicated case of croup. Finally, there is no current evidence that humidity, given by vaporizer, inhalation of steam at home, or by “croup tent” in the hospital, is effective.

Spasmodic croup is an entity of unknown pathogenesis; many presume it to be allergic. Episodes are brief, begin in the evening, occur without a prodromal upper respiratory infection, and tend to be recurrent. Corticosteroids may be effective in this disorder but generally are unnecessary.

A more serious form of infection-produced upper airway obstruction is epiglottitis, or, more properly, supraglottitis. Once a common and devastating disease, the advent of the *Haemophilus influenzae* vaccine has all but made epiglottitis a disease of the past. Epiglottitis can be differentiated from croup in a couple of important ways. Children tend to be older (3–7 years) and the course of the illness is much more rapid and severe; sore throat and fever develop, and within hours the child assumes a characteristic posture, with protrusion of the jaw, drooling, refusal to swallow, muffled phonation, and an anxious appearance. Complete airway obstruction can occur if no intervention is taken.

If epiglottitis is suspected, then endotracheal intubation or tracheostomy should be performed “semielectively” as soon as possible. Any attempt to visualize the epiglottis by forcible depression of the tongue may precipitate total airway obstruction and is therefore contraindicated. When the diagnosis is in question, a lateral x-ray film of the neck is a reliable means of detecting swelling of the epiglottis without the risk associated with direct visualization. Initial antibiotic treatment is with a cephalosporin such as ceftriaxone or cefotaxime. Racemic epinephrine and corticosteroids are of no value in this disease.

Bacterial tracheitis is also associated with significant morbidity and mortality. This disorder starts out mild, similar to viral croup, but progresses in severity over days (unlike croup, which improves over days, or epiglottitis, which progresses rapidly over hours). Thick, purulent secretions, usually caused by *Staphylococcus aureus*, accumulate in the trachea and may obstruct the airway, resulting in cardiopulmonary arrest. The keys to therapy are clinical suspicion of the diagnosis, endoscopic removal of secretions, attention to maintenance of a patent airway, and antibiotic therapy.

A retropharyngeal abscess classically presents after an upper respiratory infection (URI) with fever, stridor, and neck swelling that is often associated with a head tilt (torticollis). However, in older children, stridor is usually absent and less specific symptoms such as neck stiffness and sore throat are present. A lateral radiograph is often of benefit; the diagnosis can be made if the retropharyngeal space is widened more than twice the diameter of the cervical vertebrae. Frequently, antibiotic therapy is not sufficient and surgical drainage is required.

Laryngomalacia and congenital stridor are terms used for an entity that usually is manifest in the first few months of life. Characteristically, the infant appears to be normal except for stridor, which is particularly audible when the infant is supine or excited. With additional airway compromise, such as during episodes of upper respiratory tract infection, the stridor may be accentuated, and the infant may require medical attention. Direct laryngoscopy reveals the epiglottis, arytenoid cartilage, and aryepiglottic folds to be “floppy” and drawn into the larynx during inspiratory effort. The condition commonly becomes more severe during the first year of life but then gradually improves, with complete clinical recovery.

Since infants and toddlers commonly explore their world by taste as well as by touch, ingested and aspirated foreign bodies are a problem in this age group. The anatomic site of the foreign body is the gastrointestinal tract twice as often as the respiratory tract. The most common areas of obstruction are the esophagus at the level of the cricopharyngeus muscle, the aortic arch, and the gastric inlet. In the respiratory tract, foreign bodies tend to lodge in the bronchi more commonly than in the trachea or the larynx. Radiographs have a high false-negative rate, and therefore if a foreign body is suspected, bronchoscopy should be undertaken.

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5. RESPIRATORY FAILURE AND STATUS ASTHMATICUS

Olakunle B. Akintemi

Reviews
Therapy
Outcome

Respiratory failure is the most common serious emergency encountered by practitioners caring for children. The respiratory system consists of the lungs and the “respiratory pump.” The lungs (including large and small airways, alveoli and pulmonary circulation) function primarily to exchange oxygen and carbon dioxide across the alveolar-capillary membrane. The “respiratory pump” consists of the nervous system (central and peripheral), and chest “bellows” (i.e., respiratory muscles, thoracic cage), which ventilate the lungs. Respiratory failure is caused by either the failure of lungs to exchange oxygen (oxygenation failure) or failure of the “respiratory pump” to ventilate the lungs (ventilation failure). Respiratory failure is therefore defined as the “inability of the respiratory system to maintain adequate oxygen and carbon dioxide homeostasis” (i.e., failure of oxygenation and carbon dioxide elimination). The availability of arterial blood gas sampling has led to the establishment of objective criteria to define respiratory failure. Therefore, it may also be defined as an arterial Po_2 <60 mm Hg or an arterial Pco_2 >50 mm Hg.

Respiratory failure may be acute or chronic and is subclassified as (1) hypoxemic respiratory failure (Type I), and (2) hypercapnic failure (Type II, “ventilatory failure”). Acute hypoxemic (Type I) failure is characterized by arterial Po_2 ($Pa\ o_2$) <55 mm Hg when fraction of inspired oxygen (Fio_2) is 0.60 or greater. The three major mechanisms of hypoxemia are alveolar hypoventilation, ventilation perfusion mismatch, and intrapulmonary shunt. With hypoventilation, the alveolar to arterial oxygen difference [$P(A\text{-}a)o_2$] is normal. In contrast, both ventilation-perfusion mismatch and shunt result in increased $P(A\text{-}a)o_2$ level. Ventilation-perfusion mismatch can be distinguished from shunt by response to supplemental oxygen. Type II respiratory failure is characterized by an elevated $Paco_2$ (>45 mm Hg) and respiratory acidemia (pH <7.30).

The precipitating causes of respiratory failure in infants and children are extensive and depend on the age of the patient. Causes include pneumonia, bronchiolitis, viral croup, epiglottitis, status asthmaticus, foreign body aspiration, submersion, smoke inhalation, hydrocarbon aspiration, septic shock, and neuromuscular disorders. The most common of these are pneumonia, bronchiolitis, status asthmaticus, and septic shock. Respiratory failure is often preceded by signs of respiratory distress, increase in the work of breathing to compensate for the hypoxemia. It therefore represents a failure of these compensatory mechanisms. Signs of respiratory distress include tachypnea, hyperpnea, chest wall retractions, nasal flaring, inspiratory stridor (upper airway obstruction), restlessness, and tachycardia. Other signs are grunting, see-saw (abdominal) breathing, and head bobbing. Without recognition and effective therapy, respiratory distress may progress to respiratory failure. Diminished or absent breath sounds, bradypnea, or irregular, shallow respiration herald onset of respiratory failure. Other signs (although late) include apnea, cyanosis, hypotonia, and decreased level of consciousness or response to pain.

Early recognition and the prevention of progression to cardiopulmonary arrest are the most important components in the management of respiratory failure. The Pediatric Assessment Triangle and Rapid Cardiopulmonary Assessment are two clinical methods for recognizing respiratory (and circulatory) failure. The Pediatric Assessment Triangle consists of observation of the general appearance of the child (mental status, muscle tone), work of breathing (rate, effort), and circulation (skin, color, mucous membrane). The Rapid Cardiopulmonary Assessment is similar to the assessment triangle. It is essentially a rapid assessment of airway, work of breathing, color, circulation, and central nervous system perfusion.

If the child is in respiratory failure, the first priority is to establish a patent airway and provide adequate ventilation with maximum supplemental oxygen. The goal of therapy is to maximize oxygen delivery (with high Fio_2) and minimize oxygen demand (avoid cold stress, treat fever). If air entry is inadequate and breath sounds are not heard after achieving airway patency, assisted ventilation with bag-valve-mask should be provided. If the child is unable to maintain a patent airway, or the airway is obstructed, endotracheal intubation and mechanical ventilation may be needed.

Mechanical ventilation is used to provide respiratory support for failing respiratory system until its function can return. The physiologic objectives are to support alveolar ventilation ($Paco_2$, PH), improve arterial oxygenation ($Pa\ o_2$, $Sa\ o_2$), reduce work of breathing, and improve lung volume. The overall clinical effects of mechanical ventilation are (1) reversal of hypoxemia; (2) correction of respiratory acidosis; (3) relief of respiratory distress; (4) prevention and reversal of atelectasis; (5) prevention of respiratory muscle fatigue; (6) reduction of myocardiac or systemic oxygen consumption; and (7) stabilization of chest wall for adequate lung expansion.

Intermittent negative pressure ventilation and intermittent positive pressure ventilation (IPPV) are the two types of mechanical ventilation. The two basic modes of IPPV are (1) time-cycled, pressure-limited ventilation, and (2) time-cycled, volume-limited ventilation. These ventilators provide various methods of interfacing with the patient's breathing effort (ventilator mode). These modes include assist control ventilation; intermittent mandatory ventilation (IMV), in which patient breaths spontaneously with periodic mandatory; and machine breaths. The mandatory or machine breaths may be time triggered (controlled IMV) or patient triggered (synchronized IMV [SIMV]). Other modes are continuous spontaneous ventilation, in which all breaths are initiated and ended by the patient. Examples of continuous spontaneous ventilation include pressure support ventilation (each breath is augmented by positive pressure), continuous positive airway pressure (CPAP), and bilevel CPAP or bilevel positive airway pressure (BiPAP [pressure support with CPAP]). Bilevel positive airway pressure-support ventilation applied by face or nasal mask is an effective method of noninvasive mechanical ventilation for children with respiratory failure secondary to neuromuscular disease and other restrictive lung diseases, and may obviate the need for intubation in some patients with respiratory failure (e.g., from obesity, hypoventilation, or end-stage cystic fibrosis).

Some patients, especially those with acute respiratory distress syndrome (ARDS) and severe hypoxemic respiratory failure, fail to improve despite mechanical ventilation. This has led to development of new approaches for providing ventilatory support. These include permissive hypercapnia, high frequency oscillatory ventilation, inhaled nitric oxide, intratracheal pulmonary ventilation, extracorporeal membrane oxygenation (ECMO) and liquid ventilation with perfluorocarbon.

As stated earlier, status asthmaticus is one of the most common causes of respiratory failure in children. According to the American Thoracic Society, status asthmaticus (SA) is defined as an acute attack in which the degree of airway obstruction is severe from the beginning or increases in severity, and is not relieved by the usual treatment. Simply, it is an episode of asthma that is refractory to bronchodilator therapy and may result in ventilatory failure, respiratory acidosis, and death.

Asthma is the most common chronic illness in childhood, with an estimated prevalence of 5–10% (see Chap. 65). Inflammatory, immunologic, biochemical, and cellular mechanisms are involved. Inflammatory cells (mast cells, basophils, eosinophils, neutrophils, lymphocytes, macrophages, and cytokines) interact with chemical mediators (histamine, leukotrienes, prostaglandins, platelet activating factor, nitric oxide, and eosinophilic and neutrophilic chemotactic factor) to produce the changes characteristic of asthma. Thus, the hallmarks of asthma are (1) airway inflammation with microvascular leakage; (2) reversible bronchoconstriction; (3) bronchial hyperresponsiveness; and (4) mucociliary dysfunction.

Despite advances in pharmacotherapy and better understanding of asthma, mortality increased between 1977 and 1988. However, it is encouraging that since 1988 the rate of death from asthma has stabilized but at rates 50% higher than in 1979. Factors that are associated with increased risk of death are (1) severity of asthma; (2) prior history of life-threatening attack that required mechanical ventilation; (3) undertreatment; (4) poor compliance; (5) poor access to medical care; (6) psychological and psychosocial problems; (7) race/ethnicity; (8) age (adolescents); (9) overuse of b agonists; (10) poverty; and (11) urban environment. Three groups of patients who die from asthma have been identified. The first group (slow-onset fatal asthma) present with gradual and progressive worsening of symptoms over days ultimately resulting in ventilatory failure. In the second group (acute asphyxic asthma), attacks progress rapidly to respiratory compromise in 1–2 hours. The third category, with unstable asthma and acute deterioration, has features similar to the first 2 groups.

Autopsy reports in most patients dying of status asthmaticus reveal overdistended lungs with air trapping, extensive mucus plugging of medium-to-small airways, and thickening of the airway smooth muscle. The most prominent feature is airway obstruction. Because of severe airway narrowing, airway resistance increases. The overall effect is development of air trapping, hyperventilation, and increase in functional residual capacity, residual volume, and total lung volume. Due to all of these changes, work of breathing increases and a higher inspiratory force is needed to overcome the higher elastic recoil forces in the lungs and thorax. Other changes include development of ventilation-perfusion mismatch, increased dead space, and hypoxemia. Eventually, when oxygen demand exceeds oxygen delivery to the

muscles, fatigue, respiratory acidosis, carbon dioxide retention, and respiratory failure develop.

The initial evaluation of a child who presents with either an acute exacerbation or severe asthma is rapid cardiopulmonary assessment and immediate resuscitation. After stabilization, the next step is to assess the severity of airway obstruction and the risk of ventilatory failure. Subjective and objective methods are used. These include signs and symptoms (breathlessness; ability to talk; ability to lie down; alertness; respiratory rate, pulse rate, and wheeze; use of accessory muscles; and pulsus paradoxus), and objective measures (peak expiratory flow rate, arterial blood gas, pulse oximetry). Although arterial blood gas measurements are not necessary in assessing children with mild-to-moderate asthma, they should be considered in status asthmaticus. Hypercapnia indicates severe airway obstruction, but its presence alone is not an indication for intubation.

Management of status asthmaticus includes early supplemental oxygen, a frequently or continuously administered b2-adrenergic agent (albuterol, terbutaline), a nebulized anticholinergic agent (ipratropium), and a corticosteroid. Delivery of b2-adrenergic agents may be achieved by either nebulization or metered-dose inhaler (MDI) with spacer or face masks. Subcutaneous epinephrine may be indicated in children with severe bronchospasm who are unable to tolerate nebulization treatment. Intravenous (IV) terbutaline should be considered in children unresponsive to nebulized b2-adrenergic treatment. A corticosteroid should be administered early, orally or parenterally. Incremental benefit from the addition of methylxanthine (aminophylline) appears to be offset by the increased incidence of adverse effects. Intravenous fluid should be administered in limited quantity and monitored carefully to prevent overhydration and pulmonary edema. Antibiotics are not routinely indicated but may be considered in cases of suspected bacterial, mycoplasma, or *Chlamydia pneumoniae* pneumonia.

Adjunctive therapy for patients refractory to b agonists and corticosteroids includes IV magnesium sulfate, helium-oxygen (heliox), and ketamine. Although there is insufficient evidence to recommend the routine use of magnesium sulfate, it may be considered in severe airway obstruction with impending respiratory failure. Heliox is a mixture of 60–80% helium and 20–40% oxygen. Because of its low density (one third that of room air), it reduces airway resistance by converting turbulent to laminar flow, thereby reducing work of breathing. The exact role of heliox in status asthmaticus is unknown. Limited data suggest it may be a temporizing measure that may avert the need for intubation and mechanical ventilation.

Signs of impending respiratory failure include worsening fatigue, decreasing level of consciousness, and a $Paco_2$ of >42 mm Hg. The decision to intubate should be made on clinical grounds (decreased level of consciousness, coma, apnea). According to the 1997 National Institutes of Health guidelines, “it is best done semielectively before the crisis of respiratory arrest.” Controlled intubation (rapid sequence intubation) is the preferred method. Ketamine increases catecholamine levels and also has sedative and bronchodilator actions. It is the method of choice for sedation during rapid sequence intubation. Alternative sedatives include propofol and benzodiazepines (e.g., midazolam). Guidelines for mechanical ventilation include (1) volume-limited or pressure control ventilation mode; (2) “controlled hypoventilation” with low rate and prolonged expiratory time; (3) “permissive hypercapnia” using low tidal volume with adequate mean airway pressure and allowing the $Paco_2$ to rise above 40 mm Hg.; and (4) avoiding high peak airway pressure and further hyperinflation to avoid barotrauma (pneumothorax, pneumomediastinum, pneumoperitoneum) and ventilator-induced lung injury. Finally, status asthmaticus may be prevented by identifying high-risk patients, recognizing symptoms early and providing treatment, developing special/crisis plans for these patients, educating patients and physicians, and improving access to emergency care.

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6. DIABETIC KETOACIDOSIS

Stuart A. Weinzimer and Craig A. Alter

Diabetic ketoacidosis (DKA) is a life-threatening, preventable complication of diabetes mellitus (see Chap. 81) characterized by inadequate insulin action, hyperglycemia, dehydration, electrolyte loss, metabolic acidosis, and ketosis. It is associated with a significant mortality rate and is the most frequent cause of death in children with type I diabetes mellitus. Children whose diabetes has not yet been diagnosed may present with DKA, so the diagnosis must be considered in any child with confusion or coma of undetermined etiology. In children whose diabetes has already been diagnosed, DKA can usually be prevented by patient and family education, frequent monitoring of blood glucose and urinary ketones during intercurrent illness, adequate oral hydration, and supplemental insulin ("sick day rules").

Diabetic ketoacidosis is defined as a blood sugar >240 mg/dL, ketonemia/ketonuria, and a pH <7.3. The primary abnormality is insulin deficiency, which leads to hyperglycemia both because of decreased glucose utilization and increased gluconeogenesis. As glucose levels exceed the renal threshold of 180 mg/dL, an osmotic diuresis occurs, resulting in the loss of extracellular water and electrolytes, and worsening of the hyperglycemia. Insulin deficiency also leads to accelerated lipolysis with subsequent conversion of free fatty acids to b-hydroxybutyric and acetoacetic acids. This results in a metabolic acidosis. (Acetone is also formed and gives a fruity odor to the patient's breath, but it does not contribute to the acidosis.) Potassium, primarily an intracellular ion, is translocated out of the cell into the plasma in exchange for hydrogen and is lost in the urine. Thus, virtually all patients with DKA develop a "total body" deficiency of potassium, regardless of their serum potassium level. Phosphate, another predominantly intracellular ion, is handled similarly. Deficiency of 2,3-diphosphoglycerate, a phosphate-containing glycolytic intermediate in red blood cells that facilitates release of oxygen from hemoglobin, may contribute to the development of lactic acidosis complicating the ketoacidosis. Although insulin deficiency is the principal abnormality, elevated counterregulatory hormones (glucagon, cortisol, catecholamines, and growth hormone) contribute to both the accelerated gluconeogenesis and lipolysis.

Diabetic ketoacidosis is not difficult to recognize in a child with known diabetes who is dehydrated, hyperventilating, and obtunded. In the child whose diabetes has not yet been diagnosed, however, it may be confused with Reye syndrome, toxic ingestion (especially salicylate or alcohol), and central nervous system (CNS) infection or trauma. Persistent vomiting may suggest gastroenteritis, or with abdominal pain, acute appendicitis or other intra-abdominal process. The diagnosis of diabetes (if not already established) is suggested by a history of polyuria, polydipsia, polyphagia, nocturia, or enuresis in a previously toilet-trained child. Weakness and unexplained weight loss may also be presenting features. When the diagnosis of DKA is suspected, an attempt should be made to identify precipitating causes (e.g., infection, stress, or noncompliance). In a child with known diabetes, it is important to review briefly the recent blood sugar history and to ascertain not only the usual insulin dosage but also the quantity and timing of the most recent injection.

The physical examination should focus initially on the adequacy of the airway, breathing, and an assessment of the circulatory status (pulse, blood pressure, peripheral perfusion), degree of dehydration (including weight if possible), and mental status (Glasgow Coma Scale [GCS]). Deep, rapid respirations (Kussmaul breathing) and a fruity odor to the breath are classic signs but are not present in every patient. A careful search should be made for a source of infection that may have precipitated the episode of DKA. Bedside determination of the blood glucose with a glucose monitoring device and evaluation of the urine for glucose and ketones should be performed as quickly as possible, and treatment should be initiated without waiting for the results of the laboratory assessment to become available.

The laboratory evaluation of patients suspected to have DKA includes determination of the blood glucose, plasma, or urinary ketones, serum electrolyte concentration, blood urea nitrogen (BUN), creatinine, osmolarity, and a baseline calcium and phosphorus. A baseline blood gas measurement should also be done to determine the pH and Pco_2. While venous blood gas measurements may suffice in milder episodes of DKA, an arterial blood gas measurement should be obtained in patients suspected to have incomplete respiratory compensation and/or those expected to require bicarbonate therapy (see below). If hyperlipidemia is present, the serum sodium concentration may be artefactually lowered. Similarly, the serum sodium will be reduced approximately 1.6 mEq/L for each 100 mg/dL rise in glucose because of the reequilibration of the intra- and extracellular compartments at a higher osmolarity. In the presence of ketones (and lactate), a large anion gap acidosis will be present. The degree of elevation of the BUN and creatinine, as well as the hematocrit, may indicate the extent of dehydration (and the possibility of renal damage). The initial serum potassium may be low, normal, or high, depending on the degree of acidosis and the quantitative urinary losses.

The acute management of DKA is directed at correction of the dehydration, electrolyte loss, hyperglycemia, and acidosis. Initial fluid therapy is aimed at rapid stabilization of the circulation to correct impending shock, but as in other forms of hypertonic dehydration, too rapid fluid administration must be avoided. Fluid replacement in excess of 4 $L/m^2/24h$ has been associated with the development of potentially fatal cerebral edema in DKA. For this reason, an initial fluid bolus is usually advised to expand the vascular compartment and improve peripheral circulation, but once the patient has been stabilized, subsequent rehydration is accomplished with caution. Typically, one aims to correct the fluid defect gradually, over 36–48 hours. Gradual correction is particularly important in children at an increased risk of developing cerebral edema. This includes children with altered mental status, history of symptoms >48 hours, pH <7.0, glucose >1,000 mg/dL, corrected sodium >155 mEq/L, extreme hyperosmolarity (>375 mOsm/L), or age <3 years. A corrected sodium level that fails to rise with treatment may signify excessive free water accumulation and an increased risk of cerebral edema. Therefore, rehydration fluids should contain at least 115–135 mEq/L sodium chloride to ensure a gradual decline in serum osmolarity and minimize the risk of cerebral edema. Early potassium replacement is also important, to correct the potassium depletion that occurs because of both the severe initial intracellular losses and the subsequent potassium shift from the extracellular to the intracellular compartment (that occurs when treatment with insulin is initiated and the acidosis is corrected). Potassium is administered only after urine output is ensured to prevent hyperkalemia in the setting of unrecognized renal impairment. Potassium is usually given at a dose of 20–60 mEq/L of fluid, half as the chloride salt and half as the phosphate salt, to replace the phosphate losses simultaneously. Electrocardiographic monitoring facilitates early recognition of either hyperkalemia (peaked T waves) or hypokalemia (flat or inverted T waves) and the development of potentially dangerous cardiac arrhythmias. Serum calcium should be monitored if phosphate is given, since phosphate administration may precipitate hypocalcemia.

Insulin therapy is typically initiated after the patient has been stabilized with an initial fluid bolus. As with fluid replacement, the aim of therapy is gradual correction: reduction of the blood glucose by 50–100 mg/dL/h. Usually, the glucose falls significantly with initial rehydration alone. Continuous "low-dose" insulin infusion is the preferred route in most patients because of the predictability of the rate of fall in blood glucose, the ability to closely titrate the insulin dose to the metabolic needs, and avoidance of erratic absorption from subcutaneous sites during dehydration. The usual dosage is 0.5–1.0 U/kg/h, which may be titrated up or down according to the clinical response. Dextrose is added to the intravenous (IV) solution when the serum glucose level falls below 300 mg/dL, and is titrated to provide a continued gradual decline in blood glucose to target levels. This is easily accomplished with the simultaneous use of two IV solutions, which differ only in the dextrose concentration (the "two-bag" system). Usually, the lowering of the blood glucose concentration precedes the decrease in ketones. Thus, in the situation of continued acidosis with a glucose <300 mg/dL, it is important not to decrease the insulin dosage, but rather to add glucose. Determination of serum ketones, though helpful diagnostically, is not an accurate guide to clinical improvement, as only acetoacetate is measured by the usual method and not b-hydroxybutyrate, which predominates early (but not later) in the course of untreated DKA.

Specific therapy for the acidosis of DKA remains controversial. Frequently, dramatic improvement results simply from initial expansion of extracellular fluid volume, reestablishment of adequate peripheral perfusion, and insulin administration. An elevation in blood pH following bicarbonate administration may be attended by worsening acidosis in the CNS, since carbon dioxide (but not bicarbonate) diffuses across the blood-brain barrier. Furthermore, the organic acids in DKA, in contrast to metabolic acidosis from other causes, are metabolized to bicarbonate. Thus, administration of "additional" bicarbonate may result in a late alkalosis. Bicarbonate may have a place in the treatment of DKA but only in the more severe degrees of acidosis (pH <7.10, which may be associated with myocardial depression) and in the setting of inadequate respiratory compensation. If bicarbonate is given, the dosage is calculated to bring the pH only to around 7.20, paying attention to the sodium administered concomitantly; slow infusion is preferable to bolus injection.

Acute cerebral edema is a rare, potentially catastrophic complication of DKA that occurs without warning within the first 24 hours of treatment, and which may be fatal. This is to be distinguished from the asymptomatic brain swelling detectable on computed tomography scan that may occur in some children with DKA. Although a number of causes of acute cerebral edema have been suggested from uncontrolled, retrospective studies, the etiology in many cases is not known. Increased risk of cerebral edema has been associated with rates of fluid administration greater than 4 L/m ^{2}/24h, and corrected sodium levels and effective plasma osmolality that decline over the course of treatment. Therefore, careful monitoring of neurological status, input/output log, and corrected sodium and effective osmolality is essential for early recognition of cerebral edema. Treatment of cerebral edema is aimed at lowering intracranial pressure: IV mannitol (an osmotic diuretic), intubation/hyperventilation, and if needed, ventriculostomy.

It is clear that therapy requires frequent modifications based on an individual patient's response. This can only be accomplished with a carefully maintained flow sheet that includes such items as vital signs, neurologic status (GCS), intake and output volumes (“Is and Os”), weight, insulin dosage administered, and measurement of blood glucose, urinary ketones, serum electrolytes (with calculation of corrected serum sodium and effective serum osmolality), calcium, phosphorus, BUN, and creatinine (plus blood gases as necessary). Measurements are performed hourly at first and less frequently as the patient's condition stabilizes.

In contrast to those in DKA, patients with new-onset diabetes who are not significantly dehydrated and whose serum electrolytes are normal may usually be treated with subcutaneous insulin and oral fluids. In these patients, an IV fluid bolus may not be indicated and, in fact, may be harmful.

Rarely, a patient will present with an extremely high blood glucose with absent or inappropriately low urinary ketones. This syndrome, known as hyperglycemic hyperosmolar nonketotic coma, usually occurs at the extremes of age and is due to a combination of severe dehydration (due to inadequate access to fluids) and insulin deficiency. It is associated with an extremely high mortality rate and must be treated with caution.

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7. ACUTE ABDOMEN

Kenneth B. Roberts

Abdominal pain is a common, usually self-limited problem in children, but it is dangerous to presume that abdominal pain represents a benign illness, since in the child whose pain signals the need for operative intervention, delay in diagnosis may be catastrophic. It is imperative that certain important diagnoses be entertained whenever abdominal pain is the complaint.

In the newborn, the acute abdomen may reflect obstruction or perforation. Specific entities include necrotizing enterocolitis, malrotation, volvulus, congenital bands, atresias, meconium ileus, and aganglionic megacolon. Septicemia is also an important consideration in this age group. During the first months of life, volvulus is the chief concern; incarcerated inguinal hernias should also be considered. Intussusception is most common between the ages of 3 months and 3 years, with a peak between 5 and 9 months. The classic clinical presentation is of an infant with colicky pain, drawing up his legs as the intense pain comes, and then resting quietly between episodes. Characteristically, a sausage-shaped mass is palpable in the right upper quadrant, representing a portion of ileum trapped within the colon. Mucosal fragments and blood are passed per rectum, giving the stool the appearance of currant jelly. The classic triad of abdominal pain, vomiting, and bloody stools is not always present, however, and reports continue to appear emphasizing painless intussusception, with lethargy as the presenting sign. A radiographic enema study (using barium or air) not only is diagnostic, but also may be therapeutic, since the pressure is generally sufficient to reduce the intussusception; excessive pressure may result in perforation, so a surgeon should be notified and available when the procedure is performed. Even in patients requiring laparotomy to reduce the intussusception, it is unusual to find pathologic “lead point” areas, such as a Meckel diverticulum, and the cause usually remains unclear.

After the age of 2 years, appendicitis is the principal diagnostic consideration in a child with an acute abdomen. Appendicitis can and does occur during infancy, but it is so uncommon that the correct diagnosis is usually not suspected until the appendix has perforated and the infant has become quite ill. In the older child, as in the adult, pain begins periumbilically and then migrates to the right lower quadrant. Vomiting is common only as a secondary sign, as in infants with intussusception; the occurrence of pain prior to the onset of vomiting is an important diagnostic feature. Anorexia is the rule but is too nonspecific to be useful. The converse may be helpful, however: The child with abdominal pain who is hungry is unlikely to have appendicitis. Fever and neutrophilic leukocytosis are not required for the diagnosis, since they are often not present early in the course of the disease; rather, they are correlated with late gangrenous changes or actual perforation of the appendix.

The initial step in the pathogenesis of appendicitis is considered to be obstruction of free communication between the appendix and the cecum. Venous congestion produces edema, which perpetuates the congestion, leading to ischemic necrosis and ultimately to perforation, with spillage of intestinal contents into the peritoneum. When engorgement alone is present, periumbilical pain is produced; later, as the peritoneum is irritated, the pain is referred to the right lower quadrant, and cutaneous hyperesthesia and rebound tenderness may be demonstrated. The classic point of maximal tenderness in adults with appendicitis was described by McBurney as occurring 1.5–2.0 in. from the anterior-superior iliac spine on a line to the umbilicus (McBurney point). The actual location of the appendix determines the presence or absence of other signs, such as pain on stretching the iliopsoas muscle (“psoas sign”), or urinary findings as a result of contact between the inflamed appendix and the right ureter. Many clinicians use the child's ability to hop as useful reassurance that appendicitis is not present. The rectal examination is time honored, but may be more tradition than a necessary or valuable addition to an adequate abdominal and general examination.

Diagnostic clues on x-ray examination include the absence of gas in the right lower quadrant; scoliosis; presence of a “sentinel loop”; and signs of ileus, perforation, or peritonitis. In addition, because of the importance of obstruction in the pathophysiology of appendicitis, much attention has been directed to fecaliths. It seems clear that in patients with established fecaliths in the appendix, the risk of the development of appendicitis, often with perforation, is increased, leading some authors to urge strongly that elective appendectomy be performed in any patient with a radiographically demonstrable “appendicolith.”

Because the morbidity with appendicitis increases when gangrene or perforation occurs, early diagnosis and operative intervention have been stressed. In the past few decades, the approach has evolved. First, it was stressed that a 10–20% rate of negative appendectomies was appropriate to avoid waiting too long. A period of in-hospital observation for patients whose clinical diagnosis was uncertain was shown to permit a reduction in the rate of negative appendectomies without an increase in the rate of perforation. Currently, the emphasis is on radiographic techniques to establish a diagnosis in the emergency department. Ultrasonography has the advantages of not exposing the patient to radiation and of identifying alternative etiologies of the pain. Computed tomography with rectal contrast has excellent performance characteristics and appears to be a cost-effective alternative to in-hospital observation.

Even when the diagnosis of appendicitis is clear, the time that it takes to prepare acutely ill, dehydrated, febrile children for surgery is well worthwhile. Fluid therapy is geared to restoring intravascular volume, particularly since anesthetic agents will cause vasodilatation and further compromise the circulation if intravascular volume is deficient. If gangrene or perforation of the appendix is suspected clinically, the preoperative administration of antibiotics is a logical addition to fluid therapy. Postoperatively, peritoneal drains are not beneficial and appear to prolong the duration of fever. Early in the course, gram-negative sepsis is an uncommon but life-threatening complication; wound infection, though much less serious, is frequent following perforation or gangrene of the appendix, occurring in as many as 18% of patients. Intra-abdominal abscesses are later complications in 2–6%, the result of persistent combined aerobic and anaerobic infection. Antibiotics administered perioperatively and for several days after surgery may prevent the development of a late abscess, but antibiotics are generally considered insufficient to treat an abscess once it has developed, and reexploration is commonly required.

The clinical picture of appendicitis may be mimicked exactly in children by the disorder designated acute mesenteric lymphadenitis. The pain in this condition is often severe, but the child typically does not appear as ill as one with appendicitis. Close observation and repeated examinations usually permit differentiation of the two conditions, although laparotomy may be required. The visualized lymph nodes are acutely inflamed, often described as “succulent.” Bacteria, such as streptococci and members of the Yersinia group, and viruses have been implicated.

Other causes of severe abdominal pain in childhood are myriad and include basilar pneumonia; pyelonephritis; sickle cell disease; pericarditis; herpes zoster; myocarditis (including rheumatic fever); Henoch-Schönlein syndrome; food poisoning; and metabolic disorders, such as hyperlipidemia, hypoglycemia, porphyria, and diabetic ketoacidosis. Torsion of the testis or ovary and pelvic inflammatory disease must also be considered. A detailed history and careful physical examination are the main tools in establishing at least a tentative diagnosis and identifying the child who requires immediate surgical attention.

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   An extensively referenced review by pediatric surgeons of appendicitis (pp. 733– 739), intussusception (pp. 746–752), malrotation and midgut volvulus (pp. 752–758), incarcerated inguinal hernias (pp. 758–759), gall bladder disease (pp. 759–761), adhesive small-bowel obstruction (pp. 761–762), and special considerations in immunosuppressed or neurologically impaired children (pp. 762–766). For a shorter surgical review, see Pediatr. Rev. 14:302–311, 1993.

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   Using logistic regression, the authors found rectal tenderness to be superfluous if the presence or absence of rebound tenderness had already been determined. While we are challenging traditional teaching, see Ann. R. Coll. Surg. Engl. 72:304–308, 1990, for a review of barium enemas revealing that the base of the appendix is well below McBurney's point in 70% of adults.

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8. ACUTE RENAL FAILURE

Richard A. Cohn

Acute renal failure (ARF) represents an abrupt decrease in renal function with consequent inability to maintain normal electrolyte, urea, creatinine, water, and acid base balance. The hallmarks are oliguria (<200 mL/m^2/d), acidosis, hyperkalemia, and azotemia. Causes may be classified as follows: prerenal (e.g., renal hypoperfusion as a result of hypovolemia, hypotension, or heart failure); postrenal (e.g., obstructive uropathy, stones, or tumors); or renal (i.e., parenchymal disorders of the kidney). The renal disorders are (1) acute tubular necrosis (ATN), representing significant ischemic injury; (2) nephrotoxic injuries from medications (nonsteroidal anti-inflammatory drugs, calcineurin inhibitors, gold, cisplatinum), chemical toxins (radiographic contrast media, ethylene glycol, bromide, carbon tetrachloride, mercury), antibiotics (cephalosporins, amphotericin B, aminoglycosides, penicillins), or endogenous metabolites (hypercalcemia, hyperuricemia, and myoglobinuria); and (3) a variety of disorders, such as the hemolytic-uremic syndrome, rapidly progressive glomerulonephritis, acute interstitial nephritis, and vasculitis.

The initial diagnostic consideration is to identify prerenal and postrenal causes of ARF, since they are often reversible; moreover, if untreated, prerenal insufficiency can develop into ATN. In addition, patients with stable chronic renal insufficiency may have an acute deterioration in renal function related to dehydration, urinary tract infection, hypertension, obstruction, electrolyte imbalance, or acidosis, which, if successfully treated, may obviate the need for dialysis.

Laboratory studies can aid in separating prerenal causes from primary renal tubular dysfunction. In the former, the kidney responds “normally” to hypoperfusion by conserving salt and water, with resulting oliguria, high urine osmolality, and normal findings on urinalysis; urine-plasma creatinine ratio >30, urinary sodium concentration <20 mEq/L; and fractional excretion of sodium (FENa) <1%. In ATN, salt and water conservation are impaired, with ensuing isosthenuria, urine-plasma creatinine ratio <20, urinary sodium concentration >30 mEq/L, and FENa >2%; casts, protein, and cellular elements are often seen in the urine. Occasionally, patients with ATN are not oliguric, although their degree of renal functional impairment may be as great as in those patients with oliguria.

Factors that contribute to the pathophysiology of ATN include (1) mechanical intratubular obstruction to urine flow, (2) renal vasoconstriction, and (3) cellular alterations including renal tubular cell polarity, reactive oxygen molecules, changes in intracellular calcium, and nucleotide metabolism.

Diagnosis of the cause of ARF and treatment usually are approached in a stepwise fashion. First, remediable causes of ARF are corrected: hypotension, hemorrhage, dehydration, sepsis, heart failure, and other causes of renal hypoperfusion, as suggested by the history and physical findings, must be appropriately managed. Then, if obstruction within the urinary tract appears likely, it must be identified; ultrasonography, computed tomography (CT) scan, cystourethrography, and retrograde pyelography of one kidney, particularly in the presence of anuria or intermittent polyuria, may be required.

Established ARF often requires 14–21 days to resolve, and, during this period, therapy is directed toward reestablishing homeostasis. Fluids are replaced in proportion to insensible losses plus urine output. Minimal sodium and often no potassium replacement is necessary. Phosphate-binding antacids, calcium, calcitriol, and alkali therapy may be required to correct hypocalcemia, hyperphosphatemia, and acidosis, respectively. Nutritional considerations include protein of high biologic quality (essential amino acids) and sufficient caloric intake to minimize catabolism. Dosages of medications excreted by the kidney must be modified in proportion to the severity of ARF. Infectious complications, a leading cause of death in ARF, are minimized by removing unnecessary indwelling tubes (especially urinary catheters); prophylactic antibiotics are to be avoided. Finally, renal replacement therapy (especially continuous hemofiltration) is indicated when fluid, electrolyte, acid base, and uremic problems become unmanageable with conventional medical therapy (see Chap. 78, Chronic Renal Failure).

Prophylaxis with mannitol and furosemide in high-risk patients (e.g., prior to open heart surgery) may prevent the development of ARF. Similarly, these drugs may avert full-blown renal failure when given to patients with impending ARF, but only after restoration of effective circulating volume. When unsuccessful in reversing ARF, mannitol and furosemide may convert the course from oliguric to nonoliguric, facilitating clinical management of the patient.

Recovery is heralded by the onset of diuresis and may result in extreme polyuria, necessitating careful electrolyte, fluid, and drug therapy as renal function improves. Most children regain normal renal function, but some, particularly those with glomerular and vascular disorders, may have hypertension or a reduction in renal function or urinary concentrating ability as permanent sequelae.

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9. INCREASED INTRACRANIAL PRESSURE

Olakunle B. Akintemi

Intracranial pressure (ICP) averages 2 mm Hg (27 mm H_2O) in neonates, 5 mm Hg (68 mm H_2O) in young infants, 6–13 mm Hg (82–177 mm H_2O) in children 1–7 years of age, and 5–15 mm Hg (65–204 mm H_2O) in adults. Intracranial pressure increases transiently during coughing, sneezing, and straining without any adverse effects to the brain. However, sustained increased ICP is associated with many pathological conditions and, if uncontrolled, may lead to displacement of brain tissue, brainstem compression, and irreversible brain damage.

The volume within the intracranial cavity comprises three compartments: brain (about 80%), blood (about 10%), and cerebrospinal fluid (CSF) (about 10%). The total intracranial volume is constant and fixed. According to the modified Monro-Kellie doctrine, “An increase in the volume of one of the compartments of the brain, i.e., brain, blood, or CSF, must be compensated for by a decrease in the volume of one or more of the other compartments in order for the total brain volume to remain fixed.” Therefore, an increase in volume (due to mass, tumor, edema) results in compensatory changes in the blood and CSF compartments.

The major compensatory mechanisms that preserve ICP within normal limits are movement of CSF into the subarachnoid space, increased CSF absorption, and reduction of intracranial blood volume. Intracranial pressure begins to rise once the compensatory mechanisms are exhausted or lost.

Compliance is the ability of the brain to accommodate changes in intracranial volume without change in ICP. The pressure-volume curve of the intracranial compartment is shown in Figure 9.1. At normal intracranial volumes (point 1), ICP is low and remains low with an increase in volume. Compensatory mechanisms are therefore adequate, and compliance is high. However, at point 2, compliance is low and further increase in volume will increase ICP. Finally, with ICP already high (point 3), a small increase in intracranial volume will result in marked increase in ICP (3–4).

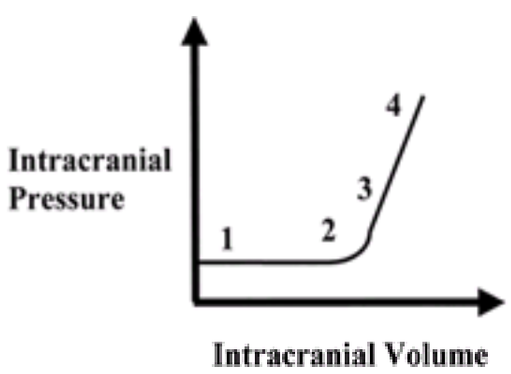

FIG. 9.1. The pressure-volume curve of the intracranial compartment.

Cerebral blood flow (CBF) is determined by cerebral perfusion pressure (CPP), cerebral metabolic rate for oxygen ($CMRo_2$), arterial carbon dioxide tension ($Paco_2$), and oxygen tension (Pao_2). In the absence of brain injury and under normal conditions, autoregulation enables brain perfusion to remain constant over a range of CPP and mean arterial pressure (MAP). When ICP increases, CPP decreases (CPP = MAP - ICP). If autoregulation is intact, decrease in CPP causes vasodilatation (decrease in cerebrovascular resistance [CVR]) and an increase in CBF, as described in the equation CBF = (Arterial Pressure - ICP)/CVR. Under pathological conditions such as head injury, however, the ability of the brain to maintain a constant flow over a wide range of CPP is lost (loss of autoregulation). Cerebral blood flow varies directly with $Paco_2$ and $CMRo_2$, and indirectly with Pao_2. Thus, high $Paco_2$ levels cause cerebral vasodilation and increase in CBF, whereas low $Paco_2$ levels cause vasoconstriction and decrease in CBF. Hypoxia causes cerebral vasodilation with subsequent increase in CBF.

At all ages, cerebral edema (vasogenic, cytotoxic) is a common cause of elevated ICP. Other causes of increased ICP differ with age. In the newborn, congenital hydrocephalus and hypoxic-ischemic encephalopathy are the most common causes. In infants and early childhood, head trauma, meningitis, brain tumor, and acute diabetic ketoacidosis are leading causes. In later childhood and adolescence, meningitis, brain abscess, head injury, and pseudotumor cerebri are common causes of increased ICP. Pseudotumor cerebri is characterized by increased ICP, normal CSF content, elevated opening CSF pressure with lumbar puncture, and a normal brain with normal or small ventricles on computed tomography (CT) or magnetic resonance imaging (MRI). It may be idiopathic or secondary to otitis media (otitic hydrocephalus), drugs (hypervitaminosis A and D, corticosteroid withdrawal, oral contraceptives), or metabolic disorders (hyperthyroidism, hypoparathyroidism).

The signs and symptoms of increased ICP depend on the child's age and the rate of ICP increase. With slow increase in ICP, symptoms may include early-morning headache, vomiting without nausea, personality changes, lethargy, fatigue, and drowsiness. Other symptoms include memory loss, decline in school performance, diplopia, and failure to thrive. Signs include macrocrania (infants and children), delayed closure of the anterior fontanelle, tense and bulging anterior fontanelle, separation of the sutures, cranial nerve VI and III palsies, and “setting sun” sign. Papilledema is a late and uncommon sign in infants.

Alteration in the level of consciousness is a prominent feature of acute increase in ICP. Other symptoms include vomiting, cranial nerve VI and III palsies, “setting sun” sign, eye deviation, and abnormal (shrill) cry. The classic Cushing triad (bradycardia, hypertension, and irregular respiration) is due to brainstem compression and is a late, preterminal finding of herniation.

If ICP continues to rise unabated, parts of the brain may move from their normal location into other locations (herniation), impinging on nerves and blood vessels. There are 3 anatomic sites where herniations can occur: below the falx cerebri (cingulate herniation), through the tentorial notch into the posterior fossa (transtentorial or uncal herniation), and through the foramen magnum (cerebellar herniation). Bilateral transtentorial, the most common herniation, is commonly associated with cerebral edema. Both cerebral hemispheres are displaced downward through the tentorial notch. Signs and symptoms include alteration in the level of consciousness, miosis or mydriasis, impaired upper gaze, irregular respiration, and decorticate and decerebrate posturing.

Evaluation of the child with increased ICP consists of a good history, thorough physical examination, neuroimaging, and some laboratory tests. Relevant history includes febrile illness, duration of illness, prior headache (early morning), vomiting, trauma (accidental or inflicted), irritability, and drug ingestion. History of seizure disorder, diabetes, liver disease, and ventriculoperitoneal shunt placement must be sought.

Relevant physical examination includes vital signs, pattern of respiration, pupillary response, extraocular movement, eye deviation at rest, and fundoscopy. The head must be examined for swellings, depressed skull fracture, hematoma, and presence of shunt catheter and valve.

Other relevant examinations include general neurological examination, Glasgow coma score (GCS) and skin (petechiae, purpura). The GCS is a quick method of estimating level of consciousness. The score combines eye opening, motor response, and verbal response. Although it was created to assess patients with acute head injury, it is useful to convey level of consciousness in a standardized format.

Prompt neuroimaging (if patient is stable) with a CT or MRI is necessary in unresponsive patients and in those with focal neurological signs. Findings on head CT may include cerebral edema, mass lesion (epidural, subdural hematomas), penetrating brain injuries, and depressed skull fractures.

Additional laboratory investigations depend on the history and physical examination. These include complete blood count, blood culture, arterial blood gas, blood urea nitrogen, creatinine, liver enzyme, ammonia, measured and calculated osmolality, and toxicology screen. A lumbar puncture is deferred until a head CT has been obtained. If the CT shows either a mass lesion or effacement of the lateral ventricles and cisterns, lumbar puncture is contraindicated, since the drop in lumbar pressure may precipitate transtentorial herniation.

Guidelines for ICP monitoring in children are not well established, and its overall effect on outcome is questionable. Intracranial pressure monitoring is not beneficial in hypoxic-ischemic encephalopathy, but is recommended for adult patients with head injuries and a GCS <8. Types of ICP monitors are intraventricular (ventriculostomy), intraparenchymal, subdural, and epidural. A ventriculostomy catheter is the ideal monitor because it is the most effective, reliable, and accurate method of measuring ICP. Complications of ICP monitoring include exacerbation of cerebral edema, infection, intracranial hemorrhage, and malposition.

The first priority in the management of the child with increased ICP is to secure the airway, ensure that the child is breathing, and restore and maintain circulation. Glasgow coma score <8 is an indication for endotracheal intubation. Because of the risk of aspiration, and increase in blood pressure and ICP associated with awake intubation, rapid sequence induction and Sellick maneuver (cricoid pressure) are recommended.

If a surgically remediable lesion is identified (e.g., hematoma, tumor, penetrating injury, shunt malfunction), appropriate measures should be taken to reduce ICP prior to surgery. The traditional approach to reducing ICP includes hyperventilation, mannitol, elevation of the head of bed to 30°, barbiturates, sedation, neuromuscular paralysis, and hypothermia. Hyperventilation effects a reduction in cerebral blood volume by causing vasoconstriction in response to lowered $Paco_2$. It is important to keep $Paco_2$ between 30 and 35 mm Hg because further reduction in $Paco_2$ may lead to cerebral ischemia. Indiscriminate and prolonged (>24–48 hours) hyperventilation should be avoided. Although the exact mechanism of action of mannitol is unknown, it is thought that it decreases CSF formation rate, brain water content, and blood viscosity. Onset of action of mannitol is 15–30 minutes, and the effects may last up to 4–6 hours.

The current approach in increased ICP management is to monitor and optimize CPP. Cerebral perfusion pressure should be maintained by restoring normovolemia, treating hypotension, and in refractory ICP elevation, vasopressor therapy to induce hypertension. Although current guidelines recommend that the CPP be maintained above 70 mm Hg in adults, there is controversy about the optimal CPP in children. However, it is prudent to maintain CPP of 50 mm Hg or greater in infants up to age 1, 60 mm Hg or greater in children aged 1–10 years, and 70 mm Hg or greater in children older than 10 years and adolescents.

Xenon CT and continuous transcranial Doppler are new methods of monitoring CBF. Continuous fiberoptic jugular bulb venous saturation and near-infrared spectroscopy are used to monitor adequacy of cerebral perfusion (balance between cerebral oxygen delivery and demand) and guide therapy in traumatic brain injury.

Other therapies for elevated ICP include appropriate antibiotics (for meningitis), oxygen, and anticonvulsants (fosphenytoin, phenytoin). Antimetabolites (free radical scavengers, excitatory amino acid antagonists) are being studied; there is currently no evidence, however, that free radical scavengers and excitatory amino acid antagonists improve outcome in intracranial hypertension.

Reviews

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Management

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10. STATUS EPILEPTICUS

Spencer G. Weig and Kenneth B. Roberts

Status epilepticus is defined as a seizure lasting longer than 30 minutes or acute repetitive seizures over a 30-minute period without intervals of consciousness. Mortality in children overall is 4%, but this increases to 13% in children with either an acute central nervous system (CNS) insult (e.g., trauma) or a progressive encephalopathy. Morbidity, though, is higher, establishing status epilepticus as a true medical emergency.

In children receiving anticonvulsant therapy, noncompliance or changes in the medication regimen and intercurrent infections are frequent precipitating causes of status epilepticus. In patients without previous seizures, status epilepticus may be associated with a new onset idiopathic seizure disorder, a remote history of CNS insult (e.g., cerebral palsy), or a multitude of acute processes, including fever, anoxia, systemic or CNS infection, cranial trauma, neoplasm, or severe metabolic disturbances with encephalopathy.

The pathophysiology of status epilepticus is unclear. Severe physiologic disturbances, each a consequence of the repeated seizures, contribute to the hazards of this state, and may themselves precipitate or prolong seizure activity; these disturbances include hypoxia, hyperpyrexia, acidosis, hypotension, and hypoglycemia. Added to these systemic alterations are cellular changes, such as edema of cerebral cells. These factors collectively may explain the self-sustaining nature of the repeated, persistent, and often refractory seizures. Vomiting and aspiration constitute a further compromising, sometimes fatal complication.

Prompt attention must be directed toward (1) the institution of general supportive measures, (2) the cessation of seizure activity, (3) the prevention of rapid return of seizure activity, and (4) a thorough investigation of the causes precipitating the prolonged seizure state.

General supportive measures include ensuring a patent airway, protecting the body against injury, and establishing an intravenous route for the administration of appropriate drugs and hydration. Vital signs must be carefully monitored and the patient observed for signs of respiratory failure or worsening neurologic status.

For the seizures to be terminated promptly, a therapeutic level of anticonvulsant must be achieved rapidly. A benzodiazepine is generally considered the drug of choice. Diazepam gel (Diastat) can be administered rectally at home by the parent to abort status in a child with prolonged or repetitive seizures. Traditionally though, diazepam (Valium) has been administered intravenously. It acts rapidly, but the effect is poorly sustained; repeated or large doses may result in apnea, bradycardia, or hypotension. Lorazepam (Ativan) is an attractive alternative to diazepam, since its duration of effectiveness is longer. Phenobarbital has a slower onset of action than either of the benzodiazepines but is effective for a much longer period than diazepam and may be continued as a maintenance anticonvulsant after the acute episode. Phenobarbital, in the doses usually administered to control status epilepticus, will decrease the level of consciousness and may depress respirations, particularly when used in conjunction with a benzodiazepine. Phenytoin may also be used for status epilepticus. Depression of respirations and a decrease in the level of consciousness are not problems encountered with the usual doses; the drug is a myocardial depressant, however, and must be infused slowly. Its prodrug, fosphenytoin (Cerebyx), may permit somewhat more rapid administration. If seizures persist despite administering a benzodiazepine, phenobarbital, and a phenytoin drug, other drugs that have been used in refractory status include thiopental or pentobarbital (to induce coma) and intravenous valproic acid (Depacon). The use of a constant infusion of midazolam (Versed) in refractory status appears promising. The use of a propofol infusion is being studied but may be dangerous in children.

Investigation of the cause of status epilepticus requires a thorough evaluation of the history and prompt laboratory studies. In patients receiving long-term anticonvulsant medication(s), blood levels of the drugs should be measured. Serum concentrations of electrolytes, glucose, calcium, and urea nitrogen should also be measured to diagnose treatable conditions in children with unexplained status. Lumbar puncture is necessary in the child suspected of having meningitis or encephalitis. If the cause for status is unclear or if there is suspicion of CNS trauma, hemorrhage, infarction or mass, an emergency head CT scan should be obtained once the patient is stabilized.

Recent experimental work indicates that sustained seizure activity per se may have damaging effects on neurons, and it appears that the longer the duration of seizures, the more difficult control becomes. Thus, recognition of the severity of the problem must be prompt and the approach to therapy rapid and aggressive. With adequate treatment, however, the short- and long-term prognoses in status epilepticus are far more dependent on the cause for the seizures than on the actual duration of seizure activity. Since the risk for developing future afebrile seizures in a child who presents with status as a first seizure may be as low as 30%, chronic anticonvulsants may not be indicated.

Reviews and Collections

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11. HEAD TRAUMA

Olakunle B. Akintemi

Trauma is the leading cause of death in the pediatric population. Overall, 75–85% of fatal childhood injuries are due to head trauma. The estimated annual rate of head injuries in children is about 200 per 100,000 population. The major causes of head trauma in children are falls (playground, infant-walkers, heights, open window in high rise apartments), motor vehicle accidents, motor vehicle-pedestrian collisions, bicycle accidents, child abuse, and recreational activities.

The head consists of scalp, skull, brain, and its contents (coverings, tissue, blood, and cerebrospinal fluid [CSF]). Head injury may involve injury to one or more of the contents of the head. Head injuries therefore include (1) scalp injuries (lacerations, “scalping” injuries, subgaleal hematoma, cephalhematoma), (2) skull fractures (linear, diastatic, basilar, depressed, and open), and (3) brain injuries (diffuse and focal).

The scalp is composed of five layers: skin, subcutaneous tissue, galea aponeurosis, loose areolar tissue, and pericranium. Because of the scalp's rich blood supply, scalp lacerations may result in hypotension or shock (especially in young infants). Subgaleal hematoma is a collection of blood between the aponeurosis and pericranium (subgaleal space). It is associated with forceps delivery, vacuum extraction, and minor head trauma in infants younger than age 1 year. Complications include hypovolemia, anemia, and hyperbilirubinemia. Skull fractures may be classified as linear, depressed, compound, or basilar. Most skull fractures (about 75%) are linear and are usually due to falls. Because a significant amount of force is required to fracture a skull, there is a greater likelihood of intracranial injury. Most children are asymptomatic and have a soft tissue swelling and tenderness over the fracture site. Falls from heights less than 3 ft, absence of historical symptoms (loss of consciousness, seizures, emesis, change in behavior), and normal scalp examination (i.e., no scalp hematoma) are associated with low risk of intracranial complications. Depressed skull fractures result from either a significant blow to the head or falls onto a concrete floor, and are usually associated with underlying brain injuries. Although these fractures may be palpable or diagnosed by skull radiographs, a head computed tomogram (CT) is recommended to estimate the degree of depression and detect underlying brain injuries. A neurosurgical consult is recommended in all cases of suspected depressed skull fracture. Any bone fragment depressed below the inner table of the skull and more than the thickness of the skull must be elevated.

Open (compound) skull fractures have a direct communication between the scalp laceration and the brain tissue. They are at risk of contamination and require early surgical debridement and closure of the dura. Basilar skull fractures account for 3–4% of head injuries in children, and are characterized by CSF otorrhea or rhinorrhea, ecchymosis in the mastoid region (Battle sign), hemotympanum, and periorbital ecchymosis (raccoon eyes). Because of a high incidence of intracranial injury (10–40%), a cranial CT is recommended in all patients with basilar skull fractures.

Complications include CSF leakage or fistula, VII or VIII cranial nerve palsies, hearing impairment (due to fracture of vestibulocochlear apparatus), and meningitis (1%). It is recommended that all patients with basilar skull fractures should be admitted, and serial neurological examination performed. Prophylactic antibiotics are not recommended because they have not been shown to prevent bacterial meningitis.

Diastatic fractures occur in the suture lines (especially the lambdoid). The most significant complication of these fractures is development of “growing” skull fracture. Growing fractures are usually seen in infants and young children younger than 3 years. They are due to herniation of cerebral tissue and arachnoid membrane through a dural tear, with subsequent enlargement and erosion of adjacent skull bone.

Brain injuries may be diffuse or focal and involve either neuronal tissue (concussion, contusion) or cerebral vasculature (epidural and subdural hematoma, intraparenchymal and subarachnoid hemorrhage). The mechanism of brain injury involves two phases: primary and secondary injury. Primary injury occurs at the time of the initial impact. It is due to mechanical (traumatic) force that disrupts the neural elements of the brain. Secondary injury is due to physiologic and biochemical response (free radicals, excitatory amino acids, L-glutamate, and L-aspartate) to the primary injury. These include loss of autoregulation, cerebral edema, increased intracranial pressure (ICP), decreased cerebral blood flow, brain ischemia, and cell death. One of the goals of treatment is to prevent or reduce secondary brain injury.

Concussion is a brain injury accompanied by transient loss of neurologic function. It is manifested by brief loss of consciousness, amnesia (in older children), confusion, sleepiness, pallor, irritability, and, in some cases, vomiting. Neurologic examination is normal and recovery is uneventful.

Diffuse axonal injury (DAI) is a brain injury due to shearing forces that stretch and tear axons. It is accompanied by widespread microscopic damage, increased ICP, abnormal neurologic findings, posturing, and prolonged coma. The mechanism of injury in DAI is either from shaken baby syndrome (infants younger than 1 year) or primary impact injury to the brain (older children). Infants are more vulnerable to diffuse brain injuries because of (1) relatively large head size with increased head-body ratio; (2) weak neck muscles (less protection); (3) incomplete myelination, which predisposes to shearing injury; and (4) thin, pliable cranium providing less protection. Children are also more likely to develop diffuse cerebral swelling due to cerebral hyperemia. In shaken baby syndrome, retinal hemorrhages, interhemispheric subdural hematoma, seizures, and bulging or tense anterior fontenelle may be observed.

Cerebral contusion is characterized by prolonged coma or obtundation, and can occur either beneath the surface of the impact (coup lesion) or opposite the site of impact (contracoup).

Epidural hematoma is a collection of blood between the skull and the dura. Although relatively uncommon in children (<3% of hospitalized patients), it may occur after minor injury. Most patients (75%) have an overlying fracture. The origin of the bleeding is either arterial (middle meningeal) or venous (meningeal, diploic, deep-venous sinus), and unlike adults, the classic lucid interval followed by rapid neurologic deterioration is uncommon. Most patients require immediate burr-hole evacuation, although some patients may be treated conservatively.

Acute subdural hematoma is a collection of blood between the dura and arachnoid membrane and is usually venous in origin. Subdural hematomas are life-threatening, 5–10 times more common than epidural hematomas, more likely to occur in infants, are usually caused by child abuse, and have poorer prognosis. They usually occur from laceration of the brain and cortical arteries, and rupture of bridging veins between the dura and cerebral cortex. An underlying skull fracture may or may not be present. Because of the severity of injury, the classic lucid interval is rarely seen. Most patients present with severe and progressive neurologic deterioration. Large subdural hematomas require immediate evacuation through a craniotomy. Chronic subdural hematomas are rare in children older than 2 years, and result from trauma and child abuse. Associated signs and symptoms include seizures, increased ICP, irritability, failure to thrive, enlarged head circumference, and retinal hemorrhages.

An intracerebral hematoma is a collection of blood in the brain parenchyma. Most intracerebral hematomas occur from cerebral contusion and are associated with severe brain injury and, hence, poor prognosis.

Although most intraventricular hematomas are minor and require no treatment; obstructive hydrocephalus requiring external drainage may occur with larger hemorrhages.

Subarachnoid hemorrhage occurs from disruption of blood vessels on the cerebral cortex, resulting in hemorrhagic CSF and meningeal irritation. Treatment is usually not required and prognosis is excellent.

Penetrating injuries from bullet wounds, air rifles, BB guns, sticks, pencils, and toys are neurosurgical emergencies. The foreign object(s) should be left in place until

removed by a neurosurgeon in the operating room.

The initial assessment of a child with head injury consists of rapid assessment and management of airway (with C-spine control), breathing, and circulation; rapid neurologic evaluation; a thorough history; and meticulous physical examination. The rapid neurologic evaluation assesses level of consciousness, and pupillary size and reaction. Level of consciousness is classified as alert, responsive to verbal stimuli, responsive to painful stimuli, or unresponsive. History should include mechanism of injury (fall, motor vehicle collision, inflicted trauma), loss of consciousness, changing level of consciousness since injury, lethargy, irritability, headaches, seizures, and visual changes. A complete set of vital signs (temperature, pulse, respiration) must be obtained. Bradycardia, hypertension, and irregular respirations (Cushing triad) suggest increased ICP with brainstem compression and impending herniation. The scalp is examined for lacerations, swellings, and depression, and in infants the anterior fontanelle is palpated. Signs of basilar skull fractures should be noted. Pupillary response, extraocular muscles, muscle tone, posture, deep tendon reflexes, and motor movement are evaluated. The Glasgow coma scale, which consists of evaluation of eye opening, best motor response, and best verbal response, is a more detailed neurologic evaluation used to assess level of consciousness in head injuries. However, because of underdeveloped verbal skills, the best verbal response must be modified in infants and young children. Fundoscopic examination should be performed if nonaccidental trauma is suspected. Presence of retinal hemorrhages in children younger than 3 years probably indicates child abuse. Finally, a complete head-to-toe examination should be performed on all traumatic injuries (chest, abdomen, musculoskeletal survey, etc.)

Once the initial assessment is completed, and depending on the severity of the head injury, some laboratory studies may be obtained. These include a complete blood count, type, and crossmatch; and amylase, electrolyte, liver, renal, and coagulation panels. A pulse oximeter should be placed and an arterial blood gas obtained to assess oxygenation and ventilation. The child with severe head injury, depressed level of consciousness, or focal neurological signs should be examined by head CT (without contrast) immediately. Other indications for obtaining head CT include infants younger than 12 months, scalp hematoma, skull depression and penetration, basilar skull fractures, bulging fontanelle, falls greater than 3 ft, and presence of a ventriculoperitoneal shunt. History of loss of consciousness, emesis, seizures, and behavioral change has low sensitivity and predictive value for intracranial injury. The role of skull radiography is questionable and is indicated when child abuse is suspected (as part of skeletal survey), to exclude or confirm depressed fracture or penetrating injury and foreign body detection. The presence of a skull fracture does not predict intracranial injury: 90% of children with a skull fracture do not have intracranial injury, and 50% of those with intracranial injury do not have a skull fracture. Therefore, skull radiography is not a reliable predictor of intracranial injury.

Head injuries are classified as mild, moderate, or severe on the basis of history, and findings on physical and neurologic examination. Children with mild head injury may be discharged home with specific instructions given to parents about observation and precaution. Those with moderate head injury may be observed for at least 6 hours after the injury. Children who improve during this observation period may be discharged home if parents are reliable. Those who fail to improve should be admitted for at least 24–48 hours. Other indications for admission include severe head injury, multiple trauma, suspected child abuse, and preexisting neurologic and hematologic disease (hemophilia, idiopathic thrombocytopenic purpura).

The goal of management of severe head injury is to protect the brain from secondary injury by preventing hypoxia, maintaining cerebral perfusion pressure, and treating increased ICP. Some recent studies suggest that fluid resuscitation with hypertonic saline increases systolic blood pressure, cardiac output, and cerebral perfusion pressure, and decreases ICP. Patients should be admitted to a tertiary care facility and seen by a neurosurgeon, pediatric intensivist, and trauma surgeon. Guidelines for the management of severe head injury were published recently by the American Association of Neurological Surgeons.

Posttraumatic seizures occur in 6.5–10% of children with head injuries and in up to 50% of those with penetrating injuries. These seizures are classified as immediate, early, or late. Immediate seizures occur within seconds of the trauma and are due to traumatic depolarization. Prognosis is excellent and anticonvulsants are not required. Early seizures occur within the first week after the trauma and are due to focal brain injury. Most children have excellent prognosis, although 25% may develop late seizures. Late seizures occur after the first week, and are associated with focal brain scarring and posttraumatic epilepsy. Anticonvulsant prophylaxis (phenytoin) for posttraumatic epilepsy is controversial, although some studies suggest that phenytoin may prevent early, posttraumatic seizure.

Children, in general, have better outcomes and lower fatality rate than adults with similar severity of injury. But infants, toddlers, and mid-to-late adolescents have a higher mortality rate than school-aged children.

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    This study attempts to answer these questions: What are the indications for obtaining head CT after head injury in children? What is the role of skull radiographs in the evaluation of head injury? Clinical symptoms correlate poorly with intracranial injury (Arch. Pediatr. Adolesc. Med. *153: 15–20, 1999;* Pediatrics *104:861–867, 1999). Intracranial injury may occur with subtle signs and symptoms (especially in infants younger than 12 months). Presence of a skull fracture increases the risk of intracranial injury, but intracranial injury can occur in the absence of skull fracture. (*Lancet *349:821–824, 1997.) The authors suggest the following guidelines for obtaining head computed tomography (CT) after head trauma: altered mental status, focal neurologic deficits, signs of a basilar skull fracture, seizure, or a palpable depression of the skull. In addition, they also suggest that head CT should be considered in neurologically normal children with history of loss of consciousness, vomiting, headache, drowsiness, and amnesia. Skull radiograph is recommended in infants younger than 1 year with a hematoma or contusion.*

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12. ACCIDENTAL INJURIES AND INJURY CONTROL

Evan Charney and Kenneth B. Roberts

Accidents are the leading cause of death in childhood after the neonatal period—through age 38, in fact—and account for nearly 43% of the deaths in childhood. Moreover, there are several hundred nonfatal accidents for every fatal one, suggesting something of the enormity of this health problem in human and economic terms. The fatalistic view that accidents are “an act of God” and not inherently controllable is similar to the way infectious diseases were viewed a century ago, and, as with infectious disease, it is expected that improved information and increased understanding will lead to better control. In fact, the number of deaths caused by unintentional injuries in children and adolescents (0–19 years) has dropped 45% in the past 2 decades. Although it is unrealistic to expect that all accidental deaths can be prevented, a reduction in the annual death rate by 25% in childhood would save more children each year than the total number who die from childhood leukemia and all other malignancies combined.

The term “accident prevention” has generally been replaced by “injury control.” Accidents may or may not be preventable; injury control focuses on the prevention or reduction in frequency and severity of injuries and their sequelae that result from accidents. To illustrate the distinction between an accident and an injury, consider that a crash-activated air bag does nothing to prevent a motor vehicle collision, but it does make it possible for individuals to escape injury or incur only minor injuries despite the occurrence of the accident.

A conceptual approach to the problem that has gained considerable support because of its usefulness in devising injury countermeasures considers three phases: the pre-event phase; the event phase; and the post-event phase. Activities during the pre-event phase are aimed at preventing the “accident” from occurring; examples include routing traffic away from elementary schools and reducing the temperature of the water in hot water heaters. Once the event has occurred, efforts are directed to reducing the severity of injuries that will be sustained; examples include seat belts and smoke alarms. The post-event phase consists of medical treatment, from first aid to trauma centers and specialized burn units. In recent decades, progress has been made in all three phases.

Another important concept considers an “active-passive” dimension—how much volitional involvement is required of a person to avoid or minimize injury. In general, countermeasures that reduce or remove the hazard and those that do not require individual cooperation to be effective have been the most successful. For example, in Great Britain, a law that required safety grilles in front of fireplaces markedly reduced the number of burns sustained by children. In the United States, limiting the number of children's aspirin tablets in a single bottle and, somewhat later, the introduction of a safety cap did more to decrease deaths from salicylate poisoning than did the earlier establishment of a network of poison information centers. Perhaps the most dramatic example of the effectiveness of a single preventive act was the decline in motor vehicle deaths by 20% in a single year—from 55,000 to 46,000 in 1974—following the lowering of the speed limit to 55 mph. As average highway speed increased subsequently, so did highway fatalities.

Motor vehicle deaths account for the single largest number of accidental fatalities: more than one third of accidental deaths in children 1–4 years old, more than one half of accidental deaths in those 5–14 years old, and more than three quarters of accidental deaths in those 15–24 years old. The rate of automobile-related fatalities increases sharply throughout childhood, particularly in adolescence. While the accidental death rate in this century has decreased by 80% in those younger than 15 years, it has decreased by less than half for 15- to 24-year-olds, largely because of motor vehicle–related deaths. Pedestrian injuries have declined in the past 2 decades, but there is evidence that the decline relates to children walking less rather than to specific countermeasures such as “traffic calming.”

Drowning is the second most common cause of accidental death throughout childhood, and in some states exceeds motor vehicle injury as the leading cause of death in 1- to 4-year-olds. The rate of fatal drownings has steadily decreased over the past 4 decades, representing a significant improvement in safety, as many more people use swimming pools and have access to lake and ocean bathing than in the past. However, residential swimming pools remain a potential drowning hazard, particularly for 1- to 4-year-olds, and mandatory pool fencing appears a more effective countermeasure than education regarding the importance of supervision or attempting to teach youngsters in this age group how to swim.

Burns are the next most frequent cause of accidental death in children younger than 15 years. These deaths, primarily the result of house fires, are most common in children between 1 and 4 years of age. The fatalities are due to smoke inhalation and respiratory failure, hypovolemic shock and renal failure (from fluid loss through the burned skin), and overwhelming infection, contributed to by impaired immunocompetence in the severely burned patient. Serious but nonfatal burns affect 150,000 children annually; these are particularly tragic injuries, which often require long periods of hospitalization, repeated surgery, and extensive rehabilitation, with major psychological sequelae for the child and family.

Firearms are tied with poisoning as the third most common cause of accidental death in the 15- to 24-year age group. Firearm-related deaths have risen in frequency in the 5- to 9-year age group, and closely follow fires and burns.

Foreign bodies represent the fourth leading cause of accidental death in the 1- to 4-year age group, with food items frequently the agent.

Bicycling and sports-related injuries are a more frequent cause of morbidity than mortality. The greatest risk is head injury, which accounts for one third of the emergency department visits, two thirds of the hospitalizations, and three quarters of the deaths from bicycling. Helmets have been demonstrated to reduce head injury by 85%, and brain injuries by 88%. An “all-sports helmet” is an attractive countermeasure, proposed to address injuries not only from bicycling, but also from falls on playgrounds, skating, and other activities.

Poisonings are less common causes of accidental death in young children, but there are at least 200 nonfatal cases for every poisoning fatality. Although the management of poisonings (particularly in toddlers) occupies a significant amount of patient, family, and physician time, the fatality rate for poisonings is a small fraction of the rate for motor vehicle deaths, drowning, or fire/burns. Moreover, recovery from poisoning is usually complete, unlike the residual morbidity often complicating a burn injury. Although many more toddlers than older children are accidentally poisoned, the vast majority of fatal poisonings are adolescent suicides.

The variation by gender in injury and case fatality rates is striking; boys have twice the accident death rate of girls (4 times the rate in individuals 15–24 years of age, largely due to motor vehicle deaths). This sex ratio holds true for deaths from drowning, firearms, and toxic ingestions, but the rates are approximately equal for burn fatalities. Social class is a potent factor as well. Poor children are at greater risk of accidental injury than are children who are not poor, particularly for pedestrian injuries, burns, and drownings.

A number of studies have helped define common antecedents in the behavior of adults and children involved in accidents. Families in which a child has sustained a serious accident have a higher proportion of acute and chronic illness, and the mother, in particular, is often preoccupied or absent from the home. Boys who have accidents are more likely to be described as risk takers or as having recently undergone stress. These studies have increased our understanding of the psychology of accidents but have been difficult to translate into specific preventive action.

Efforts to alter the behavior of children and adults to prevent accidents through health education or information activities have generally not been successful, especially when conducted at a general untargeted level. Legislation and regulation can be particularly effective. The two modalities may be most effective when used together: legislation and regulation to “get peoples' attention,” and health education and information to “get the message out.”

The role of physicians in the management of accidental injury is an important one. Once a serious injury has occurred, physicians are involved as clinicians. In the

strategy of accident prevention, they must be teachers for their own patients and, in the public arena, advocates for reforms that will protect all children from injuries.

General Reviews

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Injuries Associated with Motor Vehicles

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Drowning

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Firearms

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Bicycle, Sport, and Playground Safety

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Burns

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22. Scholer, S., et al. Predictors of mortality from fires in young children. *Pediatrics* 101:e12, 1998. (Available at: www.pediatrics.org/cgi/content/full/101/5/e12.)
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    A practical overview, with a table contrasting the various degrees of burns, a diagram to estimate surface area burned, and helpful color photographs.
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    When education and legislation were combined, annual burn admissions were reduced in Washington state by one half over a decade.

Poisonings

See Chap. 13.

13. ACUTE POISONING

Olakunle B. Akintemi

In 1998, about 2.2 million poisonings were reported by the American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC TESS). Of these, 67% occurred in children younger than 19 years of age, 53% in children younger than 6. The majority of these poisonings were clinically insignificant, and therefore did not require evaluation in the emergency department. Because poisoning is not a “reportable disease,” the total number of poisoning cases reported by the AAPCC may grossly underestimate the actual incidence. Additionally, data from drug abuse, suicide attempts, medical examiner cases, drug reactions, drug interactions, and common poisonings easily treated at home are not included. Overall, there were 775 fatalities, but children younger than 6 years account for only 2.1% of these fatalities.

The toxic exposure typically occurs in the home with ingestion of products such as cosmetics and personal care products, cleaning substances, analgesics, plants, vitamins, and cough/cold medications. The infectious disease model of the interaction among the host (child), the agent (toxin), and the environment can be applied to the epidemiology of poisonings. The characteristics of the “host” (child) that make it more likely for the host to become “poisoned” include age (1–4 years and adolescents) and sex (boys 1–4 years; and female adolescents). Host variable factors that contribute to poisonings include misperception of the substance as something other than its actual identity; curiosity about taste; smell of the substance; imitation of “adult behavior”; peer pressure; risk-taking, attention-gaining, and noncompliant behavior. Others include suicidal ideation, experimentation, and depression. Characteristics of the agent (toxin) that predispose the host to poisoning include taste, color, attractiveness, and smell. Parental variables and the physical and psychosocial environment are characteristics of the environment that predispose the host to poisonings. Parental variables include parental illness or disability, failure to store a “poison” properly, lack of supervision, child abuse, Munchausen syndrome by proxy; distraction (phone calls, unanticipated visits); cultural practices (home remedies); and ignorance about toxicity of the agent or poison prevention measures. Finally, presence of illicit drugs, visitor medication (i.e., grandparents), and acute environmental stressors (recent relocation, arrival of a new baby) may predispose to poisonings.

The principles of management of acute poisonings are (1) provision of basic or advanced supportive care, (2) identification of the poison or agent, (3) reduction of absorption (decontamination), (4) enhancement of poison elimination or breakdown, and (5) administration of specific antidotes.

Because the most life-threatening systemic manifestations of poisonings are respiratory failure, hypotension, cardiac dysrhythmias and seizures, life support must have priority. The initial assessment is therefore to identify and correct life-threatening problems of ***A****irway* (A), ***B****reathing* (B), ***C****irculation* (C), and central nervous system (CNS) ***D****epression*/***D****isability* (D) (see Chap. 1). A cardiorespiratory monitor should be considered; high flow oxygen and pulse oximetry provided. Intravenous access may be necessary and shock should be treated initially with isotonic fluid (normal saline, lactated ringers) and vasopressors (dopamine, dobutamine, epinephrine, and norepinephrine) for shock unresponsive to crystalloids. Respiratory failure must be managed by securing the airway and providing mechanical ventilation (see Chap. 5). Occasionally, some patients have severe cardiopulmonary compromise refractory to these supportive measures (fluids, vasopressors, mechanical ventilation), and may require advanced supportive techniques.

Glucose and naloxone are important considerations for the patient who presents with altered sensorium and may have hypoglycemia or narcotic intoxication. Glucose infusion (0.5–1.0 g/kg) should be provided as either 10% or 25% dextrose in water. Naloxone (0.1 mg/kg or 2 mg) can be administered intravenously (IV), intramuscularly (IM), or through the endotracheal tube (ET). It is important to assess response of the patient (either positive or negative) to naloxone and glucose administration. Flumazenil (a g-aminobutyric acid [GABA] antagonist) reverses the action of benzodiazepines; it is indicated only if there is a reliable history of ingestion, and clinical symptoms and signs consistent with benzodiazepine poisoning. Indiscriminate use may result in seizures and cardiac dysrhythmias in cases of carbamazepine, tricyclic antidepressant, or chloral hydrate overdose.

Once the patient is stabilized, the next step is to identify the poison (agent, toxin) and assess the severity of poisoning. This is accomplished by obtaining a complete history, conducting a meticulous physical examination, and obtaining some laboratory tests. History should include what was ingested, where, when, how much, and who witnessed the event. It is also important to ask about what medications (prescription, over-the-counter, and illicit) are at home, and family members may be asked to bring any container or substance suspected of being involved in the incident.

Physical examination must include CNS signs and symptoms (coma, agitation, seizures, and hallucination); eyes (pupillary size, “doll's” eyes, icewater calorics, eye movement); and vital signs (temperature [hypothermia, hyperthermia], heartrate [bradycardia, tachycardia, arrhythmias], respiration, and blood pressure). Assessing the breath for certain odors, drooling, meningeal signs, and skin examination (needle track marks, warmth, dryness, pallor, erythema) are sometimes useful in the assessment. Certain clues in physical examination, signs, and symptoms may be helpful in classifying an ingestion into a particular toxidrome. The toxidromes include sympathomimetic (mydriasis, tachycardia, hypertension, hyperthermia, and seizures); cholinergic (diarrhea, diaphoresis, urination, miosis, muscle fasciculations, bradycardia, bronchosecretions, emesis, lacrimation, and salivation); anticholingergic (hyperthermia, dry mouth, flushed skin, dilated pupils, delirium, and urinary retention); and narcotics (miosis, bradycardia, hyperventilation, hypotension, and coma). These toxidromes reflect derangements in the autonomic nervous system but may not be useful in cases of multidrug ingestions. Breath odor (acetone, bitter almond, fruitlike, garlic, vinegar, violet) or skin color (cyanosis, gray, jaundice) may be helpful.

Laboratory tests (general, specific) may provide clues to diagnosis but should be individualized based on the history, and clinical signs and symptoms. Initial laboratory tests may include complete blood count (CBC), serum electrolytes, renal and hepatic function tests, anion gap, serum osmolality, arterial blood gas, and cooximetry. An elevated anion gap metabolic acidosis is seen in poisonings with methanol, toluene, alcohol (ethanol), paraldehyde, salicylates, strychnine, iron, ibuprofen, or ethylene glycol poisoning. Low (reduced) anion gap without metabolic acidosis is seen in lithium, iodine, and bromide poisoning. Osmolar gap is the difference between the measured osmolality (using freezing depression method) and the calculated osmolality. An elevated osmolar gap (indicating unmeasured osmoles) is suggestive of poisoning by methanol, ethanol, mannitol, sorbitol, isopropyl alcohol, ethylene glycol, acetone, or propylene glycol. Hemoglobin saturation is measured with a cooximeter, using three different wavelengths of light. This is useful in cases of carbon monoxide poisoning (carboxyhemoglobin level), and methemoglobinemia (methemoglobin level). A CBC is sometimes useful in cases of iron poisoning. Some studies suggest that a total white blood cell count >15,000 mm^3 and glucose level >150 mg/dL correlate with iron level >300 µg/dL. A toxicology screen is a useful adjunct to confirm ingestions suspected by history and physical examination, but has a limited role in the initial management of the poisoned child. It may also be useful in children presenting with unexplained seizures, altered mental status or coma of unclear etiology, or unexplained metabolic acidosis. Toxicology screens identify a large number of drugs (mostly drugs of abuse); specific assays performed vary among laboratories are expensive and time consuming and, as noted, do not alter initial management. Certain drugs and toxins are not included in a routine toxicology screen. These include lithium, organophosphates, ethylene glycol, cyanide, solvents and hydrocarbons, isoniazid, calcium channel blockers, antihypertensives, and benzodiazepines (alprazolam, midazolam, clonazepam). When a known single agent is involved, drug levels (iron, lead, acetaminophen, digoxin, lithium, salicylate, theophylline) should be determined. Chest radiograph may be indicated in cases of aspiration pneumonitis (hydrocarbon ingestion), and noncardiogenic pulmonary edema. Abdominal radiographs (seizures or ventricular dysrhythmia) may be useful in iron ingestion. In cases of tricyclic antidepressant overdose, a QRS duration ³160 ms is predictive of toxicity.

The term gastrointestinal decontamination is used to describe the various methods of preventing toxin absorption. These include induction of emesis with syrup of ipecac, gastric lavage, administration of activated charcoal, whole bowel irrigation, and administration of cathartics. Factors to be considered when choosing a method of decontamination are seriousness of the ingestion, substance ingested, and time since ingestion. There is no certain evidence that gastrointestinal decontamination improves clinical outcome. Both the American Academy of Clinical Toxicology and the European Association of Poison Centers and Clinical Toxicologists have issued position statements about gastrointestinal decontamination.

Syrup of ipecac induces emesis in 90% of patients approximately 15–30 minutes after administration. Additionally, it results in incomplete evacuation of the stomach and its efficacy diminishes with time. Although it remains useful for home treatment of toxic ingestions (following a call to the physician or poison control center), its use in the emergency department is doubtful and should be abandoned. Adverse effects include persistent vomiting, diarrhea, CNS depression, cardiotoxicity, and

Mallory-Weiss tear. Ipecac may delay administration or delay the effectiveness of activated charcoal, resulting in prolonged stay in the emergency department. It should not be administered in infants younger than 6 months, in patients with decreased level or impending loss of consciousness, and after ingestion of corrosives or hydrocarbons.

Gastric lavage may be indicated in patients with life-threatening ingestions who present within 60 minutes of ingestion, or when ipecac-induced emesis is ineffective or contraindicated. Factors determining effectiveness of lavage include physical characteristics of the toxic agent (tablets, capsules, liquid, plants), rate of absorption of the toxic agent, diameter of the lavage tube, and the volume and ratio of instillation of lavage solution. Its efficacy in children, however, is questionable; there are few indications for its use, and it may cause serious complications. Moreover, it is a technically difficult procedure in conscious, screaming, and gagging young children. Gastric lavage is contraindicated when airway protective reflexes are lost, unless the patient is intubated.

Activated charcoal is probably the most effective decontaminating agent available. It binds to almost all substances except alcohols, iodide, acids, bromides, lithium, cyanide, alkali, heavy metals (arsenic, lead, zinc, iron, mercury), and boric acid. It binds to toxins in the gut, prevents reabsorption of substances that undergo enterohepatic circulation, and enhances back diffusion of drug from the bloodstream to the gut lumen.

Multiple-dose activated charcoal therapy is a form of “gastrointestinal dialysis” that promotes clearance of systemic drugs. Repeated doses of charcoal create a concentration gradient between blood and intestinal fluid, resulting in passage of drugs into the intestinal lumen. Toxins with small volume of distribution, low plasma protein binding, circulating active metabolites, and enterohepatic circulation are ideal for multiple-dose charcoal therapy. Some of these include theophylline, tricyclic antidepressants, phenobarbital, digoxin, carbamazepine, phenothiazines, and salicylates. However, based on experimental and clinical studies, multiple-dose activated charcoal therapy should be considered only after ingestion of life-threatening amounts of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Complications of activated charcoal include pulmonary aspiration, bowel obstruction, and charcoal bezoars.

Whole bowel irrigation using polyethylene glycol electrolyte lavage solution (GoLYTELY, NuLYTELY) is occasionally reserved for ingestions of large tablets, tablet bezoars, or packets of illicit drugs (“body packers” or “body stuffers”). However, the procedure is labor intensive and time consuming, and may cause abdominal cramps, profuse diarrhea, and vomiting.

The administration of cathartics as sole decontaminating agent in the management of the poisoned child is not recommended. Although commonly used in combination with activated charcoal, there are conflicting data about efficacy. Sorbitol should be avoided in children younger than 3 years of age. If a cathartic is used, it should be limited to a single dose given with the first dose of activated charcoal.

Excretion of the toxin may be enhanced by alkalinization or acidification of urine, hemodialysis, hemoperfusion, or plasmaphoresis. Finally, specific antidotes such as fomepizole (for ethylene glycol and methanol) and *N*-acetylcysteine (for acetaminophen) may be indicated.

Disposition of a patient following a toxic ingestion includes parental education about injury prevention, and psychiatric evaluation for adolescents with intentional ingestion.

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14. FEVER AND ANTIPYRESIS

Kenneth B. Roberts and Olakunle B. Akintemi

Perhaps the most common and the most distressing sign of childhood illness to both parents and pediatricians is fever. Although the cause is usually viral, self-limited, and benign, fever is considered synonymous with disease and, thus, often elicits considerable concern. The physician's responsibility is to establish a correct diagnosis and initiate treatment if indicated, meanwhile ensuring that the child is comfortable. A more long-term goal is parental education about the use of thermometers and the meaning of fever.

It is generally accepted that 37.0°C (98.6°F) is “the normal” body temperature, but it should be clear that body temperature is like other biologic phenomena in that not every member of the population has exactly the same temperature. It should be noted specifically that infants, on the average, have a higher basal temperature than do older children or adults; 50% of 18-month-olds have daily temperatures in excess of 37.8°C (100.0°F) without associated illness. Only after age 2 years does the downward trend begin, reaching a “normal” 37.0°C during adolescence. There is a diurnal variation in body temperature, with temperature lowest at approximately 4 A.M. and highest in the late afternoon and early evening. Oral temperatures are generally 0.5–0.6°C lower than rectal temperatures, and a probe inserted 14 cm into the rectum will record a temperature as much as 1.3°C higher than that measured by the usual clinical thermometer placed only 2–6 cm inside the rectum.

Fever of any magnitude in neonates may be the only sign of sepsis; in infants 7–24 months old, there appears to be a higher incidence of bacteremia if the temperature is above 39.5°C (see Chap. 2). In older children, fever may persist for days or weeks and still be of obscure cause; the designation *fever of unknown origin* should be applied only when fever has persisted for more than 3 weeks. (Some authors are content with a 2-week duration, as in adults, but in children many viral infections will persist past 14 days.) Infections (such as tuberculosis), cancer (especially leukemia), and collagen-vascular disorders (especially juvenile rheumatoid arthritis) must be thought of in the differential diagnosis of fever of unknown origin, but the majority of children will prove to have a more common illness, although perhaps with an unusual presentation. Despite the increasing availability of sophisticated tests, including various scans, the history and physical examination remain the most discriminating tools in formulating a diagnosis.

Although fever may portend serious illness, it is rarely harmful per se. It causes an increase in the basal metabolic rate of approximately 12% per degree centigrade elevation above 37.8°C, and the associated insensible loss of water may lead to dehydration if there is no compensatory increase in fluid intake. The pulse rate increases approximately 20–25 beats/min per degree centigrade of fever, which may be deleterious if the child's myocardium is already strained because of cardiac disease or anemia. Seizures are a common concern, but “febrile seizures” are associated more with a rapid rise in temperature than with the absolute height attained, although it is unusual for convulsions to occur if the maximal temperature is 39°C (102°F) or less. Febrile seizures are often associated with the initial fever spike in an illness and uncommonly occur twice in the same illness, so it is unclear how much antipyretics contribute in the prevention of convulsions. When surveyed, parents also express concern that fever, if left untreated, will continue to spiral upward to levels at which brain damage will occur; the hypothalamic “thermostat” does not permit body temperature to exceed 106–107°F, however.

Many authors have argued teleologically and on the basis of in vitro experiments and clinical observations that fever is a beneficial host response to infection. In some specific bacterial diseases, notably neurosyphilis, fever therapy has been clinically effective, and multiplication of some viruses is limited by elevation of the temperature from 37°C to 40°C (98.6°F to 104°F). However, there has not yet been popular acceptance that fever is a symptom that represents the host's attempt to contain an infection; rather, fever is generally equated with disease and treated as though it were a disease itself.

The most compelling reason to reduce fever under the usual conditions in childhood is patient discomfort. Certain antipyretic measures, such as sponging with ice water, not only may be ineffective because of shivering and increased thermogenesis, but also may produce more discomfort than the untreated fever and are therefore to be discouraged. The pharmacologic agent most frequently used to reduce fever currently is acetaminophen. Acetaminophen became popular in the 1960s as a “harmless” alternative to aspirin, free from the bothersome side effects noted with salicylate (notably, gastric irritation and platelet dysfunction), and less likely to cause serious poisoning. It is clear that acetaminophen is not harmless, however; large overdoses can be fatal. Deaths result from fulminant liver damage, the signs and symptoms of which are characteristically delayed 2–3 days. Treatment of acetaminophen overdose includes the administration of repeated doses of *N*-acetylcysteine.

Ibuprofen is more active per unit weight as an antipyretic than acetaminophen, resulting in a longer duration of action at the same dosage level. The difference between the drugs may not be clinically relevant, however, as equivalent results can be obtained by altering the dosages. In recent years, some clinicians have recommended to parents that they alternate acetaminophen and ibuprofen. It is not clear that this practice has pharmacologic benefit beyond that of prescribing appropriate doses of a single drug for a limited period of time. The rationale may be that “it gives parents something to do,” but the downside may be the perpetuation of “fever phobia” and dosage errors related to a confusing regimen.

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15. LEAD POISONING

Evan Charney and Kenneth B. Roberts

Lead, an element with no known therapeutic use, has long been recognized as a toxic substance. In the past, the problem of concern was overt lead encephalopathy, which is now very rare, causing many to believe that “the lead problem” has been controlled. However, lead remains in the environment, and it is now clear that there are long-term neurobehavioral, cognitive, and developmental effects at even low exposure levels.

There are multiple sources of lead in the environment; lead in food, water, and air accounts for a “basal intake,” entering the body directly by ingestion or inhalation. Where the environmental dust, dirt, and paint are contaminated with lead—notably in urban soil and in the paint in deteriorated housing—significant additional lead will be ingested directly or indirectly by hand contamination and repetitive mouthing behavior typical of young children.

The average blood level of lead in children in the United States has steadily decreased since lead was removed from gasoline, from 15 µg/dL in 1976–1980 to 2.7 µg/dL in 1991– 1994. The percentage of U.S. children 1–5 years old with blood lead levels >10 µg/dL has decreased from 88.2% to 4.4%. Rates were substantially higher in certain populations, however. In black children aged 1–5 years living in older housing, 22% had blood lead levels of 10 µg/dL or higher. Of poor children living in older housing, 16% had elevated blood lead levels, and 11.5% of all children in older housing in large urban areas had elevated blood lead levels. Of houses built before 1978, approximately 85% contain lead-based paint; those built before 1950 pose the greatest risk to children. In absolute numbers, nearly 900,000 U.S. children have blood lead levels >10 µg/dL.

Inorganic lead enters and leaves the body chiefly through the gastrointestinal tract. Normally, 10% of ingested lead is absorbed, but nutritional status greatly influences absorption: deficiencies of iron, protein, calcium, and vitamin D can increase lead absorption five-fold. Once absorbed, lead is distributed into three body pools. Bone is the largest reservoir, with 90% of body lead incorporated in hydroxyapatite crystals, but without effect on the skeletal architecture. The bone marrow and soft tissues are a second body pool, with more active turnover than that in bone. Clinically, the most important pool is the rapidly exchangeable lead in red blood cells and parenchymal organs. The central nervous system (CNS) is freely permeable to soluble lead, and animal studies indicate no threshold to lead accumulation in the CNS; these studies also demonstrate that lead in the CNS is relatively difficult to mobilize.

The impairment in erythropoiesis caused by lead does not result in a profound anemia. Lead interferes with sulfhydryl-containing enzymes, disrupting the synthesis of the heme porphyrin structure from aminolevulinic acid and causing the free erythrocyte protoporphyrin (FEP) concentration to rise. Free erythrocyte protoporphyrin was used as a screening test for lead exposure, but it is an insensitive indicator of blood lead levels below 25 µg/dL; whole blood lead is the only currently accepted diagnostic test for lead poisoning. Erythrocyte protoporphyrin determination may be helpful in case management, however, since a marked elevation correlates with long-term lead ingestion (over the 120-day life span of the erythrocyte), whereas blood lead reflects only current exposure.

The clinical manifestations of early lead intoxication are subtle and relatively nonspecific; the fetus may be particularly sensitive to lead exposure, as lead is transferred directly across the placenta. There appears to be an association between modest elevation in lead levels in the first 2–3 years of life (perhaps as low as 20–30 µg/dL) and behavior disturbance, irritability, abnormal fine motor skills, adaptive function, and language function, which become manifest in the early school years. Although considerable work has been done on the neurobehavioral effects of blood lead levels below 20 µg/dL, particularly in a number of careful longitudinal prospective studies over the past decade, separating the specific toxic effect of lead from a myriad of confounding variables remains difficult, particularly at progressively lower blood lead levels. Available evidence indicates a decrease of 2–3 IQ points per 10 µg/dL blood lead elevations over 10 µg/dL at age 3 years.

The adverse neurobehavioral effects of lead at higher levels are more straightforward. Although most children with blood lead levels of 50–80 µg/dL are not overtly symptomatic, anorexia, vomiting, and intermittent abdominal pain may be present. More serious CNS toxicity, caused by a hemorrhagic encephalopathy with increased intracranial pressure, is manifested by lethargy, irritability, ataxia, and clumsiness. Progression to stupor and refractory convulsions occurs as lead levels rise above 100 µg/dL, levels rarely seen in the United States today.

Therapy for lead intoxication involves both environmental and medical management. An investigation of the child's environment to identify and eliminate the source(s) of lead is the most important intervention. Aggressive efforts by the physician and public health agencies are often required to remove the child from the source(s) of lead and ensure “environmental detoxification.” Current methods of home hazard abatement involve removing all peeling or deteriorated lead-containing interior and exterior surfaces in the child's home, replacement of window casements, and careful cleanup of residual lead-contaminated dust. Hazard abatement strategies are currently undergoing reassessment (e.g., surface encapsulation), as the minimum “safe” blood level for children has been progressively lowered. The process of abatement itself may be hazardous and, if not carefully done, may further contaminate the home environment.

Medical management is based on nutritional assessment and chelation therapy. As previously mentioned, nutritional status affects the amount of ingested lead that is absorbed. Iron deficiency in particular should be investigated, since it is commonly found in the low-income population subject to lead poisoning and has been associated with similar neurobehavioral impairment in young children. Calcium Disodium Versenate ($CaNa_2EDTA$ or, simply, EDTA) is the mainstay of chelation therapy for blood levels above 45 µg/dL, preceded by dimercaprol (BAL) when blood levels exceed 69 µg/dL. Both drugs must be given parenterally, are potentially toxic, and should be administered by clinicians experienced in their use. An oral agent, succimer (DMSA), is also available. For blood lead levels between 25 and 44 µg/dL, the effectiveness of chelation therapy in decreasing the adverse effects has not been demonstrated, although some clinicians advocate its use in selected cases. Succimer is currently being studied for children with lead levels in this range.

The 1991 guidelines of the Centers for Disease Control and Prevention identified the increased importance of primary prevention efforts (i.e., elimination of lead hazards before children are poisoned) as the blood lead level of concern is lowered. The goal of all prevention activities should be to reduce children's blood lead levels to below 10 µg/dL. During the 1990s, debate arose over whether all children needed to be screened (vs. selected screening of those at high risk), focusing attention away from the reservoirs of lead, old housing, and soil. Advocates for primary prevention point out that existing data are ample to identify where the lead is; what is required is the will (and resources) to eliminate lead from the environment. The problem is no longer a generalized one but is limited to certain areas, referred to as the “ghettoization” of lead poisoning. In retrospect and in comparison to the current situation, the elimination of lead from paint, gasoline, and solder appears to have been straightforward and “simple,” though it was by no means easy to achieve. The remaining task is financially daunting but can be accomplished if there is sufficient advocacy, legislative action, and resources.

Reviews and Guidelines

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Primary Prevention

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16. CHILD ABUSE AND NEGLECT

Robert D. White

Recognition and management of child abuse by the pediatrician demands a full measure of clinical acumen, skill, and diplomacy. The results of mistreatment may be immediately apparent or so subtle as to be overlooked for years. Therapy is difficult, and success depends on patient and sympathetic treatment of the entire family to interrupt a cycle of aggression usually initiated decades before the birth of the child. This disease, to a greater extent than most, exemplifies the roles of the pediatrician as child advocate and family counselor.

The incidence of child abuse probably exceeds 500,000 cases/year in the United States. In children younger than 3 years, 25% of fractures and 10–15% of trauma are “nonaccidental.” Death by battering occurs in 2,000 children yearly, while three times that number suffer permanent brain damage.

The cause of child abuse defies simple classification. It seems clear that most abused children are “exceptional,” but this description includes not only demanding, handicapped, or chronically ill infants, but highly intelligent and active children as well. Many aberrant personality traits can be found retrospectively in abusive parents, but most are sufficiently common in the general population to make accurate identification of a battering parent extremely difficult prior to one or more episodes of abuse. Many abusive parents were themselves beaten in childhood or by a spouse; thus, aggression toward their own children is often less an expression of hatred than a learned response to anger or adversity.

The diagnosis of child abuse requires a high index of suspicion by the examining physician. In only a few cases does a malevolent, hostile parent bring to the physician a child with the classic signs of subdural hematoma and multiple fractures in various stages of healing; far more often, the battered child is one of several patients in a crowded emergency room or office with a minor bruise, burn, or laceration, accompanied by attentive parents. Abuse should be considered in a child under 3 years of age with any form of trauma (except from an automobile accident), especially when the history of the trauma is vague or discrepant, or when there has been a delay in seeking medical attention. Child abuse or neglect should also be considered in the differential diagnosis of “failure to thrive.” In addition, evidence of battering may take many unusual forms, such as retinal hemorrhage, duodenal hematoma, drug overdose (usually with sedatives or narcotics), and sexual abuse.

Evidence of previous trauma should be searched for during general examination of the child, and the previous medical record should be thoroughly reviewed for a pattern of repeated trauma. Many cases of child abuse are missed because only cursory attention is given to these portions of the medical evaluation during treatment for traumatic injuries. In some situations, a series of radiographs of the skull, extremities, and ribs is indicated to demonstrate old fractures, metaphyseal abnormalities, or subperiosteal hemorrhages that would otherwise be missed. Discussion with parents of the circumstances surrounding an unusual or suspicious injury must be thorough but should be devoid of any hint of accusation.

When abuse is evident or highly suspicious, steps must be taken to protect the child from the dangerous environment; often, hospitalization is warranted, even if the actual injury is minor. Removal of the child from the home allows a cooling-off period for the parents, as well as time to evaluate the family environment in adequate depth. The physician should carefully document the injuries suffered (photographs are very helpful), the history given by the parents, and the medical therapy rendered. Notification of state authorities is mandatory but should be done without prejudgment. As pointed out earlier, the stereotypical malevolent parent is rarely seen; most parents who batter their children are also capable of loving them and caring for them well when intervention by medical and social personnel is offered with understanding and sympathy.

Therapy is directed toward rehabilitation of the family unit whenever possible. Psychological evaluation of the parents delineates the emotional framework and the stresses that promote battering; the parents' understanding of their own behavior may be a major therapeutic step. When the parents are able to enjoy their child and have a secure resource to turn to when stress mounts, it may be safe to return the child to the home. Continued liaison, as with a trained home visitor, is advisable to provide the parents with competent, ongoing support and to serve as an “early warning device” to detect the potential recurrence of abuse. This approach appears capable of reducing the risk of subsequent battering to less than 5%, but such programs are not available in many areas. Parents' groups have formed in some communities to help fill this void. The failure to provide ongoing support has serious consequences; when an abused child returns to the home without therapeutic intervention, the risk of further abuse is approximately 50%, with death resulting in up to 10% of children.

Sexual abuse requires special considerations. Sexually abused children may present after a disclosure or because of a symptom, sign, or disorder specific to sexual abuse, such as a sexually transmitted disease, genital pain, injury, infection, or developmentally inappropriate sexual behavior. They may also present with a variety of nonspecific behavioral difficulties (such as sleeping or toileting difficulties), which are similar to those due to other stressors. The physician's approach should include a careful interview of the child, an informed general examination, with attention to the genitals and anus, and cultures for sexually transmitted diseases, if indicated by the local epidemiology or the history given by the child. The diagnosis is made on the basis of the history. The physical examination is rarely diagnostic in and of itself and may often be normal, because injuries may heal completely or because the sexual acts experienced by the child caused no physical damage. If there is the possibility that physical evidence of recent sexual abuse can be obtained, however, the child should be examined by a physician with proper forensic training and supplies for documentation of sex crimes. In addition to a referral to child protective services, the physician should also refer the child to a mental health provider to assess the need for treatment. Parents also may need treatment and support to cope with the trauma of the situation.

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Valuable guide to diagnosis and reporting.
11. McCann, J., et al. Genital findings in prepubertal girls selected for non-abuse: A descriptive study. *Pediatrics* 86:428–439, 1990.
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Specific Aspects of Abuse: The Physician's Role

13. American Medical Association Council on Scientific Affairs. AMA diagnostic and treatment guidelines concerning child abuse and neglect. *J.A.M.A.* 254;796–800, 1985.
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Careful preparation of a child for the rigors of testifying can help prevent some of the potential risks. (For some children, testifying may be therapeutic; see J. Pediatr. *113:647–653, 1988.)*

Prevention

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17. SUDDEN INFANT DEATH SYNDROME

E. Kaye Gable and Robert D. White

For centuries, infections were the leading cause of death in infancy. Now with the development and extensive use of antibiotics and vaccines, other causes of infant mortality are increasingly apparent. Foremost among these is the sudden infant death syndrome (SIDS), which is now the leading cause of death in infants 1–12 months of age. First recognized in the early 1960s, SIDS is, by definition, sudden, unexpected, and unexplained, even after a careful autopsy, thorough history, and death scene investigation. While the precise etiology of this disorder remains obscure, recent epidemiological studies have established the link between SIDS and sleeping prone. Since 1991, with the initiation of public awareness campaigns to reduce the incidence of prone sleeping, SIDS rates have fallen approximately 50%. The United States introduced the “Back to Sleep” campaign in 1992. At that time, the incidence of SIDS was 1–2/1,000 births with about 7,000 cases annually. The latest figures available from 1996–97 show a rate of 0.7/1,000 births (about 2,800 cases).

Sudden infant death syndrome has several notable epidemiological characteristics. Almost 95% of the cases are infants 1–6 months old. Virtually all deaths occur while the infant is asleep. While signs of vigorous activity are occasionally present, there is no warning cry. Infants nearly always appear to have been in good health, although in half, an upper respiratory infection has been present the week prior to death. Viruses can be isolated from the nasopharynx and stool of infants with SIDS more often than from control infants, but there is no evidence of sepsis resulting from either viral or bacterial agents. Despite the unexpectedness of SIDS, there are recognizable risk factors associated with an increase in SIDS. The syndrome is most common in winter months, lower socioeconomic groups, prematurely born infants, low birth weight infants, males, and certain ethnic groups such as Native Americans. Certain maternal risk factors are also associated with SIDS: smoking, alcohol and drug abuse, age less than 20 years, and anemia.

The pathologic findings of SIDS are provocative. Intrathoracic petechiae, often associated with pulmonary congestion, edema, and microscopic areas of mild inflammation, are present in about 90% of the infants. Some investigators have found thickening of the pulmonary arterial musculature, prolonged retention of brown fat, extramedullary hematopoeisis, and changes in the carotid bodies, all suggestive of chronic hypoxemia. On the other hand, the thymus and adrenals show no evidence of chronic stress, and the bladder and rectum are usually empty, indicating an acute agonal event.

While no one theory explains all SIDS deaths, most research is currently centered on the central nervous system, particularly the brain stem. One theory proposes that death is due to respiratory insufficiency, possibly secondary to acute upper airway obstruction by laryngospasm or muscular relaxation of the oropharynx. This is consistent with the sudden, silent death during sleep and the striking localization of petechiae presumably secondary to strongly negative intrathoracic pressures developed during agonal gasps. Sleeping prone on soft bedding with excess swaddling could lead to upper airway obstruction and subsequent hypercarbia. An alternative hypothesis proposes neurogenic imbalance, either in brainstem control of respiration or in the autonomic nervous system. This theory is attractive because it provides an explanation for the observed excess of premature infants and infants with neurologic abnormalities, and because it implies a chronic disorder, consistent with the changes found in the pulmonary vasculature, carotid body, and brown fat. A third possibility is that SIDS is the result of a fatal cardiac arrhythmia, which is also consistent with a sudden, silent death. Many investigators endorse the “triple-risk model” of SIDS, which states that SIDS results from the intersection of 1) a vulnerable infant who possesses some underlying abnormality in cardioventilatory control, 2) a critical period in the development of homeostatic control (usually 2–6 months), and 3) exogenous stressor(s).

The recent success of the “Back to Sleep” campaign demonstrates that there are strategies that can help reduce the incidence of SIDS. While supine sleeping has reduced SIDS rates 30–50% in the countries that have recommended it, there are other risk factors for SIDS that can be reduced by public education. Recent epidemiological studies confirm that prenatal maternal smoking increases the risk of SIDS two- to three-fold. Exposure of infants to passive household smoke also increases the risk of SIDS two-fold and appears to be dose related. In January of 1995, the Consumer Product Safety Commission announced the results of a 2-year investigation of the relationship between SIDS deaths and soft bedding. The study concluded that as many as 30% of the 6,000 SIDS deaths in 1994 were likely due to suffocation brought about by rebreathing CO_2-laden expired air when an infant slept face down on soft bedding. A protective association between breastfeeding and SIDS has been found in some case control studies but not in others. Many have argued that, when controlled for higher socioeconomic status, the association disappears. However, studies from New Zealand, where all socioeconomic status groups have a high incidence of breastfeeding, show that breastfeeding is associated with a 50% reduction in the rate of SIDS.

Pediatricians should keep in mind that a thorough investigation into every unexpected child death is mandatory if we are to truly understand SIDS. Other diagnoses must be looked for, including child abuse. The American Academy of Pediatrics Committee on Child Abuse and Neglect estimates that 2–5% of deaths attributed to SIDS may actually be due to child abuse. It is impossible on autopsy to tell the difference between SIDS and intentional suffocation. Sudden death in multiple infants in the same family is extremely unlikely to be due to SIDS and should always raise suspicion.

The pediatrician's role in SIDS is important, and extends well beyond the care of the infant (see Chap. 34, Death, Dying, and Mourning). The events preceding death should be recorded thoroughly and compassionately. The parents should be informed of the provisional diagnosis, emphasizing that SIDS is a definite, although poorly understood, clinical entity; that an autopsy should be performed to confirm the diagnosis; and that blaming themselves for the child's death is unwarranted. Extended counseling for the parents is vital. The counselor should understand the patterns of parental grief and must be comfortable with his/her own feelings about death. Valuable support is also available from parents' groups that have been organized in most major cities.

Occasionally, an infant is successfully resuscitated from a SIDS-like event. These so-called near-misses of apparent life-threatening events (ALTEs) present a serious dilemma in management. Infectious and metabolic disorders should be ruled out as possible causes of the acute episode. Seizures, arrhythmias, gastroesophageal reflux, and prolonged sleep apnea are often impossible to exclude with certainty but should be investigated nevertheless. Fatal episodes occur subsequently in approximately 10–25% of infants with a previous near-miss. Prevention of SIDS even in this high-risk group is not always possible. The decision to send an infant home, with or without an apnea monitor, or to observe him in the hospital for a prolonged period must be made with the knowledge that each choice carries obvious risks but no certain benefit. There is no statistical evidence that home monitoring prevent SIDS. The parents' capabilities and their informed consent help determine the course of management.

Reviews

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   This is a meta-analysis of 39 articles that relates parental smoking and sudden infant death syndrome. For more on the association of smoking with SIDS, see B.M.J. *313:195–198, 1996; and* Pediatrics *90:905–908, 1992.*
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One of the most difficult dilemmas for a pediatrician is to know how to be compassionate with parents of an apparent SIDS victim, yet still explore the circumstances surrounding the death sufficiently to exclude infanticide. (Preceding events may tip off a clinician to the possibility of impending SIDS/infanticide: J. Pediatr. *117:351, 1990. See also the American Academy of Pediatrics Committee on Child Abuse and Neglect statement:* Pediatrics *98:1216–1218, 1996; and Chap. 16.*

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Apparent Life-Threatening Events

12. Palfrey, S. Overcoming ALTEphobia: A rational approach to spells in infants. *Contemp. Pediatr.* 16:132–157, 1999; and When and how to manage infants who have “spells.” *Contemp. Pediatr.* 16:79–113, 1999.
    A good discussion of the differential diagnosis of spells and how to sort out their cause. The second part discusses the rare indications for home monitors.
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18. CHILD HEALTH SUPERVISION

E. Kaye Gable and Pamela J. Reitnauer

One of the most rewarding aspects of pediatric practice is following children as they grow and develop over time. Health supervision visits are scheduled at regular intervals during childhood to allow the physician to assess a child's growth and development, as well as to form a relationship with the family. Well-child visits had their origins at the turn of the century with the establishment of free milk stations to dispense safe, pasteurized milk for infants. In the 1930s, immunizations were added to well-child visits, followed by advice about nutrition, child-rearing, and development. Historically, the schedule of visits coincided with the immunization schedule for early childhood. With the success of current vaccines and safe food handling practices, the threat to children's health and well-being changed from infectious diseases to “new morbidities” brought about by social issues (for example, poverty, increasing divorce, single parent households, and social isolation). New technology, such as neonatal intensive care units, has contributed to an increasing population of children with special health care needs.

Overall, 25–50% of children's visits to a physician's office are for well-child care, a proportion that decreases with age (about 55% of visits by infants, and 15% of visits by 6- to 10-year-olds). Because visits for well-child care take longer, on average, than do visits for evaluating or treating illness, they account for close to one half of a pediatrician's office time.

Health supervision consists of those measures that help promote health, prevent mortality and morbidity, and enhance subsequent development and maturation. In 1994, *Bright Futures* was published by the National Center for Education in Maternal and Child Health. More than 17 organizations worked on and supported this document. *Bright Futures* provides guidelines for health supervision that are appropriate for the challenges facing today's families. Specifically, it states that health supervision should be (1) longitudinal; (2) personalized to fit the individual; (3) contextual (i.e., viewing the child in the context of their family and community); (4) supportive of the child's self-esteem; (5) based on a health diagnosis; (6) focused on the strengths as well as problems of the family; (7) part of a seamless system that includes community-based health, education, and human services; and (8) complimentary to health promotion and disease prevention efforts in the family, the school, the community, and the media.

Components of the diagnostic process for health supervision include the following: interview, assessment of growth and development, physical examination, observation of the parent-child interaction, screening procedures, preventive measures, and anticipatory guidance. Anticipatory guidance has three major components: gathering information, establishing a therapeutic alliance, and providing education and guidance. The success of health supervision is largely determined by the extent to which the parent, child, or adolescent is willing to change or adapt their behavior in response to advice given. A survey of mothers in one study has revealed that physicians are their main source of parenting information and that child health supervision was valuable. Assurance of physical health and normal development was more important than discussion of behavioral, family, or safety issues. Thus, the physician is empowered to raise pertinent issues that affect the welfare of the child.

Well-child visits provide an opportunity for health promotion counseling about preventable conditions such as injury, dental disease, cardiovascular disease, and lead exposure, as examples. Education about and implementation of immunizations during well-child visits exemplify the approach to prevention of serious infectious diseases (see Chap. 105). A key component of health promotion is screening. The criteria for effective screening include (1) identifying a disorder or risk factors for potential illness, (2) indication that the disorder has a relatively high prevalence in the population, and (3) existence of some means of effective treatment or intervention. The American Academy of Pediatrics has issued screening guidelines/health policy statements for a number of conditions.

Health promotion can begin with a prenatal visit scheduled during the last trimester of pregnancy. The visit may be the first meeting between the physician and the parents, and allows an opportunity to cover topics such as family and social history, whether the child will be breast- or bottle-fed, whether there will be help from others, and parental expectations. The schedule of health supervision visits from newborn to late adolescence is shown in Table 18.1, which lists some key elements of the visits abstracted from the *Bright Futures* guidelines. The schedule of health supervision visits suggests the amount of care for children not at undue risk. Special populations, such as children with chronic illnesses and disabilities or in foster care, will require more frequent visits and interventions.

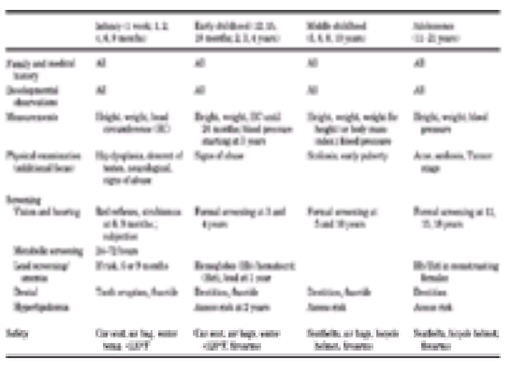

TABLE 18.1. Some recommendations for preventive pediatric health care

General Recommendations and Guidelines

1. American Academy of Pediatrics Committee on Practice and Ambulatory Medicine. Recommendations for preventive pediatric health care. *Pediatrics* 105:645–646, 2000.
   Summary chart of recommended ages and topics for scheduled visits for well-child care.
2. American Academy of Pediatrics Committee on the Psychological Aspects of Child and Family Health. *Guidelines for Health Supervision III.* Elk Grove Village, IL: American Academy of Pediatrics, 1997.
   Thorough guidelines for each visit, prenatal to late adolescence. Particularly valuable for interview questions, including developmental and behavioral areas.
3. Green, M. (ed.). *Bright Futures: Guidelines for Health Supervision of Infants, Children and Adolescents.* Arlington, VA: National Center for Education in Maternal and Child Health, 1998.
   A comprehensive guide to health supervision. Includes specific advice on anticipatory guidance (see websites below).
4. Foye, H. Anticipatory guidance. In: Hoekelman, R. (ed.). *Primary Pediatric Care.* St. Louis: Mosby-Year Book, 1997.
   An excellent discussion of how to provide anticipatory guidance during health supervision visits.

Special Age Groups

5. American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health. The prenatal visit. *Pediatrics* 97:141–142, 1996.
   Objectives and recommendations for the prenatal visit, including establishing relationships, gathering information, and providing information and advice.
6. Kendig, J. Care of the normal newborn. *Pediatr. Rev.* 13:262–268, 1992.
   Discusses prenatal visit, newborn examination, and parent counseling. (See also Pediatr. Clin. North Am. *39:199–211, 1992; and Chap. 35.)*
7. Elster, A., and Kuznets, N. *American Medical Association Guidelines For Adolescent Preventive Services (GAPS).* Baltimore: Williams & Wilkins, 1994.
   Comprehensive discussion of adolescent age-specific guidance.

Content of Visits: Screening

8. American Academy of Pediatrics Committee on Infectious Diseases. *Report of the Committee on Infectious Disease* (25th ed.). Elk Grove Village, IL: American Academy of Pediatrics, 2000.
   The "Red Book," a concise textbook on immunizations and diseases.
9. Haggerty, R. Child Health 2000: New pediatrics in the changing environment of children's needs in the 21st century. *Pediatrics* 96(Suppl.):804S–812S, 1995.
   A discussion of the new morbidities facing children and how pediatricians will need to respond to them.
10. Bass, J., et al. Childhood injury prevention counseling in primary care settings: A critical review of the literature. *Pediatrics* 92:544–550, 1993.
    Review of 20 studies confirms effectiveness of office-based counseling; also see Chap. 12.
11. American Academy of Pediatrics Committee on Practice and Ambulatory Medicine. Eye examination and vision screening in infants, children, and young adults. *Pediatrics* 98:153–157, 1996.
    Age-specific recommendations for vision screening.
12. American Academy of Pediatrics Committee on Genetics. Newborn screening fact sheet. *Pediatrics* 98:473–500, 1996.
    Description of metabolic conditions amenable to screening in the newborn period.
13. American Academy of Pediatrics Committee on Nutrition. Cholesterol in childhood. *Pediatrics* 101:141–147, 1998.
    Recommendations for the identification and treatment of children who are at highest risk for the development of atherosclerosis in early adult life.
14. American Academy of Pediatrics Committee on Environmental Health. Screening for elevated blood lead levels. *Pediatrics* 101:1072–1078, 1998.
    Guidelines for the screening for elevated lead levels and treatment approaches.
15. American Academy of Pediatrics Task Force on Newborn and Infant Hearing. Newborn and infant hearing loss: Detection and intervention. *Pediatrics* 103: 527–530, 1999.
    The statement endorses the implementation of universal newborn hearing screening. In addition, the statement reviews the primary objectives, important components, and recommended screening parameters that characterize an effective universal newborn hearing screening program.

Special Populations

16. American Academy of Pediatrics Committee on Practice and Ambulatory Medicine, and Committee on Fetus and Newborn. The role of the primary care pediatrician in the management of high-risk newborn infants. *Pediatrics* 98: 786–788, 1996.
    Guidelines for providing neonatal care and the shared responsibility with neonatologists.
17. Berger, S., et al. Caring for the graduate from the neonatal intensive care unit, at home, in the office, and in the community. *Pediatr. Clin. North Am.* 45:701–712, 1998.
    Discusses health supervision and follow-up care for the graduate of the neonatal intensive care unit.
18. American Academy of Pediatrics Committee on Early Childhood, Adoption and Dependent Care. Health care of children in foster care. *Pediatrics* 93:335–338, 1994.
    Guidance for health supervision of children in foster care.
19. American Academy of Pediatrics Committee on Children with Disabilities. General principles in the care of children and adolescents with genetic disorders and other chronic health conditions. *Pediatrics* 99:643–644, 1997.
    Guidelines to assist physicians in the care of children with special needs.

Evaluation of Effectiveness

20. Cheng, T., et al. Expectations, goals, and perceived effectiveness of child health supervision: A study of mothers in a pediatric practice. *Clin. Pediatr.* 35:129–137, 1996.
    Survey of mothers to assess expectations and goals in child health supervision and variability of demographic issues in the perception of effectiveness.

Useful Websites

21. Available at: http://www.brightfutures.org.
    Updated site with complete information on Bright Futures *guidelines.*
22. Available at: http://www.aap.org.
    American Academy of Pediatrics webpage with link to comprehensive updated policy statements.

19. PHYSICAL GROWTH

Margaret E. Mohrmann, Craig A. Alter, and Kenneth B. Roberts

The growth of a child occurs in four phases—fetal, infantile, juvenile, and adolescent—that are distinguished by differences in controlling influences, characteristic growth velocity, and factors commonly responsible for abnormal growth.

The size of an infant at birth, which correlates poorly with ultimate adult height, is affected primarily by maternal size and secondarily by other intrauterine factors such as maternal nutrition and use of tobacco and alcohol, placental adequacy, and intrauterine infection. Children who suffer a growth-retarding insult during the early fetal period of active cell division do not show “catch-up” growth in the postnatal period; growth potential is irrevocably lost. On the other hand, if growth is slowed in the third trimester, a time of cell enlargement rather than division and differentiation, later compensatory growth frequently occurs and growth potential may be realized. Those infants that will catch up usually do so within the first 6 months.

During the first 12–24 months after birth, the time of greatest postnatal growth velocity, the infant “seeks his or her own curve.” That is, by age 2–3 years, the child's stature reflects his or her own genetic endowment rather than his or her mother's size and health. Growth during the remainder of childhood occurs at a rate of 5–6 cm (2 in.) per year, along the percentile band achieved by 2–3 years. Adolescence is characterized by an abrupt, short-lived increase in growth velocity (the “growth spurt”), mediated by gonadal hormones, growth hormone–insulin-like growth factor I (IGF-I). Adult height may to some degree be predictable by the midparental height (maternal height plus paternal height, divided by two). This “target” height in centimeters can be estimated by adding 6.5 cm to the midparental height for boys and subtracting 6.5 cm from the midparental height for girls.

Differential rates of growth of various body parts result in marked changes in body proportions during childhood; the school-aged child not only is bigger than the infant, but also is quite different in appearance. Head growth, for example, a passive phenomenon reflecting growth of the brain, is rapid in early infancy but is largely completed in the first years of life. As the rest of the body continues growing, the head comprises a decreasing fraction of total body size and weight. Also, the limbs grow faster than the trunk throughout childhood; the upper segment–lower segment ratio decreases from 1.7:1 at birth to 1.0:1 at 10 years of age. This disparity in growth velocity between the limbs and the trunk may be most visible during the pubertal growth spurt. The rapid growth of the limbs often produces a gangling appearance, and the child has to wait for trunk growth to catch up in order to “grow into his arms and legs.”

Another factor contributing to the changing appearance with age is the relationship of height velocity to weight velocity. During the final trimester of gestation, weight velocity exceeds height velocity, so a full-term newborn looks fat compared to a prematurely born infant. During early childhood, the relationship is reversed, and height velocity exceeds weight velocity. This may be a source of great concern to parents who see their “fat, healthy” baby becoming “skinny,” despite reassurance from the physician that their child's height and weight are both progressing normally on the growth curve. Generally around age 5, the pattern changes to a pattern referred to as “adiposity rebound.” Weight velocity exceeds height velocity, and by age 9 or 10 children tend to look chubby again. During the adolescent growth spurt, height velocity greatly exceeds weight velocity, explaining the “loss of baby fat” at this age.

Full expression in postnatal life of an individual's genetically determined growth potential depends on the normal integration of numerous factors; thus, failure to reach that potential may be due to one of a myriad of possible causes.

Short stature in childhood and adolescence is considered to be a height that is less than the 5th percentile for age. Since 5% of the normal population will fall into this category, by definition, a “normally” short child needs to be distinguished from one who is pathologically short. This is best done by reviewing previous growth data: “normally” short children grow at a normal growth rate, albeit less than the 5th percentile, whereas most children who are short because of an underlying abnormality have decreased linear growth. The two causes of “normal” short stature are familial short stature, and constitutional delay of growth and adolescence.

Children with *familial short stature* may be either small or normal in size at birth, but by age 2 to 3 years they are below the fifth percentile in height. Thereafter, they grow at a normal growth rate to an ultimate height that is consistent with their family. Bone age is consistent with chronologic age rather than height age (i.e., the age at which the child's height is at the 50th percentile), and puberty occurs at the normal time.

Constitutional delay of growth and adolescence (the so-called “late bloomer”) is distinguished from familial short stature in that, although short stature is present in childhood, adult height potential is significantly better. Like the latter, a gradual growth deceleration is frequently observed between about 9 months and 2 to 3 years of age, followed by a normal prepubertal growth rate thereafter. However, bone age is consistent with *height* age rather than *chronologic* age, and sexual development is *delayed*, with puberty occurring at a time appropriate for the bone age. Thus, children with constitutional delay grow for a longer time before going through their pubertal growth spurt and fusing their epiphyses; this results in improved adult height. Often a history of delayed puberty is present in other family members. Children with constitutional growth delay characteristically present in adolescence at a time when the discrepancy in both height and sexual development is greater because their peers are undergoing their pubertal growth spurt. It is seen more often in males than in females, but it is not known whether this represents selection bias (i.e., due to the greater social stigma of short stature in males than in females) or a true difference in incidence.

Reassurance that normal sexual development will occur and that a normal adult height will be attained is the only therapy needed in many children. In these cases, regular follow-up is indicated to provide adequate psychological support of the patient and family, and to be sure that an underlying disorder of sexual development does not exist. In equivocal cases, serum testosterone, dehydroepiandrosterone-S (DHEA-S), and gonadotropins should be measured to distinguish adrenarche from pubarche, and to exclude primary hypogonadism (See Chap. 29, Sexual Development). In boys 14 years of age or older, however, a short course of intramuscular testosterone enanthate or cypionate to stimulate endogenous pubertal development is frequently beneficial; some physicians favor the use of anabolic androgens in children older than 10 years to allow their height to catch up to their genetic potential at an earlier age, and thus prevent the psychological trauma associated with delayed puberty and short stature in adolescence.

Children with an abnormal growth rate, who are discordantly small for their family, or who are extremely short (i.e., more than 3 standard deviations below the normal mean) should be evaluated for a possible underlying disorder. Because of the heterogeneity of causes of poor growth, the distinction as to whether the weight or height is more affected and whether the growth retardation is proportional or disproportional frequently provides valuable clues to the likelihood of various abnormalities. A detailed history, including birth history and parental heights and timing of pubarche, and a meticulous physical examination are obtained in all children; arm span and upper-lower segment ratio and a search for dysmorphic features may also be helpful. The number of teeth present may provide an approximation of skeletal maturation, but this assessment generally requires x-rays. Radiographic estimation of the bone age provides information that may be helpful not only diagnostically, but also for determining an approximate adult height prediction. Selection of other laboratory tests is directed by findings from the history and physical examination. Abnormal causes of growth retardation may be “primary” (i.e., congenital) or acquired.

Primary growth failure (formerly called “primordial dwarfism”) is found in a heterogeneous group of disorders, including placental insufficiency, the skeletal dysplasias, and many dysmorphic syndromes, with or without chromosomal abnormalities. In general, children with primary growth failure exhibit intrauterine growth retardation with low birth weight, slow growth velocity, and short adult stature. Affected children appear to have a decreased growth potential that is independent of familial influences; this may be due to a defect in the responsiveness of somatic tissues to growth-promoting factors or to an irreparable interruption of cell multiplication early in fetal life. Bone age is usually consistent with chronologic age. Babies born to mothers who smoked or ingested alcohol during pregnancy fall into this category, as do babies with chronic intrauterine infection or whose mothers had eclampsia or preeclampsia. Gonadal dysgenesis (Turner syndrome) (see Chap. 29) is an important dysmorphic syndrome that frequently is recognized because of the associated growth retardation; patients with Russell-Silver syndrome, and Noonan syndrome may

also present in this manner. If the child is short but his limbs appear disproportionate to his trunk, a skeletal dysplasia (e.g., achondroplasia or hypochondroplasia) or rickets is suggested. Growth charts specific for certain diseases (e.g., Turner syndrome, Down syndrome, achondroplasia) are available.

Acquired disorders of growth can be divided into those in which the weight is more affected than the height (i.e., a thin, short child) and those in which the reverse is true. Both caloric insufficiency and chronic systemic disorders may result in abnormal somatic growth and tend to be characterized by greater retardation in weight than height (i.e., a thin, short child). In infants, this would be termed "failure to thrive" (see Chap. 21). Pulmonary, cardiovascular, and central nervous system diseases are usually easily identified as causes of retarded growth, but gastrointestinal and renal diseases are often less obvious. Inflammatory bowel disease may present with short stature as the predominant complaint; bowel symptoms may be absent, atypical, or mild but less distressing than the growth failure. Renal tubular acidosis and renal parenchymal destruction secondary to urinary tract obstruction and infection are subtle, frequently overlooked causes of growth failure. The bone age is usually somewhat retarded in chronic systemic diseases. Provision of adequate calories and/or correction of the primary disease alone will frequently result in catch-up growth, the extent of which depends on the timing of the insult, and its severity and duration.

Unlike caloric inadequacy and chronic systemic disease, endocrine disorders are characterized by greater retardation in height than weight, the result of which is a chubby appearance. Affected children do not appear ill, and generally present because of their growth retardation or abnormal growth velocity; frequently the diagnosis is delayed because of the subtlety of the associated signs and symptoms. Although the height is more affected than the weight, these children are rarely morbidly obese; they are distinguished from children with exogenous obesity by their poor interval growth. Hypothyroidism is the most common endocrine cause of poor growth. In longstanding hypothyroidism, immature body proportions may be found (i.e., relatively large upper/lower body ratio); the bone age is significantly retarded and may even be more retarded than the height age. In contrast, in the child with growth hormone deficiency, body proportions are normal. "Doll-like" or "cupid" facies are typical and thought to be due to relative facial bone immaturity; bone age is consistent with, or somewhat more advanced than, the height age, but delayed for chronologic age. A characteristic apron of fat may be seen. A tumor of the sellar or suprasellar region (particularly a craniopharyngioma) must be excluded in all cases; other causes include cranial irradiation and birth trauma. Growth hormone deficiency may also be associated with syndromes resulting in midline brain (and facial) abnormalities, including cleft lip and palate, and septo-optic dysplasia (de Morsier syndrome). Rarely, growth failure may be due to growth hormone resistance (Laron syndrome). A profoundly disordered psychosocial environment may produce a picture indistinguishable from growth hormone deficiency ("deprivation dwarfism"); removal of the child from the abnormal environment results in dramatic catch-up growth and a normalization of previously decreased growth hormone levels. Cushing syndrome and rickets are other infrequent hormonal causes of short stature. Prematurely increased sex steroids from adrenals or gonads cause short adult stature, but in childhood rapid growth associated with an advanced bone age leading to premature epiphyseal fusion and cessation of growth are found.

Specific laboratory evaluation of the growth-retarded child depends on the clinical findings. If the weight is primarily affected, nutritional evaluation, and measurement of blood urea nitrogen, serum electrolytes, complete blood count, sedimentation rate, and urinalysis are reasonable screening procedures in the otherwise asymptomatic child; further testing is performed as appropriate. If the height is more affected than the weight, an endocrine cause (or Turner syndrome) is suspected. Serum thyrotropin (thyroid-stimulating hormone) measurement is the single most sensitive screening test for hypothyroidism. Evaluation of growth hormone adequacy is more difficult because of the pulsatile nature of growth hormone secretion. IGF-I may be used as a screening test, but is affected by age (being low in infants), and by nutritional, pubertal, and thyroid status. Measurement of IGF–binding protein 3 (IGF-BP3) has been shown to improve the diagnostic accuracy of IGF-I alone. Growth hormone deficiency is confirmed by the demonstration of a poor growth hormone response (less than 10 ng/mL) to provocative testing. Although severe growth hormone deficiency can be shown clearly by these methods, children with partial degrees of deficiency may be missed. Karyotype should be performed on all females with growth retardation of undetermined etiology to identify Turner syndrome.

The present availability of unlimited supplies of recombinant human growth hormone, as well as its efficacy and relative safety, has resulted in its use in an ever-widening spectrum of disorders. Currently, growth hormone is approved by the Food and Drug Administration as therapy for poor growth in children with growth hormone deficiency, Turner syndrome, or chronic renal insufficiency. Use of growth hormone for other children, including those with familial short stature, remains controversial.

Normal Growth

1. Pomerance, H. Growth and its assessment. *Adv. Pediatr.* 42:545–574, 1995. (Available at www.cdc.gov/growthcharts.)
   An extensive review of measurements and growth charts. For a background review of growth assessment, see Adv. Pediatr. *42:545–574, 2000.*
2. Smith, D., et al. Shifting linear growth during infancy: Illustration of genetic factors in growth from fetal life through infancy. *J. Pediatr.* 89:225–230, 1976.
   Describes the growth patterns of infants "seeking their own curve." (See also Pediatrics *62:529–534, 1978; for description of characteristic growth deceleration in first few years of life in many children with constitutional short stature.)*
3. Gluckman, P. Fetal growth: An endocrine perspective. *Acta Paediatr. Scand.* 349(Suppl.):21–25, 1989.
   Fetal growth is constrained largely by uteroplacental function and substrate availability; hormonal mediation of growth is different in utero as well.

Abnormal Growth: Reviews

4. Vogiatzi, M., and Copeland, K. The short child. *Pediatr. Rev.* 19:92–99, 1998.
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5. Rimoin, D., and Graham, J. Syndromes associated with growth deficiency. *Acta Paediatr. Scand.* 349(Suppl.):3–10, 1989.
   Comprehensive review of dysmorphic and chromosomal syndromes associated with proportionate and disproportionate growth retardation, and of disorders associated with hypopituitarism.
6. Botero, D., and Lifshitz, F. Intrauterine growth retardation and long-term effects on growth. *Curr. Opin. Pediatr.* 11:340–347, 1999.
   A good discussion of advances in understanding fetal growth factors and causes of intrauterine growth retardation, as well as the long-term growth disabilities and trials of human chorionic gonadotropin therapy.

Systemic Disease

7. Underwood, L. Growth retardation in chronic diseases: Possible mechanisms. *Acta Paediatr.* 88(Suppl. 428):93–96, 1999.
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8. Rosenthal, S., et al. Growth failure and inflammatory bowel disease: Approach to treatment of a complicated adolescent problem. *Pediatrics* 72:481–490, 1983.
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9. Chan J. Renal tubular acidosis. *J. Pediatr.* 102:327–340, 1983.
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10. Allen, D. Growth suppression by glucocorticoid therapy. *Endocrinol. Metab. Clin. North Am.* 25:699–717, 1996.
    Not only a review of the growth-suppressing effects of glucocorticoids, but also a consideration of growth hormone therapy in steroid-dependent children. (For more on the effects of inhaled corticosteroids, see Eur. Resp. J. *11:1167–1177, 1998.)*
11. Lewis, D. What was wrong with Tiny Tim? *Am. J. Dis. Child.* 146:1403–1407, 1992.
    The author uses the clues from Dickens' prose to discuss what might have caused short stature, crippling, and weakness that would have led to death in 1 year if untreated. The reader gets to "play along."

Hormonal Effects on Growth

12. Hintz, R. The role of auxologic and growth factor measurements in the diagnosis of growth hormone deficiency. *Pediatrics* 102:524–526, 1998.
    A review of the difficulties in establishing the diagnosis of growth hormone deficiency.
13. Cohen, P., and Rosenfeld, R. Physiologic and clinical relevance of the insulin-like growth factor binding proteins. *Curr. Opin. Pediatr.* 6:462–467, 1994.
    In addition to decreased insulin-like growth factor (IGF) I (somatomedin C), IGF–blood protein 3 levels are low in growth hormone deficiency.
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15. Lee P., and Witchel, S. The influence of estrogen on growth. *Curr. Opin. Pediatr.* 9:431–436, 1997.
    Estrogen appears to be necessary for normal skeletal growth and maturity.

Deprivation Dwarfism

16. Powell, G., Brasel, J., and Blizzard, R. Emotional deprivation and growth retardation simulating idiopathic hypopituitarism. *N. Engl. J. Med.* 276:1271–1278, 1967; and *N. Engl. J. Med.* 276:1279–1283, 1967.
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Tall Stature

17. Alpert, B. Tall stature. *Pediatr. Rev.* 19:303–305, 1998.
    The focus is on Marfan syndrome, but a table lists other disorders associated with tall stature.
18. American Academy of Pediatrics Committee on Genetics. Health supervision for children with Marfan syndrome. *Pediatrics* 5:978–982, 1996.

Reviews the criteria for diagnosis as well as what the title promises.

Psychosocial Aspects of Short Stature

19. Gordon, M., et al. Psychosocial aspects of constitutional short stature: Social competence, behavior problems, self-esteem, and family functioning. *J. Pediatr.* 101: 477–480, 1982.
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20. Lee, P., and Rosenfeld, R. Psychosocial correlates of short stature and delayed puberty. *Pediatr. Clin. North Am.* 34:851–863, 1987.
Review of literature with regard to psychosocial problems that should be taken into account when considering therapeutic intervention.

Growth Hormone Therapy

21. Hintz, R., et al. Effect of growth hormone treatment on adult height of children with idiopathic short stature. Genentech Collaborative Group. *N. Engl. J. Med.* 340:502–507, 1999.
Final height was increased by approximately 5–6 cm after 2–10 years of therapy—with enormous variability in response. (For the effect of growth hormone in growth hormone–deficient children, see Acta Paediatr. *88[Suppl. 428]:70–71, 1999.*
22. Vance, M., and Mauras, N. Growth hormone therapy in adults and children. *N. Engl. J. Med.* 341:1206–1216, 1999.
An overview, with more on treatment of adults than most reviews. (For "considerations for the practicing pediatrician"—with 177 references—see Curr. Probl. Pediatr. *27:14–40, 1997. A summary of 4 decades' worth of experience internationally:* J. Clin. Endocrinol. Metab. *84:4307–4316, 1999.)*
23. American Academy of Pediatrics Committee on Drugs, and Committee on Bioethics. Considerations related to the use of recombinant human growth hormone in children. *Pediatrics* 99:122–129, 1997.
Not only discusses indications and "off-label" use, but discusses the ethics as well: Is short stature a "disease" or a "disability"? For more on the ethics, see J. Pediatr. *117:16–21, 1990.*
24. Lyon, A., et al. Growth curve for girls with Turner syndrome. *Arch. Dis. Child.* 60:932–935, 1985.
The situation changes with growth hormone therapy; however, see J. Pediatr. *132:319–324, 1998.*
25. Blethen, S. Complications of growth hormone therapy in children. *Curr. Opin. Pediatr.* 7:466–471, 1995.
No such thing as a free lunch. Pseudotumor cerebri, slipped capital femoral epiphysis, leukemia, and nevi are discussed; hypothyroidism also occurs occasionally, but is not mentioned.

20. INFANT FEEDING AND NUTRITION

E. Kaye Gable

Nutrition is essential for normal growth and development. Research demonstrates a relationship between early childhood nutrition and learning ability, work performance, and the possible development of adult diseases such as hypertension, osteoporosis, and cardiovascular disease. Although primary protein-energy malnutrition is uncommon in developed countries, undernutrition occurs. Thus, careful attention to the nutritional needs of children throughout life, but especially during the first year of life when brain growth is rapid, is necessary to permit children to develop to their full potential. For infants at nutritional risk, the federally funded program Women, Infants, and Children (WIC) provides formula at no cost throughout the United States.

Caloric requirements for newborns are approximately 90–100 cal/kg/d. These calories are necessary to meet the normal energy needs for basal metabolism, growth, and activity. Research over the past decade has shown that breast-fed infants consume about 7–10% fewer calories than their formula fed peers. Between 3 and 9 months of age, all infants consume 10% fewer calories than in the first 3 months, or between 9 and 12 months of age. Energy expenditure is lower in breast-fed infants than in formula-fed infants, but the reasons remain unclear. The protein requirement for a term newborn is 2.2 g/kg/d and decreases to 1.6 g/kg/d during the second 6 months of life. Premature infants have higher caloric requirements, 120–150 cal/kg/d. These high requirements are necessary to attain growth equivalent to intrauterine growth in the face of an immature gastrointestinal tract. The protein requirement for premature infants is 2.5–4.0 g/kg/d, which is necessary to promote synthesis of body tissue and postnatal growth. Even after hospital discharge, premature infants may require high caloric and protein intakes to achieve optimal growth and develop normally.

To approximate the composition of human milk, the diet of infants should contain 40–60% of total calories from carbohydrate, 7–11% of total calories from protein, and 40–55% of total calories from fat. Commercial formulas based on cow's milk or soy protein contain this distribution of calories. Fat and cholesterol should not be restricted in infancy. This is in contrast to children older than age 2, who should have approximately 30% of total calories as fat.

Breast-feeding is the optimal form of nutrition for infants. Human milk is the standard by which all other forms of alternative feeding methods should be measured in regard to growth, health, and development. The only contraindications to breast-feeding are (1) galactosemia in an infant, (2) maternal human immunodeficiency virus, (3) maternal consumption of drugs that can be found in human milk, and (4) breast cancer in the mother. The incidence of breast-feeding increased from 25% in the early 1970s to about 60% by the mid-1980s. Currently, about 60% of infants leave the hospital either fully or partially breast-fed. Increasing the rates of breast-feeding is a national health objective and one of the goals of Healthy People 2000. The target is 75% of infants breast-feeding in the immediate postpartum period and at least 50% still breast-feeding at 6 months. Advantages of breast-feeding include nutritional and immunologic benefits, and decreased incidence of respiratory infections, otitis media, and gastrointestinal infections. There are also economic benefits for the family, since the additional calories needed for lactating women cost less than infant formulas needed to sustain infants. In addition, breast-fed infants have fewer health care expenditures in the first year of life. Some supplementation may be necessary for breast-fed infants. For example, infants of vegetarian mothers (vegans), who eat no animal products, may require supplementation with vitamin B_{12}, 0.3–0.5 µg/d. Additional vitamin D, at 400 IU/d, may be necessary if there is little sun exposure. The vitamin D content of human milk is low (22 IU/L). Fluoride supplementation for breast-fed infants remains controversial. Fluoride is not present in human milk and is recommended when drinking water is not fluoridated. Most importantly, successful breast-feeding is dependent on postpartum support and follow-up.

The alternative to breast milk is commercially prepared infant formula. Based on the protein content of infant formulas, there are three main groups: cow milk protein, soy protein, and hydrolyzed casein protein. There are many other specialized formulas available, such as amino acid–based formulas and formulas made specifically for certain inborn errors of metabolism. Cow milk formula is the most common human milk substitute. Cow milk formulas contain whey and casein as protein, with added taurine to simulate the amino acid composition of breast milk. Vegetable oils supply fat, and the carbohydrate source is lactose. Lactose-free cow milk protein formula is available. This formula also contains vegetable oil as the fat source. Lactose-free cow milk formula may be used for infants with lactose or sucrose intolerance. Primary congenital lactase deficiency is extremely rare. Secondary lactase deficiency may result from any injury to the gastrointestinal mucosa, such as might occur with prolonged diarrhea. After gastrointestinal injury, a lactose-free milk-based or soy formula may be used short term until the small intestine regenerates lactase. Acute self-limited diarrheal disease in infants does not require a change to lactose-free formula. Soy formulas are lactose free and contain methionine-fortified soy protein isolate and vegetable oils. Soy protein–based formulas are used for infants with galactosemia, and lactose intolerance. There are also infants who appear to be sensitive to cow milk protein who do well on soy formula; however, 30–40% of infants who are allergic to cow milk are also allergic to soy protein. Protein hydrolysate formulas contain hydrolyzed casein. These formulas are recommended for infants allergic to intact cow milk protein and soy protein. The sources of carbohydrate and fat vary among products and should be evaluated when used for purposes other than protein allergy or sensitivity.

Vitamin and mineral supplementation are not needed in healthy full-term infants fed commercially prepared formula. Only iron-sufficient (“iron-fortified”) formula should be fed to infants, unless they have a hematologic disease for which repeated transfusions are necessary.

Introduction of solid foods is recommended at approximately 4–6 months of age when infants develop hand-eye coordination and the extrusion reflex disappears. The first solid foods should include iron-fortified infant cereal mixed with breast milk or iron-fortified infant formula, or juices. Initially, new baby foods should be added one at a time so signs of intolerance (skin rashes, diarrhea, or wheezing) can be associated with the offending food.

The introduction of cow milk is not recommended before 12 months of age. Whole cow milk contains a high concentration of protein, minerals, and electrolytes, and little iron. Low-fat cow milk should not be offered to children under age 2 years because of low caloric content, inadequate fat, and high protein, mineral, and electrolyte content, which leads to an increased renal solute load. Additionally, low-fat milk contains inadequate fat-soluble vitamins to meet the requirements of infants. Honey is sometimes given to infants. Since honey may contain botulinum spores, it is not recommended for infants.

Allergy to cow milk is difficult to precisely define. Consequently, the literature contains conflicting terminology. The incidence of true cow milk protein allergy is 1–5%. Perhaps an additional 3–5 % of infants are cow milk sensitive. Symptoms attributable to cow milk sensitivity include skin rashes, recurrent upper respiratory infections and otitis media. Anaphylaxis to cow milk protein can occur.

Several distinct patterns of gastrointestinal disorders may result from ingestion of milk protein. One is allergic colitis, which typically presents in a 1- to 2-month-old infant, with small volume, streaky bright red rectal bleeding associated with loose mucoid stool. Weight loss and other constitutional symptoms are not common. Allergic colitis can occur in infants fed soy, cow milk formula, or even breast milk. Treatment is removal of the offending antigen in either the infant's or mother's diet. A second pattern, milk protein enteropathy, presents with symptoms of malabsorption and growth failure, usually in the first month of life. Endoscopic biopsies show villus injury and in most cases a flat mucosa. Due to the degree of mucosal injury, a hydrolyzed-casein formula is recommended for infants with milk protein enteropathy. Rarely, use of an amino acid–based formula is required. The prognosis for remission is excellent, with less than 1% of affected infants maintaining a lifelong intolerance. Milk-based products may be reintroduced in the diet between 12 and 24 months with close supervision.

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21. FAILURE TO THRIVE

Pamela J. Reitnauer

Failure to thrive (FTT) can be defined as the inability to achieve or maintain an expected rate of weight gain over time. Failure to thrive is a dynamic process and its definition is based on the pattern of growth rather than size. Failure to thrive is a confusing term, often applied indiscriminately to infants who are small for their age. For the term to be useful, there needs to be a distinction between children who are “normally” small, i.e., those who have short stature (see Chap. 19), and those who are not gaining weight at a rate in accordance with their genetic potential and their linear growth. This last group is characterized by a low weight-for-length and a decreasing weight percentile on standard growth curves, and is the group to whom the label “failure to thrive” should be applied.

In the past, the causes of FTT have typically been divided into two categories: “organic” (caused by medical conditions) and “nonorganic” (nonmedical). It is now more useful to conceptualize FTT as the end result of multiple interacting risk factors that may be biological or environmental. While there are many possible causes for FTT, the common pathway is insufficient calories to meet metabolic needs.

The psychoemotional interaction between the child and the caregiver can be a significant factor that affects the growth pattern. Problems may include maternal depression, other maternal affective disorder, or reasons related to family dynamics that affect interpretation of the child's needs. Some children with FTT may exhibit behavior and/or affective disturbances. Other aspects of the child such as prematurity or a birth defect may influence interpretation of the child's physical needs.

There are a large number of conditions that can affect a child's appetite or functional state, such as chronic infection, gastrointestinal disorders, neurologic disorders, and endocrinologic or metabolic conditions. Chronic illnesses that increase metabolic rate (e.g., congenital heart disease) have implications for the nutritional state. Malabsorption as observed with cystic fibrosis or celiac disease influences the ability to adequately achieve nutritional balance. The high incidence of gastroesophageal reflux in infants (see Chap. 68) should warrant that this disorder be considered in a young child being evaluated for poor weight gain. Gastroesophageal reflux is associated with a diminished ability to retain calories and may be a particularly significant issue for children with neurological impairment who also have a decreased ability to consume calories.

Many times, the physician is the first to recognize the poor growth pattern for a child. The history is the most important aspect of the evaluation. In the outpatient setting, the practitioner can obtain important preliminary information, for example, (a) ask how formula is made, (b) watch a feeding, (c) ask about tumult in the home, and (d) try to get a sense of maternal depression as a contributing factor. Information should be collected about prenatal and perinatal history. The family history should include parental and sibling heights and weights, as well as chronic and acute disease histories. The behavioral (including feeding behavior) history and cultural background can be extremely helpful. The most accurate growth data available are necessary, which include birth measurements and any consecutive weight and linear growth values. The review of systems should be complete, and the physical examination should be comprehensive and include assessment of body fat distribution, dysmorphic features, height, weight, and head circumference. Recumbent length is determined for children younger than 2 years and standing height after age 2. The growth information should be plotted on standard growth charts, adjusting for prematurity during the first year of life. Commonly used anthropometric indices are derived from the National Center for Health Statistics (NCHS) age-and gender-specific growth charts. The majority of infants who are failing to thrive have a normal head circumference and weight reduced out of proportion to height. As malnutrition progresses, length/height is affected as well as weight; head circumference is affected last. A small head circumference with low weight for height may indicate a central nervous system defect or intrauterine growth retardation.

If an infant is fed only formula, one can calculate the caloric intake quite easily, based on volume consumed (regular formula has a caloric density of 20 calories per ounce). Expertise of a nutritionist may be necessary to help assess the daily type and quantity of food intake (especially in an older child), and to estimate as accurately as possible the caloric intake per unit weight per day. If the child is breast-fed, the expertise of a lactation consultant is warranted to assist the physician in the assessment of milk production, maternal perceptions, and related factors.

Laboratory evaluations will depend on the information collected. There is no routine panel of tests that significantly helps determine a diagnosis, and generally only a small proportion of laboratory tests may provide diagnostic assistance, such as urine pH, urine culture, hemoglobin (or hematocrit), and serum bicarbonate. If for example, diarrhea is a clinical feature, stool studies may include tests for the presence of leukocytes, occult blood, or reducing substances, and cultures for bacteria and parasites. Other investigations may include upper gastrointestinal swallowing fluoroscopy or a 24-hour pH probe. Sweat chloride determination may be warranted if cystic fibrosis is in the differential diagnosis. Developmental testing such as the use of the Bayley Scales of Infant Development should be considered.

Outpatient evaluation and management may be sufficient for some infants and toddlers. Serious malnutrition (60% below ideal body weight) warrants hospitalization. Hospitalization may also be necessary to help observe behavior and monitor caloric intake along with coordination of the multidisciplinary assessment and support of the child, especially with failure of outpatient approaches.

Treatment can be directed toward appropriate feeding, parental education, and nutrient supplements as needed. Caloric requirements must be sufficient to promote catch-up growth. Increases in energy intake can be achieved by a) increasing the number of meals, b) increasing the volume of meals, and c) increasing the caloric density of meals. The balance of nutrients is also important. Suggestions for increasing the caloric density in a formula fed infant's diet include increasing the caloric density of formula from 20 kcal/oz to 24 kcal/oz. Older children can be given higher-calorie foods, and the use of whole milk is encouraged in place of juices. Occasionally, complete or supplemental gavage feeding is necessary if oral intake is not adequate. Failure of optimal caloric intake in a monitored setting may be a clue to a medical cause of growth failure. If gastroesophageal reflux has been diagnosed, medical intervention may include combined or single therapy with prokinetic agents and acid blockade. Child protective services and/or child advocacy representatives may need to be involved with the child and caregivers to help maintain treatment programs and to encourage continuity and stability.

Early recognition and treatment of FTT is essential. The effect of early malnutrition on later intellectual function is controversial, but available evidence suggests that children with early undernutrition have eventual reduced weight and height measurements, and somewhat impaired cognitive abilities compared to matched controls.

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22. OBESITY

Kenneth B. Roberts

Childhood obesity has garnered increased attention and concern recently. Excessive weight is the most prevalent nutritional “problem” in childhood, and is referred to now as a disease and a significant public health problem. One of the reasons for this increased attention is the demonstration of increasing “fatness” of the population, both adults and children, in the three serial National Health and Nutrition Examination Surveys (NHANES) conducted approximately every 10 years. The most recent survey (1990) identified 22% of children to be overweight and 14% to be obese, a marked increase since the previous surveys. Certain subgroups were recognized to have even higher rates: of African-American adolescent girls, 25% were obese.

In addition to the increasing prevalence of overweight and obesity, there is also more evidence of morbidity from childhood obesity. In the past, concern was based on the morbidity associated with adulthood obesity (e.g., cardiovascular disease and diabetes) and on the premise that the obese child was likely to become an obese adult. There are now data to demonstrate that obesity in adolescence confers additional morbidity (and, in men, mortality) that is independent of whether the teenager remains obese in adulthood (although it is also true that most obese adolescents do remain obese as adults). Obesity-associated complications such as hepatic steatosis, pseudotumor cerebri, slipped capital femoral epiphysis, and sleep apnea remain uncommon, but the incidence of non–insulin-dependent (type II) diabetes mellitus in childhood is increasing. There is a heavy psychological burden associated with obesity, undoubtedly made worse by the common belief that obesity is under voluntary control, and reflects laziness, self-indulgence, and lack of motivation to control one's appetite. In our current culture, obesity is not fashionable, and obese individuals are generally considered unattractive by both children and adults. Fewer obese individuals marry than do nonobese individuals. There are additional consequences of the social stigma, particularly for adult women, such as less income than their nonobese counterparts and a higher rate of living in poverty.

Even if obesity were a problem only in adults, the uniform futility of treatment to take weight off and keep it off would generate attention to children and to the desire to prevent obesity. Additional support for early prevention activities is generated by the concept that there are three “critical periods” for the development of obesity: during gestation; at 5–7 years; and during adolescence. The intrauterine environment may be amenable to control with attentive prenatal care. After birth, length velocity normally exceeds weight velocity until the early school years, leading parents to complain that their children are “getting skinnier” despite remaining at the 50th percentile. The parents' observations are accurate: the percentage of body fat in a 1-year-old is 22% compared to 12.5–15.0% at age 5 years. From around 5 years of age until adolescence, weight velocity exceeds height velocity (“adiposity rebound”), culminating in the familiar chubby appearance in early adolescence (“baby fat”). Evidence is mounting that the earlier adiposity rebound begins, the more likely the child is to become overweight or obese. Add to this the recent demonstrations that energy expenditure patterns from physical exercise appear to be stable between ages 3 and 5 years, and it appears that prevention needs to begin at a very young age. Adolescence is the third “critical period,” and it is a very important one, particularly since adolescents who are obese or become obese are very likely to remain that way for the remainder of their lives. The adolescent growth spurt appears to be the last opportunity for overweight/obese children to “grow into” their bodies and avoid a lifetime of weight-related problems.

Some individuals clearly have a genetic predisposition for obesity. For example, studies suggest that adult weight status of adopted children correlates more strongly with the biologic parents than with the adoptive parents. Twin studies show double the concordance rate for overweight among monozygotic compared to dizygotic twins, independent of whether they were reared apart or together. However, the secular trend toward increasing obesity suggests that the major cause of obesity is unlikely to be genetic, since genes mutate over generations, not over a few decades. Apparently, our genetic endowment includes certain presumptions regarding energy balance, such as the expectation that we will be more active than is the case with our increasingly sedentary lifestyle, and that food will only be available intermittently. As a result, we are very efficient at storing energy from foods such as fats. This efficiency probably served a valuable protective function, but now, with energy-rich foods abundant, we are vulnerable to take in more calories than we expend. Once fat is deposited, homeostatic mechanisms make it very difficult to eliminate. The search for biologic mediators that participate in this process have identified a number of proteins, including leptin. At present, it is not clear whether any of these will be amenable to manipulation to prevent or treat obesity, except in rare conditions such as hypothalamic obesity.

Children with obese parents are at particular risk of overweight/obesity. If both parents are obese, the chance of developing adult obesity is more than doubled for both lean and overweight children younger than 10 years of age. While there may be a genetic component to the increased risk, environment is a major—and more controllable—factor: parents select, purchase, and cook the meals for young and school-aged children, and they set the example.

The first step in management is the identification of which child is overweight/obese or at risk. Attempts to make this determination have included various qualitative (i.e., looking at the child or eliciting a self-image) and quantitative measures (e.g., weight percentile for age and height). Rapidly replacing weight-for-height as the preferred method is the body mass index (BMI), the mathematical expression of the weight (kg) divided by the square of the height (m^2): BMI = kg/m^2. The major advantage of the BMI is that it correlates (in adults) with health risk. Tables and growth curves are now available to assess BMI throughout childhood. Overweight is defined as a BMI in excess of the 85th percentile for age; obesity is a BMI exceeding the 95th percentile for age. One caveat is that while BMI generally correlates well with body fatness, it may still mislabel mesomorphic individuals as overweight, even though their percentage of body fat may be normal or, in the case of elite athletes, even low.

The overweight or obese child's height is an important measurement, not only because it permits calculation of the BMI, but also because it helps direct the evaluation for an underlying cause. Most obese children have accelerated linear growth that parallels their weight gain. Further assessment of the obese child is indicated if height is less than the 50th percentile for age or if the child is developmentally delayed. Hypothyroidism should be considered if the rate of linear growth has been slow while weight increased. If the child is of short stature and is hypertensive, Cushing syndrome should be considered. If the obese child is both short and mentally slow, the Prader-Willi and Laurence-Moon-Biedl syndromes are possibilities. Serum cholesterol and triglyceride levels should be obtained in children whose families have a strong history of cardiovascular disease. Children with symptoms of diabetes mellitus should have a random glucose determination when seen; a timed postprandial test can be scheduled if questions persist. Other screening laboratory tests are unnecessary without specific indication.

The usual recommendation for treatment has been “diet and exercise,” which, though simple to advise, is difficult to follow long-term, and failure to succeed in weight loss begets additional failure. Current emphasis is on “prudent diet” and on decreasing inactivity, rather than undertaking strenuous exercise. Limiting television viewing not only decreases inactivity, but also reduces a major source of habitual snacking. Children and their parents need to be reminded that overweight and obesity develop over a long period and cannot resolve rapidly. Any “program” needs to be based on long-term changes and slow, steady weight loss, without interference with linear growth. It is especially important prior to adolescence to involve the parents, particularly if one or both are obese. The emphasis is on changing family habits, not just the habits of the obese child.

This is a time of calorie-dense fast foods and increasing portion size in restaurants. The increasing “fatness” demonstrated in NHANES reflects a society-wide trend. Although there has never been a time with more alternatives to high-fat, high-calorie foods, we appear to be devouring these and everything else in greater quantities and utilizing the resultant energy less. The overweight/obese child takes the brunt of “the fattening of America.”

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23. DEVELOPMENT AND DEVELOPMENTAL DISABILITIES

Kenneth B. Roberts

“Growing up” involves three major dynamic processes: growth (see Chap. 19), development, and sexual maturation (see Chap. 29). Development refers to the progressive acquisition of skills and abilities in the multiple spheres of functioning: motor (both gross motor and fine motor); communication/language (receptive, expressive, articulation); cognitive; and social-adaptive. Four general principles apply: (1) Development is orderly and cumulative. One milestone necessarily follows another in a regular, predictable fashion. As examples, motor development proceeds according to neurologic maturation, from head to foot (cephalocaudal progression); language begins with cooing, then progresses to babbling, words, “jargoning” (the inflection of speech without recognizable speech), phrases, sentences, and so forth; and cognitive development advances in identifiable stages: sensorimotor, preconceptual, intuitive, concrete operations, and formal operations. (2) Development is progressive. The rate at which development occurs varies from imperceptible to rapid, and the rate is not the same for all spheres, but the direction is constant. There may be temporary setbacks along the way (regressive behavior), but a continued loss of previously attained milestones is abnormal and requires attention. (3) Development in one sphere does not serve as a valid proxy for development in other spheres. For example, most cognitively impaired children have normal motor function. An impairment in one sphere may make it difficult to assess abilities in another sphere (e.g., assessing language ability in a child with severe cerebral palsy), but compromised testing should not be accepted as evidence that an ability is absent. (4) Development is affected by many factors in addition to genetic potential and neurologic maturation, including overall physical condition, nutritional state, and environmental and emotional forces. The interplay of factors is complex, and each child's uniqueness is preserved despite the apparent stereotyped nature of development; indeed, few children are “average” in all spheres at all times.

Pediatricians need to be able to assess a child's level of functioning in all of the various spheres, and to be able to put the assessment in context to portray accurately the child's true capacity, strengths, weaknesses, and needs. Parents, school systems, and government programs look to the pediatrician for guidance. As resources are developed to aid children with developmental problems, there is increased pressure—and reason—to identify children with “developmental disabilities.” Knowledge of normal developmental tasks and behavior patterns not only is necessary for assessment, but also permits guidance to be consistent with reasonable expectations.

“Developmental screening,” using tests such as the Denver Developmental Screening Test (DDST) that are validated on populations of children, has given way to “developmental surveillance,” an ongoing process based on input from multiple sources (particularly parents) and detailed longitudinal observations; screening tests such as the DDST may or may not be included. Assessment begins with the history, utilizing provocative open-ended questions to ascertain the temperament and personality of the child and immediate family members, as well as to identify concerns parents may have. Previsit questionnaires are particularly useful for soliciting concerns and helping to focus the agenda of the visit; these questionnaires convey the interest of the pediatrician in developmental issues, and may encourage parents to express concerns that might otherwise not be raised. When eliciting history, not only should the presence of “risk factors” (e.g., neonatal asphyxia, family history of developmentally delayed children) be identified, but strengths and “protective factors” (e.g., strong family support systems) should also be sought. A timetable of milestones attained should be constructed. Parental ability to chronicle development is generally quite good, although understandably better for recent events than for more distant ones. Nevertheless, it is important to document abilities by direct examination as part of developmental surveillance. The physical examination also includes identification of all major and minor abnormalities to detect the presence of a known syndrome (see Chap. 83). Office testing may be performed; the DDST, for example, identifies abilities at each age, with the important visual reminder that there is variation in the ages at which the abilities are attained. Sequential monitoring permits an assessment of the velocity at which abilities are being attained. If a problem is suggested by the history, the examination, or screening tests, more formal testing by a professional comfortable with children and experienced with tests such as the Cattell or Bayley Scales for infants and the Wechsler Scales for older children may be required.

Delays are commonly quantitated by noting the child's “developmental age” (the age at which children who are not delayed would have the same capabilities). Dividing the developmental age by the child's chronologic age and multiplying by 100 yields the “developmental quotient” or DQ. (During their first year of life, infants born prematurely should have their chronologic age adjusted for the degree of prematurity before calculating the DQ.) Such calculations should be made for each sphere of development to determine the extent of delay and whether there is a recognizable pattern.

If a developmental delay is detected, further evaluation has four goals: to identify etiology; to characterize limitations; to identify strengths and capabilities upon which habilitation can be built; and to develop a management plan. Identifying an etiology is complex and not always possible. The approach does not begin with screening laboratory tests but with further characterization. The first step is to consider the delay in the context of other findings from the history and physical examination. Is it an isolated delay in an otherwise normal child, and, if so, might the delay actually be within normal limits? If it is an isolated delay, might it indicate a specific disorder that would benefit from early identification and treatment? As examples, isolated delay in language demands assessment of the child's hearing (though it should also be remembered that the most common cause of what *appears to be* isolated language delay is mental retardation, not deafness). Isolated impairment of gross motor development, with other spheres being normal, may represent cerebral palsy (see Chap. 87) or, less commonly, skeletal or neuromuscular disease. Impairment of fine motor development generally suggests a problem of extrapyramidal function but might indicate poor vision.

If the delay is not isolated, is the pattern comparable across all spheres of development? Severe global delay (e.g., DQ below 50) warrants a search for genetic syndromes and chromosomal abnormalities (such as Down syndrome, or fragile X syndrome) (see Chap. 83). As a generalization, loss of milestones and decline in DQ over time suggests a progressive neurodegenerative disorder and possible metabolic error requiring specific testing (see Chap. 82), while a static encephalopathy, with below normal DQ that is stable over time, is more likely due to a structural abnormality and prompts neuroimaging.

Children who have severe cognitive delays are identifiable earlier than those who have mild delays. Early on, the best predictor of later intelligence is the rate of language development. At school entry, children whose ages may vary by 1 year are grouped together (e.g., 5-year-olds and nearly 6-year-olds). The 6-year-old performing at the level of the 5-year-old may be somewhat delayed (DQ 83) but does not “stick out” in class. Three years later, however, the same child with a DQ of 83 may no longer be able to keep up cognitively with classmates as he is more than one grade level behind. While cognitive development may have been “within normal limits” until then, the cognitive delay becomes apparent, and the question of mental retardation is raised. The definition of mental retardation established by the American Association on Mental Retardation (AAMR) requires the demonstration of impaired cognitive ability plus limitations in two or more of the following areas: adaptive skills; communication; self-care; home living; social skills; community use; self-direction; health and safety; functional academics; leisure; and work. Such a definition emphasizes impairment of function, with implications for habilitation, rather than focusing solely on the results of a formal intelligence test. (If all persons who score more than two standard deviations below the mean on a standard IQ test were considered retarded, the prevalence of mental retardation would be 2.5%; using the AAMR definition, the prevalence is more like 1%.) Individuals with mild retardation have IQ scores in the 50–70 range, are likely to have other family members in this range, and tend to be of lower socioeconomic status. Those with moderate or severe retardation have IQ scores below 50 and are evenly distributed among socioeconomic groups. As noted above regarding DQ, identifiable genetic disorders (e.g., Down syndrome) are more likely in the lower range of IQ.

Once delays are identified and the evaluation is completed, the physician's role is to support the child and family and to help maximize the child's abilities. The process begins with confirming the parents' concerns, or, for parents who have not expressed concerns, establishing that a developmental disability is present. Such information must be presented sensitively, with the expectation that a grief reaction (including denial, anger, and guilt) is likely (see Chap. 34). The information provided is incomplete until a focus is established on the child's potential capabilities and the availability of local resources. The pediatrician should identify the office as the child's medical home, pledging to coordinate care as consultation of specialists, services of therapists, and involvement of various agencies are required. The pediatrician must have knowledge of specific local regulations and available resources as well. Federal legislation mandates that each child who has a disability that interferes with learning must have a written plan of service: An Individual Family Service Plan for infants and toddlers birth through 3 years, an Individual Education Plan for children aged 3 through 21 years, and a Transitional Services Outcome Plan for 16-year-olds. Nevertheless, there is local variability, and advocacy is often

required to access all of the services to which the child with a developmental disability is entitled.

It is the nature of pediatricians to be reassuring, but development represents an area in which it is particularly important not to dismiss parental concerns prematurely or to be swayed by one's own denial. Concerns must be taken seriously, and developmental surveillance must be a major ongoing activity. The trap of “premature reassurance” is most likely when children are particularly “cute,” sociable, alert, and have normal motor ability. Rather than accepting excuses for delays (e.g., “He doesn't speak because his older siblings speak for him.”), pediatricians must assure themselves and the parents that development is proceeding appropriately. Children with developmental disabilities and their families require and deserve support and advocacy.

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24. ATTENTION DEFICIT HYPERACTIVITY DISORDER

Marian F. Earls

Attention deficit hyperactivity disorder (ADHD) is a neurophysiological disorder typically characterized by the central features of inattention, impulsivity, and hyperactivity. Beyond this simplistic description of ADHD, it may be better understood as a disorder of processing and production controls, mediated by frontal lobes, brain stem, and temporal lobes. As such, ADHD has potential major impact on cognitive/academic performance, behavioral characteristics, and social interaction.

The American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV) subdivides ADHD into three categories: (1) predominantly inattentive type, (2) predominantly hyperactive-impulsive type, and (3) combined type. This subdivision is reflective of the fact that children with ADHD have these characteristics to varying degrees and do not all have the same profile. This is especially true of adolescents who may be much less obviously hyperactive, but easily bored, impulsive in their work style, and disorganized. They often also have a defensive posture about their difficulties.

Children with ADHD have poor mental energy control. That is, they show inconsistency in alertness and performance and easy mental fatigue. Processing control (selective attention) is also weak, leading to poor maintenance of focus, poor saliency determination, superficial processing with poor retention, and insatiability (the need for high interest/novelty in order to focus). Problems with production control include poor previewing, inhibition, pacing and self-monitoring. Common associated problems include difficulty with memory, especially active working memory, and qualitative fine motor differences.

Examples of resulting behaviors are: failure to give close attention to details, or frequent careless mistakes; difficulty sustaining attention on tasks or play activities; poor listening; poor follow-through on instructions, and failure to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand); fidgeting with hands or feet, or squirming in the seat; leaving the seat in the classroom or in other situations in which remaining seated is expected (in adolescents or adults this may be limited to subjective feelings of restlessness); blurting out answers or interrupting; and difficulty waiting in line or waiting for a turn.

The disorder is common; prevalence is estimated at 3–10% of schoolchildren. It is not limited to children of any particular social class. At all ages, boys are affected far more commonly than girls are. Family, twin, adoption, segregation analysis, and molecular genetic studies show that it has a substantial genetic component. Severity depends on how many symptoms are present, and how significant and pervasive the impairment in functioning is.

The differential diagnosis includes such disparate conditions as normal behavior, mental retardation, severe emotional disturbance, vision or hearing deficit, hyperthyroidism, other metabolic disorders (e.g., lead intoxication, hypoglycemia), and neurologic disorders. Children with language disorders often present with secondary attentional and behavioral problems (due to frustration/misunderstanding). An accurate diagnosis is of obvious importance, as the treatment for each of these conditions is different.

The goal in obtaining medical history is to distinguish the various disorders and to assess the degree of disability. The developmental history and educational history are of great importance and should include a description of characteristic behavior at various ages, and a record of achievements and educational attainments. The social and environmental history focuses on such factors as patterns of discipline, reactions to the child's behavior, and peer relationships.

The history commonly is that the child was “colicky” as an infant, had difficulty falling (or staying) asleep, or was generally irritable. The hyperactive preschool child may be described as “clumsy,” “into everything,” and “difficult to discipline.” Temper tantrums, easy frustration, and a short attention span are characteristic of the elementary school– aged child. During adolescence, there is often improvement in the motor symptoms, but disorganization, waning motivation, and procrastination are common descriptors. Children with ADHD often *are* able to attend to interesting, stimulating activities such as video games; tasks that are repetitive and felt to be unrewarding and “boring” tend to make the inattentiveness apparent.

It is particularly important to inquire about behavior in different settings, since signs are generally not displayed equally in all situations, and the findings on the usual physical examination may be particularly misleading. A personal interview with the physician may fail to elicit hyperactive or inattentive behavior that is readily apparent in a group setting such as the classroom. The physician needs to inquire about three areas: home (family), school, and peers (friends).

The family history is likely to be positive for ADHD; the information about a previous occurrence may be most helpful in counseling. Careful inquiry may elicit a history of alcoholism, substance abuse, mental health problems, or learning problems in family members. A history of prematurity, especially very low birth weight (VLBW), in the child is significant, in that children who were VLBW generally have attentional problems at school age.

The physical examination is of value largely to rule out other diagnoses. Also, on neurologic examination, synkinesia and finger agnosia with fine motor assessment are indicative of the graphomotor differences that are almost always present for these children. Observing the child during an academic task may be most helpful in judging attentiveness and pencil grasp/facility with writing. It is very important to take time during the examination to determine from the child his/her self-perception and understanding of school performance and relationships.

Thirty-three percent of children with ADHD have social cognitive skill problems. A child with ADHD may also have Oppositional Defiant Disorder (ODD), with overt acting-out behavior. In addition, many children with ADHD, though of normal or near-normal intelligence, have learning disabilities; 40% have language-based learning problems and most have memory difficulties. Associated with learning disorders are perceptual deficits, such as difficulty with right-left discrimination, spatial orientation, and hand-eye coordination.

No laboratory or imaging studies are diagnostic of ADHD. Psychometric testing is very important and should include assessment of IQ; perceptual ability; and reading, written language, and math performance. Screening instruments should also be used to detect anxiety, depression, psychosis, and ODD. The status of hearing, vision, speech, and language should be investigated if there is any question about these abilities. The data-gathering process is incomplete until information has been solicited from the school personnel, who as previously noted may be able to provide a more valuable assessment of the child's behavior than the physician during a one-on-one interview. Minimal documentation from the school needed by the physician for treatment planning includes: (1) description of classroom observations, strengths, and weaknesses; (2) parent and teacher questionnaires (Conners, Burke, Achenbach, etc.); (3) academic performance history (report cards, writing samples, group testing); (4) cognitive skills testing (these may be of the screening variety [Kaufman Brief Intelligence Test, or KBIT] or more in-depth [Wechsler Intelligence Scale for Children–III, or WISC–III]; a score from group testing is a very poor indicator and is not adequate); and 5) academic achievement testing (these may also be screens [Kaufman Test of Educational Achievement, or KTEA] or in-depth [Woodcock-Johnson Psycho-Educational Battery–Revised, or WJ–R]; group testing is not adequate).

Treatment for ADHD must be multimodal. Although medication is highly effective for enhancing concentration and memory, and reducing impulsive response-style, it is not sufficient for addressing all the characteristics of ADHD and it does not itself develop long-term strategies. Intervention consists of: (1) demystification (child, parent, teacher); (2) classroom strategies (modifications, bypass strategies, technology); (3) resource/tutoring (especially study and organizational skills); (4) behavioral strategies; (5) parent training; (6) medication; (7) counseling (group/family); and (8) social groups.

Chemotherapeutic agents for ADHD most commonly are (1) stimulants, (2) tricyclic antidepressants, or (3) bupropion (Wellbutrin). The stimulants are methylphenidate (Ritalin), dextroamphetamine (Dexedrine), and d-l-amphetamine (Adderall). These are performance enhancers and help with attention and memory. By early adolescence, many students prefer one of the time-release (Dexedrine) or long-acting (Adderall) preparations to avoid having to take medication at school. The tricyclics have been used in students who have concurrent anxiety or behavior problems. These are imipramine (Tofranil) and desipramine (Norpramin). An electrocardiogram should be obtained before starting these. To a large extent, currently the use of tricyclics is being replaced by selective serotonin reuptake

inhibitors (SSRIs), fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox).

The stimulants are generally the most effective for the symptoms of ADHD. Response to the stimulants occurs in 60–80% of patients and is often dramatic, with observable improvement within a day or two; the effect of these drugs lasts only a matter of hours, however. The most notable side effects are: (1) appetite suppression, which is confined to the duration of the dose, and (2) rebound, which may occur as the medication wears off, and consists of irritability and increased activity. Concerns regarding adverse effects on growth have never been substantiated. The medication may be taken just on school days, but many patients need the medication on weekends and vacations to assist in other group and social activities.

The response to pharmacologic agents may be limited or augmented by emotional and environmental factors. Counseling of the family to permit venting of frustration and to eliminate blaming is an important part of the management. Assistance is often needed to help the family and child organize daily activities and establish a routine of one-step assignments for the child that can be mastered with repetition. The physician often provides a great service by lending a sympathetic ear, recognizing the problems posed by a hyperactive child with short attention span, and alleviating parental guilt by insisting that they make time for themselves. Similarly, an explanation of the child's condition to school personnel and suggestions for adjustments in the classroom program can relieve tension in class, improve the relationship between family and school, and most importantly salvage the child's self-esteem. Many treatments utilizing various methods and claiming to help the child have gained popularity from time to time; the physician may be asked about dietary manipulations (such as the Feingold Diet or the role of sugar), or optometric exercises. There are no studies that support the use of these therapies (which can be costly to the family).

No pharmacologic agents that are available will ensure learning; medications may make it more feasible for the student to concentrate, but this is insufficient to satisfy the needs of the child with a coexisting learning disorder; it is essential to remember that 40% will have language-based learning differences. For classroom strategies there is agreement on the need for repetition, the need to build on the child's strengths, the need for more individual attention and redirection to task, and the need to keep distracting stimuli to a minimum. For the concurrent problems with written output that are almost universally present, modifications in the length of assignments (classroom and homework), and untimed testing are crucial.

In considering prognosis, it is important to realize that ADHD has impact across the lifespan; that is, one does not outgrow ADHD. The degree of success is individual and related to the presence of concurrent diagnoses (learning or mental health), the development of bypass strategies, and advocacy by family, school, and other professionals involved with the child. Adolescents are high risk for depression due to “chronic success deprivation,” and behavioral issues. Untreated, ADHD is associated with an increased incidence of social disabilities, including substance abuse, delinquency, academic underachievement, and poor work record. “Cure” is unattainable; rather, successful adaptation is the desired outcome.

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25. SLEEP

Kenneth B. Roberts and Kathryn P. Wyatt

Nearly a half-century ago, rapid eye movements (REMs) were reported to occur during the sleep of infants. Since that time, REM sleep has been confirmed as distinct from quiet, non-REM sleep and has been associated with dreaming. Non-REM sleep has been subclassified into four stages on the basis of the electroencephalogram. A great deal has been learned about the physiology of sleep, but with few exceptions, these advances in understanding have not translated directly to aid the clinician; rather, the most valuable tools remain knowledge of normal age- and stage-related patterns and the application of simple behavioral techniques.

Newborns generally sleep approximately 17 out of 24 hours, with even distribution during daytime and nighttime hours. The total amount of time spent sleeping per 24 hours does not change much during the first 3 months of life, but the percentage during the nighttime hours increases. By 3 months of age, approximately 70% of infants have “settled,” that is, they regularly sleep through the night (midnight to 5 A.M.); 83% of 6-month-olds sleep through the night, and by 9 months to 1 year, the figure is 90%.

Video recordings demonstrate that most infants awaken during the night but are able to fall back to sleep quietly. By the second half of the first year, however, half of those who have been sleeping through the night develop “night waking,” that is, they awaken as usual but protest loudly about being alone. Night waking is probably related to separation anxiety, generated by the newly developed cognitive attainments of recall memory and object permanence. A pattern of waking leading to parental attention can be quickly established as a regular nightly event; fortunately for parents, the pattern can usually be extinguished in a few nights to a week with limited attention and acceptance of some crying.

As separation becomes a major issue in infancy, bedtime becomes a time of potential conflict. The child may view bedtime as a serious separation; the parent may see it as a respite! At this age, bedtime refusal is common, and bedtime rituals are often initiated, serving as soothing reassurance of affection and a quiet period to facilitate sleep. Objects such as blankets or favorite toys may reduce the separation anxiety associated with bedtime and the physical absence of the parent.

Preschool children commonly express fears relating to bedtime: fear of the dark, of insects, of animals. It is therefore understandable that parents may confuse “night terrors” (pavor nocturnus) with nightmares; these two entities are quite different, however. Children with night terrors characteristically cry out in their sleep and are inconsolable for 10–15 minutes; they do not seem to recognize their parents, they are glassy-eyed, and they have no recollection of the event in the morning. Night terrors occur in non-REM sleep and are not content laden. By contrast, nightmares generally occur in somewhat older children and have content (“bad dreams”). Counseling about night terrors includes reassurance that the child is not “working through” a hidden trauma, that the parents are not the cause, that the behavior is not intentional, and that the child will “outgrow” the behavior. The child should be observed and allowed to fall back to sleep on his own, since waking the child only prolongs the episode. In severe cases, diazepam (Valium) can be given to the child at bedtime. In contrast, children with nightmares require brief reassurance that the dream is over and they are safe in their beds.

Sleepwalking, sleep talking, and enuresis are all most common during the school-aged years. They are more frequent in boys than in girls; the presence of one increases the likelihood of another; and they are all related to the time in the sleep cycle between deep non-REM sleep and REM sleep (leading some authors to refer to them as disorders of arousal rather than of sleep). In general, the older the child is at the onset, the more likely there is to be a psychological cause and the less likely there is to be a spontaneous resolution. Sleepwalking can be dangerous, and the child requires a safe nighttime environment (enuresis is discussed in Chap. 27).

During adolescence, sleep patterns and the nature of complaints change. The most frequently voiced sleep-related concern of parents is that their teenager seems excessively tired, with spontaneous awakening on school days an unusual event and “sleeping till noon” on non–school days commonplace. To many parents, this behavior indicates ill health, perhaps an underlying chronic disease, malignancy, or involvement with drugs. The pattern is frequent enough, however, to be considered an age-related norm. The cause of the altered pattern is not precisely clear. Chronic sleep deprivation may well play a role; teenagers sleep less per night than preteens. The increasing psychological stress and metabolic requirements related to physical and endocrinologic changes may also be important.

Although parents may be concerned about excessive sleepiness, teenagers themselves, when asked, commonly acknowledge at least occasional difficulty in falling or remaining asleep. The patterns they identify are similar to those experienced by adults, particularly under stress.

The more serious sleep-related disorders, such as narcolepsy, are uncommon. Narcolepsy is characterized by excessive sleepiness, which usually occurs 3–4 hours after waking, and by cataplexy, episodes of inability to make voluntary movements although awake. Additional features are disturbed nocturnal sleep and hypnagogic hallucinations; the latter appear to reflect a disorder in the transition from wakefulness to sleep, during which hallucinations, particularly auditory, are quite vivid (as in a dream) and muscle activity is inhibited. True narcolepsy is difficult to treat. Stimulants such as methylphenidate have been tried with some success; imipramine has been used for the management of some adjunctive symptoms, such as cataplexy and hypnagogic hallucinations.

Narcolepsy is particularly rare before adolescence. A more likely (although still uncommon) cause of excessive daytime sleepiness in children is the sleep apnea–hypersomnia syndrome. Affected children suffer chronic upper airway obstruction at night, with attendant hypercarbia and hypoxemia. Enuresis and a decline in intellectual functioning may develop. Obstructive tonsils or adenoids, or both, may be responsible, and otolaryngologic consultation is warranted. In some severe cases, when no anatomic cause for obstruction can be found and removed, tracheostomy has been performed.

Perhaps related to sleep apnea is the sudden infant death syndrome (SIDS; see Chap. 17), which occurs during sleep. One of the many theories proposed to explain SIDS postulates a physiologic disturbance in sleep or in the regulation of respiration during sleep. “Sleep studies” are commonly performed in many centers in an attempt to identify infants at risk for SIDS, and parents of infants considered to be at risk may be advised to monitor their infant during sleep using an apnea alarm or cardiorespiratory monitor. The theory has not been validated, and apnea alarms have not been demonstrated to lower the rate of SIDS. Sleeping supine rather than prone has been associated with a reduction in the rate of SIDS and is currently actively promoted (“Back to Sleep” campaign).

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26. BOWEL TRAINING, CONSTIPATION, AND ENCOPRESIS

Evan Charney and Kenneth B. Roberts

Bowel control is attained at a median age of 18–24 months in the United States. More than 90% of children are “trained” by 30 months, 95% by 4 years of age, and 1–2% have not achieved bowel control by age 5. Firstborns are trained somewhat later than are subsequent children, and boys are several months behind girls in acquiring control. Of those still untrained at age 5 and older, boys outnumber girls by at least 3:1.

Toilet training is influenced by social norms as well as by physiologic maturation. In western Europe, toilet training is instituted early; almost all Swiss children are regularly placed on a potty chair between 6 and 12 months, and bowel control is essentially complete in 60% of children by 1 year and 90% by 2 years of age. Indeed, in several East African cultures, virtually complete bowel and bladder control is reported by 6 months of age, although parents actively participate by anticipating the infant's needs and can trigger defecation-on-command by placing the child in an accustomed position on the mother's outstretched legs.

Opinions about the “correct” time and method of bowel training not only vary throughout the world but also have changed in this country over time. In the 1920s and 1930s, parents were advised to finish training by 6–8 months of age. Over the next decades, psychoanalytic theory stressed the potential harm of early and strict bowel training, although that conclusion was largely based on anecdotal and retrospective case data. Current recommendations suggest that training be deferred until the child acquires sufficient developmental skills to be an active participant in the process. The child should be aware of what is required and motivated to cooperate, be able voluntarily to inhibit the defecation reflex, and be able to indicate to the parent a need (or intent) to defecate—skills generally developed by 15–18 months of age. When those maturational levels are attained, the child is provided a potty seat; one on the floor enables the child to brace arms and legs so that the levator ani muscles can act most efficiently. The child is urged (not coerced) to sit on the potty once or twice daily for not more than 5–10 minutes, and success is heartily praised. With this “child-centered approach,” the vast majority of children are trained within a few months. Those regular in temperament and bowel pattern will be trained more rapidly. Family moves, arrival of new siblings, intercurrent illness, and stress can be expected to cause setbacks in the process. Parents who make the training a power struggle or whose children's temperaments are more negative or unpredictable are likely to encounter more difficulty.

Toilet training is not the only issue in bowel function. The frequency and character of stools often are concerns to parents: too few, too many, too hard, too soft. Normal stool frequency and appearance vary in early infancy. After the greenish-black meconium stools of the first 3 or 4 days of life, the infant passes a thin transitional stool several times daily for the first week. Thereafter, stools of a breast-fed infant are yellow and semisolid, have little odor, and will vary greatly in number, commonly 8 to 10 per day but occasionally 1 every several days; extremely hard stools are uncommon. Infants fed cow milk formula will have firmer, more brownish, and generally less frequent stools. In both cases, stool frequency tends to diminish over the first 3 months of life, from initially one per feeding (or more) to one every 1–3 days. While parents commonly identify this reduced frequency as constipation, problems arise only when stools are hard and dry; the term *constipation* is better reserved for hard rather than infrequent stools. When the stools are hard, anal fissures may develop, and the associated painful anal spasm can initiate a cycle of stool retention and further desiccation. A stool softener for several days or, in recurrent cases, use of a bulk cathartic such as Maltsupex may be helpful, and the problem usually resolves. The physician needs to be alert to the child whose bowel pattern (often familial) is one of recurrent episodes of infrequent, dry, hard stools throughout infancy and childhood. Anticipatory counseling should then include intake of a high-fiber diet (bran, graham crackers, fruit, and, later, abundant fresh vegetables), and milk intake should be limited. The family can be counseled that exacerbation of the problem is likely to occur during febrile illnesses, when mild dehydration may be reflected in more constipation. In toilet training, the need for a regular and unhurried time on the toilet for these children requires emphasis, so that evacuation is complete. With attention to diet and avoidance of laxatives (except in rare instances), the small percentage of children with a tendency to chronic constipation can function well and avoid more serious problems.

A small subgroup of children have very severe chronic constipation. Some may have encopresis, defined as repeated deposition of stool in clothing (or other unorthodox sites) after 4 years of age. Boys outnumber girls with this disorder by 4:1 or 5:1. These chronically constipated children appear to have a constitutional predisposition to infrequent stool passage, possibly related to a disorder of colonic motility or anorectal function. Whether these abnormalities are a cause or a consequence of chronic stool retention is still unclear. In addition, there are “potentiators” at specific developmental stages in infancy and childhood that may convert this predisposition to a chronic clinical problem. These include inappropriately managed acute constipation and frequent anal fissures, excessive laxative and enema use, and major bowel training conflicts. Fear of using the toilet, prolonged gastroenteritis, parent-child conflicts, family psychopathologic problems, or school stress may result in manifest symptoms in the child's “vulnerable bowel.”

In these cases, stool retention over time leads to desiccation by water absorption in the terminal colon, painful defecation, and further retention. The result is a distention and stretching of the rectum and colon (megacolon), with shortening of the anal canal and disordered function of internal and external sphincters. Seepage of liquid stool around the fecal mass may result in encopresis, at times mistaken for diarrhea. When bowel movements do occur (often only with the aid of enemas), the stool may be enormous in size, reflecting the caliber of the dilated rectum, and can be of sufficient size and volume to block the household plumbing.

Once the problem has evolved to this more serious stage, an organized diagnostic and management approach with child and family is required to intervene. First, the family needs to agree to a long-term (6- to 12-month) therapeutic plan, which conveys the extent of commitment required of both physician and family for a successful outcome. A complete history and physical examination should seek out potentiators and rule out organic conditions such as spinal cord anomalies, anteriorly located anus, and associated metabolic and developmental conditions (e.g., cerebral palsy, hypothyroidism, chronic urinary tract infection secondary to stasis). Rectal examination may be performed to assess anal tone and determine the presence and consistency of stool in the ampulla, and plain radiographs may be helpful in assessing the extent of stool retention. More extensive laboratory evaluation (barium enema, rectal biopsy, manometrics) should be reserved for the small number of patients not responding to initial management. (Although Hirschsprung disease, aganglionic megacolon, is often considered, it accounts for a small fraction of these cases, almost always characterized by delayed passage of meconium in the neonatal period.)

The treatment phase begins with a complete “clean-out” to clear the colon of retained stool. This is a several-day process, involving laxatives and enemas, and a follow-up radiograph helps assess its completeness. Then a long-term program of at least 3–6 months' duration begins, incorporating a combination of regular laxative use (such as lactulose or mineral oil), diet instruction, and, most important, regular and undisturbed daily toileting time. Repeat visits are essential to monitor progress, to provide support, and to maximize the child's role in the process as age-appropriate. These visits help sort out the cases requiring more intensive psychotherapy from those in which behavioral and interpersonal conflicts ease as the symptom is controlled. In perhaps two thirds of these cases, laxative use can be markedly reduced or withdrawn after several months. However, relapses can be anticipated, and the chronic nature of the underlying problem needs to be appreciated.

The primary physician has much to offer these families: primary prevention of the problem through identification and guidance in early stages of child development for susceptible children, and long-term intervention and guidance in more severe cases.

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   *A useful review of modern fashions in toilet training, from Brazelton's classic "child-centered approach to toilet training" in the 1960s (*Pediatrics *29:121–128, 1962), and Azrin and Foxx's* Toilet Training in Less Than a Day *(New York: Pocket Books, 1974) in the 1970s to the present.*
3. de Vries, M., and de Vries, M. Cultural relativity of toilet training readiness: A perspective from East Africa. *Pediatrics* 60:170–177, 1977.
   With "nurturant conditioning," night and day dryness and bowel control were achieved by 6 months of age!

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   Of 482 middle-upper class children, 22% had stool toileting refusal for at least 1 month. Stool toileting refusal was associated with the presence of younger siblings and parental inability to set limits. (The behavioral characteristics of these children are considered in the preceding article in the same journal: pp. 50–53.)

Constipation: Reviews and Practice Guidelines

5. Abi-Hanna, A., and Lake, A. Constipation and encopresis in childhood. *Pediatr. Rev.* 19:23–30, 1998.
   An easy-to-read review with five useful tables, including key issues in parent/patient education and treatment options.
6. Baker, S., et al. Constipation in infants and children: Evaluation and treatment. A Medical Position Statement of the North American Society for Pediatric Gastroenterology and Nutrition. *J. Pediatr. Gastroenterol. Nutr.* 29:612–626, 1999.
   Algorithms and recommendations for evaluation, diagnosis, and management; special consideration is given to infants in the first year of life.
7. Felt, B., et al. Guideline for the management of pediatric idiopathic constipation and soiling. Multidisciplinary team from the University of Michigan Medical Center in Ann Arbor. *Arch. Pediatr. Adolesc. Med.* 153:380–385, 1999.
   An algorithm and clinical care guideline regarding early, accurate diagnosis; method for clean-out; and approach to promote patient and family adherence to management.

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8. Loening-Baucke, V. Encopresis and soiling. *Pediatr. Clin. North Am.* 43:279–298, 1996.
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Constipation: Radiography

9. Blethun, A., et al. Radiological assessment of constipation. *Arch. Dis. Child.* 73:532–533, 1995.
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10. Iacono, G., et al. Intolerance of cow's milk and chronic constipation in children. *N. Engl. J. Med.* 339:1100–1104, 1998.
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11. Loening-Baucke, V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. *Pediatrics* 100:228–232, 1997.
    Of 234 children with chronic constipation, 29% had daytime urinary incontinence and 34% had nighttime bed-wetting. With treatment of the constipation, 89% of those with daytime urinary incontinence and 63% of those with bed-wetting became dry.

Fiber

12. Hillemeier, C. An overview of the effects of dietary fiber on gastrointestinal transit. *Pediatrics* 96:997–999, 1995.
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13. Position of the American Dietetic Association: Health implications of dietary fiber. *J. Am. Diet. Assoc.* 97:1157–1159, 1997.
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14. McClung, H., Boyne, L., and Heitlinger, L. Constipation and dietary fiber intake in children. *Pediatrics* 96:999–1000, 1995.
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Constipation: Outcome

16. Staiano, A., et al. Long-term follow-up of children with chronic idiopathic constipation. *Dig. Dis. Sci.* 39:561–564, 1994.
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17. Sutphen, J., et al. Long-term follow-up of medically-treated childhood constipation. *Clin. Pediatr.* 34:576–580, 1995.
    *At a mean of 6.8 years, 70% were asymptomatic. (*Arch. Dis. Child. *75:36–41, 1996; at a mean of 4 years after treatment, 66% of children were free of symptoms.)*

Hirschsprung Disease

18. Rudolph, C., and Benaroch, L. Hirschsprung disease. *Pediatr. Rev.* 16:5–11, 1995.
    A general review. (If you want to read Hirschsprung's original, "Constipation in the newborn as a result of dilation and hypertrophy of the colon" from 1888, it is reprinted in Dis. Col. Rect. *24:408–410, 1981, with a brief biographical sketch.)*
19. Ghosh, A., and Griffiths, D. Rectal biopsy in the investigation of constipation. *Arch. Dis. Child.* 79:266–268, 1998.
    Based on the clinical experience of these authors, if the onset of constipation is after the first month of life, a rectal biopsy is unnecessary.

27. BLADDER CONTROL AND ENURESIS

Kenneth B. Roberts

The term *enuresis* is frequently used synonymously with bed-wetting after the age at which the child is expected to be dry (though this should more properly be termed nocturnal enuresis) Primary enuresis is distinguished from secondary enuresis in that a child with the former has never had a sustained period (e.g., 3 months) of dry nights, whereas a child with the latter begins bed-wetting after nocturnal dryness has been achieved. Recently, qualifiers have been added to distinguish children whose only symptom is nocturnal enuresis from those with additional symptoms, such as urgency, frequency, or diurnal enuresis. The former are described as having monosymptomatic nocturnal enuresis.

The age at which a child is expected to be dry at night depends on a number of factors, including who is being asked (parents, grandparents, and physicians generally have different expectations), the sex of the child (girls are dry at a younger age than boys), and the child's development in other spheres. Normally, the initial step in the development of urinary continence takes place before 2 years of age, by which time most infants are aware of having voided and can report what has (already) happened. Between 2 and 2½ years, the child develops the ability to sense a full bladder before it is emptied and to initiate voiding from a full bladder. During the next few years, the ability to retain urine voluntarily is mastered, but it is not until 4½–6 years that the child can initiate voiding at any degree of bladder fullness or start and stop the urinary stream at will.

Approximately 60% of 3-year-old children are dry at night; the incidence of bed-wetting at that age, then, is 40%. During the next 3 years, the incidence of bed-wetting declines to approximately 30% at age 4, 20% at age 5, and 10% at age 6. Of those children who still wet the bed at age 6, approximately 15%/y will have a “spontaneous cure,” leaving 7% of 8-year-olds, 3% of 12-year-olds, and 1% of 18-year-olds bed-wetting more than once a month. Boys outnumber girls at each age by a ratio of 1.5:1.

There are many possible causes of enuresis. Each of the following has been implicated: disorders such as genitourinary abnormalities and systemic diseases; faulty toilet training; developmental (maturational) delay; genetics; sleep disorder; inadequate bladder capacity; and nocturnal polyuria due to inadequate vasopressin release at night.

Abnormalities of the genitourinary tract rarely cause bed-wetting alone. Enuresis must be distinguished by history from constant dribbling, which may indicate an anomalous insertion of the ureter below the bladder neck (i.e., into the urethra), and from overflow incontinence due to a neurogenic bladder. The onset of enuresis in a previously dry child may signal urinary tract infection, especially in a girl; the enuresis responds to treatment of the infection. Two other medical conditions associated with an increased incidence of enuresis are diabetes insipidus and diabetes mellitus.

The relationship between toilet training and enuresis is not clear, although considerable discussion over the past several decades has been given to both the optimal timing and the optimal style of conducting the process. The notion of a critical period for learning skills of continence appears to have given way, but many still believe in a “sensitive period.” Noncoercive toilet-training techniques are thought by supporters to be associated with fewer later difficulties such as enuresis and encopresis (see Chap. 26); conditioning techniques to accomplish training in a short period of time also enjoy great popularity, however. Stress and psychological pressure(s) appear to play a greater role in secondary enuresis than in primary.

Some children appear to have only a developmental delay in achieving dryness; there is often a family history of a similar situation in a parent. If one parent had enuresis, the probability that an offspring will have enuresis is reported to be 45%; if both parents had enuresis, the probability is 77%. Among identical twins, concordance for enuresis is 68%, compared to the concordance among fraternal twins, which is only 36%.

As noted in Chap. 25, enuresis is considered by some to be a disorder of arousal, as are sleepwalking and sleep talking; that is, enuresis is most likely to occur during the return from deep sleep to light sleep in a somewhat confused state of near-wakefulness. Children with one of the “disorders of arousal” may well have another.

Many children with enuresis have unusually small functional bladder capacities; when asked to retain urine as long as possible, the amount finally voided is less than would be expected. (A general rule is 1 oz per year of age plus 2.) Cystometric studies have shown that many of these children with reduced functional capacities have normal bladder capacities when they are anesthetized.

Some children with enuresis void large amounts of dilute urine at night, when the normal physiologic secretion of vasopressin should be enabling them to conserve fluid.

The evaluation of a child with enuresis depends heavily on the history. How old is the child, and what developmental and maturational skills have been achieved? Is the enuresis nocturnal, diurnal (daytime), or both? Is this primary or secondary enuresis? What has been the longest dry period to date? Does the child have difficulty voiding, suggesting obstruction of the lower urinary tract? Is there associated bowel or lower limb pathology suggestive of a neurologic disorder? Is there a family history of bed-wetting? Is there sufficient social turmoil as to interfere with toilet training? What are the parental attitudes and behaviors regarding the bed-wetting: What happens when the child wets the bed? Who is responsible for changing the sheets? What has been tried? And why is help being sought at this particular time?

A complete general physical examination is warranted, with particular emphasis on the neurologic examination and an assessment of the child's behavior. A urine specimen for specific gravity measurement, urinalysis, and culture should be obtained; if lower tract obstruction is suspected, voiding should be observed. Further studies—such as a roentgenogram of the lumbar and sacral spines, or a voiding cystourethrogram—need to be performed only if findings from the history, physical examination, or examination of the urine suggest a lesion.

Treatment begins with reassurance, particularly to the child, that while the enuresis is disturbing and annoying, many children have the same problem and “grow out of it.” If the child is interested in working on “the problem,” further reassurance can be given that the physician can help.

The simplest form of treatment is withholding fluids after dinner and voiding before bedtime; this may be all that is required for some children close to dryness, but it has usually already been tried by families seeking help from the physician. Waking the child before the parents go to bed is also commonly performed and may be helpful in mild cases.

Further intervention depends on the age of the child, associated findings, the level of concern, and family dynamics, including assessment by the physician as to how much cooperation—rather than coercion—will be forthcoming. If the child is younger than age 6, the physician should discuss normal development and maturation of bladder control with the parents and attempt to reach agreement regarding appropriate expectations. For the young school-aged child with a small functional bladder capacity, many physicians recommend “bladder-stretching exercises.” The child is asked to force fluids once each day and to resist the urge to void as long as possible. When the child must void, he or she practices starting and stopping the stream while urinating into a measuring cup. The volume is recorded on a calendar; the calendar is also used as a “star chart” to identify dry nights. Rewards are given for appropriate achievements, and the family is encouraged to focus on successes,

with praise and reward, rather than on failures.

For school-aged children, some clinicians have been successful with hypnosis and imagery, having the child imagine the sensation of bladder fullness, the act of getting out of bed and voiding in the bathroom, and returning to a “nice, dry bed.” The child is encouraged to think about this image at bedtime each night.

The two most frequently used pharmacologic agents, generally imipramine (Tofranil), a tricyclic antidepressant, and desmopressin (DDAVP) have each been demonstrated to be superior to placebo, with short-term response rates between 10% and 50%. Relapses are common once either drug is discontinued, however. Perhaps the best role of the drugs is to facilitate the social process by increasing the chances of success. In such a regimen, the need to monitor and report successes and to assure social rewards is not altered by prescribing a drug.

When used as an antidepressant, imipramine requires weeks for a beneficial effect and is given in divided doses through the day. For treatment of enuresis, however, a single daily dose, given an hour before bedtime, is usually sufficient, and drug effect is recognized within days. Imipramine has a vasopressin-independent antidiuretic effect distinct from its antidepressant effect. The optimal duration of therapy is unknown, and some children, initially aided by imipramine, appear to become tolerant to its effects. It should be recognized when prescribing imipramine that overdoses can be quite serious or fatal due to myocardial toxicity.

Desmopressin is at least as effective as imipramine and is considered safer. It is generally administered intranasally.

Conditioning techniques, involving an apparatus such as the “bell and pad” enuresis alarm, are associated with the highest cure rates of the various forms of therapy proposed for enuresis (approximately 70%), mainly because they have a lower relapse rate than imipramine or DDAVP. The methods involve a form of sensor between the child and the bed that, when dampened, sets off an alarm designed to awaken the child. The relapse rate is reduced when a period of “overtraining” is included. Once the child is having dry nights, increasing amounts of fluid are provided before bedtime, and the alarm system is continued until the child can remain dry despite the added challenge. The alarm system does not simply convert enuresis to nocturia; success is generally associated with sleeping through the night without wetting.

Whatever treatment plan is prescribed, the physician needs to be aware of the child's self-concept, abilities, and pressures. Taking these factors into account, the physician, for example, may suggest that the child be responsible for the “extra” laundry caused by wet bed linen; other circumstances may prompt a different suggestion. Since the vast majority of children who wet their beds have a self-limited problem, a major goal is to minimize “emotional scars” by assuaging and redirecting anger, rechanneling frustration, and providing needed support.

Reviews

1. Schmitt, B. Nocturnal enuresis. *Pediatr. Rev.* 18:183–190, 1997.
   By all means, start here.
2. Chandra, M. Nocturnal enuresis in children. *Curr. Opin. Pediatr.* 10:167–173, 1998.
   Though this journal generally just provides updates, this is a good review as well.
3. Moffatt, M. Nocturnal enuresis: A review of the efficacy of treatments and practical advice for clinicians. *Dev. Behav. Pediatr.* 18:49–56, 1997.
   More than the title promises.
4. Wan, J., and Greenfield, S. Enuresis and common voiding abnormalities. *Pediatr. Clin. North Am.* 44:1117–1131, 1997.
   Goes beyond nocturnal enuresis to consider (briefly) anatomic abnormalities, neurologic causes, urinary tract infection (UTI), and diurnal enuresis.

Voiding

5. Kaplan, G., and Brock, W. Voiding dysfunction in children. *Curr. Probl. Pediatr.* 10:1–63, 1980.
   The anatomy and physiology. (For more on the development of urinary control in children, see J.A.M.A. *172:1256–1261, 1960.)*
6. Berger, R., et al. Bladder capacity (ounces) equals age (years) plus 2 predicts normal bladder capacity and aids in diagnosis of abnormal voiding patterns. *J. Urol.* 129:347–349, 1983.
   The title is the message.

Epidemiology

7. Oppel, W., Harper, P., and Rider, R. The age of attaining bladder control. *Pediatrics* 42:614–626, 1968.
   A literature review plus results of a 12-year prospective study of 859 children established age of initial dryness, age of final dryness, and the prevalence of dryness. Low birth weight was a risk factor, and the contribution of “relapsers” to the total pool was evident.
8. Forsythe, W., and Redmond, A. Enuresis and spontaneous cure rate: Study of 1,129 enuretics. *Arch. Dis. Child.* 49:259–263, 1974.
   The spontaneous cure rate was 14–16% per year between 5 and 19 years of age, a figure to be remembered when evaluating various treatment modalities.
9. Byrd, R., et al. Bed-wetting in US children: Epidemiology and related behavior problems. *Pediatrics* 98:414–419, 1996.
   Enuresis beyond age 5, regardless of the frequency of bed-wetting, was associated with increased rates of behavior problems in this study of 10,960 children aged 5–17 from the 1981 National Health Interview Survey. (Different answer when studied at Father Flanagan's Boys' Home in Boys Town: Children with primary nocturnal enuresis were found not to have clinically significant behavior problems: Arch. Pediatr. Adolesc. Med. *152:537–539, 1998.)*

Parental Perceptions

10. Haque, M., et al. Parental perceptions of enuresis. *Am. J. Dis. Child.* 135:809–811, 1981.
    What parents anticipate to be the age of dryness, what they perceive to be the cause of enuresis, and how they manage bed-wetting. (Attitudes of parents contrasted with those of physicians: Pediatrics *67:707–710, 1981.)*

Sleep and Enuresis

11. Neveus, T., et al. Sleep of children with enuresis: A polysomnographic study. *Pediatrics* 103:1193–1197, 1999.
    Enuresis is a predominantly non–rapid eye movement sleep phenomenon. Desmopressin (DDAVP) responders voided during the early or late part of the night, while the voids of nonresponders were evenly dispersed throughout the night.

Treatment: General

12. Glicklich, L. An historical account of enuresis. *Pediatrics* 8:859–876, 1951.
    A 27-page review of some pretty amazing approaches. (Ah, gentle reader, but what will the future think of us?)
13. Butler, R. Establishment of working definitions in nocturnal enuresis. *Arch. Dis. Child.* 66:267–271, 1991.
    To permit comparison among studies, the author tabulates the definitions used in 38 studies and attempts to achieve standard criteria for the following: severity, initial success, lack of success, relapse, continued success, and complete success.
14. Monda, J., and Husmann, D. Primary nocturnal enuresis: A comparison among observation, imipramine, desmopressin acetate and bed-wetting alarm systems. *J. Urol.* 154:745–748, 1995.
    In head-to-head studies, the alarms win. In this study, the alarm and DDAVP were equally more effective than observation or imipramine at 6 months, but the alarm was the clear winner 12 months out.

Treatment: More on Alarms

15. Oredsson, A., and Jorgensen, T. Changes in nocturnal bladder capacity during treatment with the bell and pad for monosymptomatic nocturnal enuresis. *J. Urol.* 160:166–169, 1998.
    Bladder capacity increased, which explains why responders sleep through the night rather than having enuresis converted to nocturia. A new type of alarm is based on an ultrasound bladder volume sensor that alerts the child to a full bladder before voiding occurs (J. Urol. *162:1224–1228, 1999), but it may or may not be economical enough to reach the market. For more on the 50-year history of alarms up to 1989, see* Arch. Dis. Child. *64:879–885, 1989.*

Treatment: More on Desmopressin

16. Skoog, S., Stokes, A., and Turner, K. Oral desmopressin: A randomized double-blind placebo controlled study of effectiveness in children with primary nocturnal enuresis. *J. Urol.* 158:1035–1040, 1997.
    Dosages of 400 µg and 600 µg were more effective than 200 µg or placebo.
17. Neveus, T., et al. Osmoregulation and desmopressin pharmacokinetics in enuretic children. *Pediatrics* 103:65–70, 1999.
    Nonresponders had a smaller spontaneous bladder capacity (also see Ref. 18). Responders produced less concentrated urine (also see Ref. 19). Pharmacokinetics did not differ between responders and nonresponders.
18. Rushton, H., et al. The influence of small functional bladder capacity and other predictors on the response to desmopressin in the management of monosymptomatic nocturnal enuresis. *J. Urol.* 156:651–655, 1996.
    Children with a functional bladder capacity >70% of predicted were twice as likely to respond.
19. Rushton, H., et al. Response to desmopressin as a function of urine osmolality in the treatment of monosymptomatic nocturnal enuresis: A double-blind prospective study. *J. Urol.* 154:749–753, 1995.

This study did not confirm the value of assessing urine osmolality found in Ref. 17. (Neither did Clin. Pediatr. *37:719–724, 1998, though another study concluded that enuresis is less likely if the child's first morning urine specific gravity is <1.020 than if it is <1.015:* Arch. Pediatr. Adolesc. Med. *1995;149:259–262.)*

Treatment: More on Imipramine

20. Hunsballe, J., et al. Single dose imipramine reduces nocturnal urine output in patients with nocturnal enuresis and nocturnal polyuria. *J. Urol.* 158:830–836, 1997.
Imipramine has a vasopressin-independent antidiuretic effect. (For a review of tricyclic antidepressants in children and adolescents with 92 references, see Pediatr. Clin. North Am. *45:1123–1135, 1998.)*

Treatment: More on Behavioral Methods

21. Kahan, E., et al. A controlled trial of desmopressin and behavioral therapy for nocturnal enuresis. *Medicine* 77:384–388, 1998.
Behavioral therapy plus placebo was as effective as behavioral therapy plus DDAVP and more effective than DDAVP alone.
22. Olness, K. The use of self-hypnosis in the treatment of childhood nocturnal enuresis. *Clin. Pediatr.* 14:273–279, 1975.
Of 40 children taught self-hypnosis, 31 stopped bed-wetting, 6 improved, and 3 did not improve; the process is described.
23. Hoekx, L., Wyndaele, J., and Vermandel, A. The role of bladder biofeedback in the treatment of children with refractory nocturnal enuresis associated with idiopathic detrusor instability and small bladder capacity. *J. Urol.* 160:858–860, 1998.
Biofeedback was provided by catheterizing the bladder and focusing awareness on the sensation of bladder fullness. It worked.

Role of Constipation

24. Loening-Baucke, V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. *Pediatrics* 100:228–232, 1997.
Of 234 children with chronic constipation, 29% had daytime urinary incontinence and 34% had nighttime bed-wetting. With treatment of the constipation, 89% of those with daytime urinary incontinence and 63% of those with bed-wetting became dry.

Diurnal Enuresis, Incontinence

25. Robson, W. Diurnal enuresis. *Pediatr. Rev.* 12:407–412, 1997.
The differential diagnosis considered, from "micturition deferral" to UTI to anatomic and physiologic problems. Also see Hurley, R. Enuresis: The difference between night and day. Pediatr. Rev. *12:167–170, 1990, even if only for the quote: "Wetting the bed is mainly a developmental issue, and wetting the pants is a behavioral one."*
26. Maizels, M., et al. Diagnosis and treatment for children who cannot control urination. *Curr. Probl. Pediatr.* 23:402–450, 1993.
An extensive review (48 pages, 196 references) plus suggested sources (including "lay" books) and urine alarm companies' names and addresses. Discusses incontinence as well as enuresis but clearly focuses on the latter.

28. RECURRENT PAIN SYNDROMES: ABDOMINAL PAIN, HEADACHE, AND CHEST PAIN

Evan Charney and Kenneth B. Roberts

Recurrent abdominal pain, headache, limb pain, and chest pain in childhood and adolescence, although distinctly different syndromes, are grouped together here because they share certain features of presentation and management: (1) They occur commonly in childhood, but only a minority of those with symptoms seek medical attention. (2) The recurring nature of the pain defines a syndrome distinct from isolated attacks of acute pain. (3) In a minority of children, a serious (at times urgent) medical problem is present that requires prompt identification. (4) In many cases, the symptom is exacerbated by factors in the environment of the child or family, which must be addressed to deal successfully with the problem. (5) The management involves a thorough history and physical examination (even if the child and family are well known to the physician), often a minimal laboratory investigation, and a series of scheduled visits over an interval of time for satisfactory management.

Recurrent abdominal pain may be considered a model for the other recurrent pain syndromes. It occurs in 10–15% of children between 5 and 15 years of age. It is defined as three or more episodes of abdominal pain severe enough to interrupt normal activities and occurring over a period longer than 3 months. It is chiefly a problem during the school years, with a peak incidence just before puberty in girls and perhaps somewhat earlier in boys. There are more than 100 somatic conditions that can produce or are associated with chronic abdominal pain, including gastrointestinal dysfunction; gynecologic, urologic, neurologic, and metabolic conditions; and inflammatory or infectious disease. These can range from unequivocal organic disease (e.g., Crohn disease, renal calculus) to mild dysfunction (e.g., lactose intolerance). How much pain the child reports and how much anguish and urgency accompany the complaint may be influenced (either exacerbated or diminished) by several factors: the temperament of the child, the family's and child's lifestyle or habit patterns, and current or past stressful events. Examples of relevant child or family temperament factors include whether the child is stoic or, conversely, commonly complaining of pain, and whether there is a “model” in the family for such behavior. The family's or child's lifestyle may be so hectic that there is “no time for pain”; alternatively, the child with little to do may dwell on sensations emanating from the abdomen. Critical events to consider include a history of separation, such as a death in the family, impending divorce, or other perceived or threatened losses.

The diagnostic evaluation of a child with recurrent abdominal pain should itself be a therapeutic process. It should convey to the family that the physician takes the problem seriously, understands the disruption and anguish it causes, and plans to explore it thoroughly, together with the family. It is essential that organic and environmental factors be considered together, rather than sequentially. “Ruling out organic problems” first can be an extensive (potentially never-ending) task that delays addressing important emotional and environmental factors and implies that they are less likely. Considering the influence of family and personality factors from the outset gives an important message for parents who might have difficulty accepting a multifactorial basis for their child's problem should it be introduced later, as an apparent afterthought. Moreover, if an organic problem is identified, understanding the emotional climate in the family is valuable in management.

The most useful initial diagnostic step for the physician is to recognize that the child has a recurrent pain syndrome. The child may have been seen repeatedly in the office or clinic for individual episodes and been given symptomatic medication or reassurance that nothing urgent (e.g., appendicitis) was occurring. When the parent or clinician recognizes that the problem is a long-standing one, the child should be scheduled for a longer assessment. It may be helpful to tell the parents that this problem is too important to be handled in the usual brief office visit and that a longer session will be necessary to begin a careful assessment. In particular, unless a specific organic lesion is immediately apparent, the physician should resist the impulse to order a battery of laboratory studies.

Before the next visit, office records should be reviewed and visits related to abdominal pain summarized. The next step is a thorough history and physical examination (valuable even if the patient has previously been seen in the practice). The location of the pain is important. Most children identify the periumbilical area. As pointed out by Apley (and now known as “Apley's law”), the farther the pain is from the umbilicus, the more one should suspect a specific cause. The character and timing of the abdominal pain itself are not as useful as might be hoped. In Apley's series, neither description nor severity (sharp or dull; excruciating and brief, or chronic and low-grade) helped to differentiate organic from nonorganic pain. Associated phenomena, such as headache, pallor, and vomiting, were commonly found in these children, perhaps relating to an autonomic imbalance. Symptoms such as dyspepsia, bloating after taking milk products, diarrhea, or constipation may direct attention to specific concerns.

The physician should pay particular attention to the presence or absence of the psychological factors mentioned above. What do the parents and child think is wrong? Are they worried about some serious condition (e.g., cancer, leukemia) because of prior family experience? It is helpful at some point to interview parents and child separately as well as together to provide varied insights about family interactions and individual fears.

Basic laboratory studies include urinalysis and urine culture, a total and differential white blood cell count, an erythrocyte sedimentation rate, and stool examination for occult blood.

It may take one or two visits to obtain all the necessary information, at which point the cases tend to fall into one of four categories:

1. Fairly definitely organic. Positive findings on history, physical examination, or baseline laboratory studies are suggestive of an organic lesion. This will occur perhaps 10% of the time. There may or may not be associated temperament or situational aspects as well.
2. Fairly definitely psychogenic, with little or no organic component. The family and personal history offer positive evidence of a serious emotional problem in the child (e.g., depression) or significant family psychopathologic problems. Perhaps 10% of cases will fall into this category.
3. A combination: A physiologic dysfunction is identifiable, modified strongly by one or more factors of temperament, critical event “trigger,” or lifestyle pattern. Perhaps 60% of cases will fall into this category.
4. Unclear. No strong evidence for physiologic dysfunction or psychosocial factors. Perhaps 20% of cases will fall into this category.

Patients in whom an organic lesion seems evident require whatever further diagnostic or therapeutic maneuvers are appropriate for the disease in question. For children in whom an emotional cause appears likely, it is essential to meet with the family and inform them of that impression. It is most important that the physician convey to the parents that further studies are not indicated at that time and, indeed, can be counterproductive. To continue ordering “just one more test” prevents the family and physician from addressing the emotional problem directly. It delays resolution of the problem and also identifies the child as someone with a possible chronic physical difficulty, a label difficult to shed and one with potentially adverse effects on the child's future emotional development.

If a clear secondary gain has been identified, it must be eliminated. For example, the child must return promptly to school and, once in school, must not repeatedly be sent home. The child must not receive an inordinate amount of sympathy and attention for the symptom. Many clinicians find it useful to have the child (or parent, if the child is too young) start and maintain a diary of pain episodes: when they come, what the child was doing at the time, severity, duration, measures used for relief, effectiveness of the measures. The physician should then offer to see the child regularly for several visits (on a weekly or biweekly basis), using these visits to discuss the diary and the child's daily activities, and to learn how the child and family cope with various stressors. These visits enable the physician to determine whether advice has been followed and if there are more serious problems in the family not previously appreciated. Once agreed on, these visits should not depend on the

child's having abdominal pain as a “ticket of admission.”

The majority, though not all, of the patients whose pain is on an emotional basis will respond to this management by a diminution in the frequency of—or at least in the turmoil accompanying—the episodes. Frequently, the diary itself becomes burdensome enough to the child that complaints are extinguished! The long-term prognosis may not be so optimistic, however; two thirds of patients are free from abdominal pain in adulthood, but only one third are symptom-free. If the related emotional problems are identified and dealt with, the long-term prognosis for adequate psychological functioning may be improved. The physician's major contribution to the family may be to avoid or alter a pattern in which the child learns to use bodily symptoms to cope with problems rather than confronting and dealing with problems directly.

Headaches are reported to occur at least several times per month in approximately 5% of 7-year-olds (an equal number of boys and girls). The prevalence of headaches increases throughout childhood, and by 15 years of age 20% of girls and 10% of boys report recurrent headaches.

Headache pain is produced by a limited number of mechanisms. The brain itself is insensitive to pain; the pain-sensitive structures within the cranium include veins and arteries at the base of the skull, portions of the dura, and the fifth, ninth, and tenth cranial nerves. Pain results from vasodilatation, inflammation, traction, or direct pressure by tumor or mass on these structures. Significant extracranial causes of headache include sustained contraction of scalp, face, or neck muscles, or abnormalities within the sinuses or orbit, external and middle ear, and dental structures.

There are several patterns of headache that can be distinguished in children. Migraine is the most frequent (perhaps one third of recurrent headaches in children). Other types include non-migraine vascular headache, tension-type headache (formerly called muscle contraction headache or tension headache), and headache associated with other processes, such as intracranial inflammation or other diseases of head and neck structures. Cluster headaches (several daily episodes of nonthrobbing “clusters” occurring each day for a period of weeks or months, with interval remission) are uncommon in children but do occur.

The International Headache Society (IHS) has simplified migraine terminology: What was formerly called classic migraine is now migraine with aura, and common migraine is now migraine without aura. Migraine with aura appears to have a genetic basis, with first-degree relatives having a four-fold increase in migraine. Migraine with aura is less common than migraine without aura, but in children it may be difficult to ascertain whether the child has experienced an aura (e.g., flashing lights, scotomata, an odor, or visual distortions). Familial hemiplegic migraine is classified with migraine with aura.

The IHS criteria for migraine without aura are designed to exclude important intracranial pathology. Headaches are described as lasting 4–72 hours, with at least two of the following characteristics: unilateral location; pulsating quality; moderate or severe intensity; aggravated by routine physical activity. In addition, headaches are associated with nausea/vomiting and/or phonophobia/photophobia. When applied to children, these criteria are specific but not as sensitive as in adults, since the headaches in children may last only 2 hours and some of the qualitative features are less common.

Other forms of migraine in the IHS classification are ophthalmoplegic migraine, retinal migraine, and childhood periodic syndromes that may be precursors to or associated with migraine: benign paroxysmal vertigo of childhood and alternating hemiplegia of childhood. Cyclic vomiting probably should be added to the list of such syndromes.

The diagnostic evaluation of a child with chronic headaches is largely based on the medical history: the location, frequency (including time of day), character, and severity of the pain; associated symptoms; change in pattern over time; triggering (and ameliorating) factors; family history; and social history, including the current psychological milieu. A normal physical examination, including a detailed neurologic examination, is reassuring, while focal neurologic signs, indication of increased intracranial pressure, or signs of ill health suggest the need for further evaluation. Tests rarely yield a diagnosis not already suspected. Computed tomography (CT) scan or magnetic resonance imaging should be reserved for cases where a mass lesion is suspected or a neurologic deficit identified. Skull films and electroencephalography should be obtained only on specific indication. Lumbar puncture is indicated where central nervous system (CNS) infection or bleeding is suspected, but should be preceded by CT scan in the presence of papilledema or suspected mass lesion.

The treatment plan involves attention to precipitating stressful environmental factors. Simple analgesics are usually sufficient to control most childhood headaches, even in the majority of patients with migraine. Relaxation techniques and biofeedback are increasingly used modalities of therapy. There are very few clinical trials of anti-migraine agents in children. Preadolescent children with migraine less often require strong abortive agents (e.g., ergotamine) or prophylactic agents (e.g., propranolol) than adolescents and adults, but trials in children may well identify more effective treatment than is currently provided.

The prognosis of migraine and other chronic headache (where no organic lesion is identified) is generally favorable; two thirds are significantly improved or symptom free after a decade in follow-up studies. For migraine headaches, onset in early childhood has a better prognosis than does onset during adolescence.

Chest pain occurs less commonly than does headache or abdominal pain, but the perceived seriousness of the symptom often prompts a medical consultation. More than 650,000 office visits are made annually for chest pain in patients 10–21 years of age, and in one study one fourth of adolescents reported more than three episodes in the prior year. The peak incidence in those younger than 21 years occurs in early adolescence, a somewhat older age on average than the child with recurrent abdominal pain. In most series, one third to one half of patients have no defined etiology (an even higher proportion in those with symptoms for longer than 6 months). In approximately one third of patients, a musculoskeletal cause is identified (e.g., costochondritis, anterior chest wall tenderness). A myriad of diagnoses accounts for the remaining cases, and several important ones may not immediately be evident. In adolescents, hyperventilation syndrome is common, and the associated discomfort and anxiety may be perceived as chest pain; gynecomastia in males may be “painfully” embarrassing; and occasionally depression may present as chest pain. Asthma, particularly exercise-induced asthma, is a relatively common cause of chest pain but should be identifiable. Heart disease as a cause of pain in the anterior part of the chest is extremely rare, although almost universally suspected by family and patient. It is important to remember sympathomimetic drug use, particularly ephedrine and cocaine, as a cause of acute chest pain.

The diagnostic approach outlined for recurrent abdominal pain applies to this symptom as well, based on a very thorough history and physical examination both to identify the rare serious or urgent case and to reassure the family and patient. In the physical examination, a full range of motion of upper extremities, neck, and trunk should be tested. An electrocardiogram and chest radiograph are often obtained but are rarely positive if cardiac disease is not suspected. The physician needs to deal with any functional impairment the symptom may have caused, and as with abdominal pain, several visits may be required to sort out the problem.

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2. Rickert, V., and Jay, M. Psychosomatic disorders: The approach. *Pediatr. Rev.* 15:448–454, 1994.
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Recurrent Abdominal Pain: General Reviews

3. Apley, J. *The Child with Abdominal Pains* (2nd ed.). Oxford: Blackwell, 1975.
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4. Lake, A. Chronic abdominal pain in childhood: Diagnosis and management. *Am. Fam. Phys.* 59:1823–1830, 1999.
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   Of 507 middle and high school students, 75% acknowledged abdominal pain; in 13–17%, the pain occurred weekly and was severe enough to affect activities in 21%. Of those with abdominal pain, 17% of high school students and 8% of middle school students had symptoms of irritable bowel syndrome.

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11. Hotopf, M., et al. Why do children have chronic abdominal pain, and what happens to them when they grow up? Population based cohort study. *B.M.J.* 316:1196–1200, 1998.
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"A great deal has been learned about what growing pains are not, but very little is known about what they are." Heat, massage, and simple analgesics remain the treatment.

29. SEXUAL DEVELOPMENT

Margaret E. Mohrmann, Craig A. Alter, and Kenneth B. Roberts

The process of normal sexual development can be divided into three discrete components: 1) *differentiation* of the bipotential fetal gonad and development along either male or female phenotype; 2) *maturation* (puberty) with the attainment of secondary sexual characteristics and the capacity for fertility; and 3) the *psychological* concept of *sexuality.*

Normal sexual *differentiation* of the human fetus depends on both the sex chromosome complement and the presence or absence of substances produced by the fetal testis. The presence of a single gene, termed “SRY” (sex-determining region of the Y chromosome), is necessary for intrauterine differentiation of the indifferent gonad into testes rather than ovaries. The normal fetal testis produces müllerian inhibiting factor (MIF) and testosterone. Müllerian inhibiting factor is necessary for the regression of the anlage of female internal genitalia (uterus, fallopian tubes, and upper third of the vagina). Testosterone is required for development of male internal genital structures (epididymis, vas deferens, and seminal vesicle) from the embryonic wolffian duct system; testosterone must be metabolized to dihydrotestosterone (DHT) for normal differentiation of male external genitalia. Female internal reproductive organs develop if MIF is absent, whether because of normal ovarian differentiation or testicular dysfunction; female external genitalia develop if systemic androgen action is inadequate, whether because of androgen deficiency, inability to convert testosterone to DHT, or androgen resistance. Interference with this highly organized process at any level—chromosomal, gonadal, or target organ—will result in abnormal isosexual differentiation or varying degrees of sexual ambiguity.

Klinefelter syndrome (seminiferous tubule dysgenesis), which occurs in one of 1,000 liveborn males, is the most common major abnormality of sexual differentiation. It is most frequently associated with an XXY genotype, but may include any variant with at least one Y chromosome and at least two X chromosomes. Internal and external genitalia are male because adequate masculinizing factors are present in utero. Prepubertal boys with this disorder have small testes that appear normal histologically; with the onset of puberty, the seminiferous tubules become increasingly hyalinized and fibrosed, with impairment of spermatogenesis. Puberty begins at a normal age but fails to progress. Prepubertal males may be diagnosed because of associated personality disorders and mental retardation. In adolescence or adulthood, males with Klinefelter syndrome frequently present with gynecomastia or with some degree of failure of secondary sexual development. On physical examination, a eunuchoid body habitus, female escutcheon of pubic hair, and small, firm testes are found. Hormonal evaluation of a pubertal-aged patient reveals a low serum testosterone concentration associated with elevated gonadotropins, consistent with primary testicular failure. Androgen supplementation will improve bone density, self-esteem, and body image in many patients; bilateral mastectomy may be required if the gynecomastia causes significant psychosocial problems. Psychological counseling may also be beneficial.

Turner syndrome (gonadal dysgenesis), occurring in up to 1 in 2,000 liveborn females, refers to the combination of bilateral streak gonads, sexual infantilism, short stature, and certain other somatic anomalies. It results from a loss of all or part of an X chromosome. Clinical expression of the disease is most complete in those with a 45,X complement, which accounts for more than 50% of cases; patients with mosaic or structural X chromosomal abnormalities have more variable degrees of ovarian dysfunction and of phenotypic abnormalities. Internal and external genital structures are always female, but normal secondary sexual maturation fails to occur because of absent or inadequate estrogen production. The most frequent finding in the prepubertal child is significant growth retardation (see Chap. 19); when the diagnosis is delayed, affected females present in adolescence because of absent or deficient breast development. Physical stigmata, not necessarily present in all patients, include low hairline, webbed neck, shieldlike chest, short fourth metacarpal, cubitus valgus, and multiple nevi. In the neonatal period, the diagnosis may be suggested by lymphedema of the feet and hypoplastic nails. Patients with Turner syndrome have an increased incidence of left-sided cardiac structural lesions (particularly coarctation of the aorta), renal and renovascular anomalies, and sudden death due to a dissecting aneurysm. Hypertension, autoimmune thyroid disease, carbohydrate intolerance, scoliosis, and middle ear infections also occur more frequently in these patients. Ovarian failure in infants and adolescents can be demonstrated by increased serum gonadotropins; between ages 4 and 10 years they may be normal. Documentation of an abnormal karyotype is necessary for confirmation and to exclude the possibility of Y-chromosomal material; if the latter is found, bilateral streak gonadectomy should be performed because of the risk of gonadoblastoma. Early diagnosis is important not only to identify associated abnormalities, but also to enable optimal initiation of growth hormone therapy. This significantly improves adult height prediction and permits the introduction of estrogen replacement at an age-appropriate time. Membership in national support groups and psychological counseling are helpful for many patients. Oocyte donation, in vitro fertilization, and embryo transfer have changed the outlook with regard to child-bearing.

Pseudohermaphroditism is a disorder in which the external genital phenotype is not consistent with the genotype. In the more common form, female pseudohermaphroditism, an XX karyotype, normal ovaries, and female internal genital structures are found in association with virilized external genitalia, varying degrees of phallic development and fusion of labioscrotal folds. Virilization is the result of excessive levels of androgens, usually due to congenital adrenal hyperplasia, but rarely secondary to androgen-producing adrenal or ovarian tumors, exogenous androgens, or maternal virilizing disorders or medication. Male pseudohermaphrodites have XY karyotypes, testes, and male internal structures but have incompletely masculinized external genitalia. The degree of failure of masculinization ranges from mild hypospadias to unequivocally female genitalia, as in the syndrome of complete androgen insensitivity (“testicular feminization”). Male pseudohermaphroditism is usually the result of a defect in testosterone synthesis, metabolism to DHT, or responsiveness of target-cell receptors. Microphallus, with or without cryptorchidism, may be due to congenital hypopituitarism, and, when present, may be associated with hypoglycemia and midline facial defects, such as cleft palate. Ambiguous genitalia in association with rectal or urologic abnormalities are usually due to an abnormality in embryogenesis, and not associated with any chromosomal abnormalities or errors of androgen synthesis or action.

In *true hermaphroditism*, both testicular and ovarian tissues are present. The ambiguity of the external genitalia is variable, and there may be no evidence of anomalous sexual differentiation until discordant secondary sexual development occurs at the time of puberty. Most true hermaphrodites have XX karyotypes, but sex chromatin mosaicism is not uncommon. The diagnosis is confirmed by histologic study of gonadal tissue.

Mixed gonadal dysgenesis is characterized by a unilateral testis and a contralateral streak gonad; the genotype is usually 45,X0/XY, but mosaicism may be present. Internal structures are female, but varying degrees of external genital ambiguity which may be asymmetric are found; one third of patients will exhibit physical stigmata suggestive of Turner syndrome. Patients with gonadal dysgenesis are at increased risk for both gonadal and Wilms tumors.

Management of the infant with ambiguous sexual development constitutes a medical and social emergency, not only because of the need for appropriate gender assignment, but because of the possibility of serious underlying medical conditions, such as congenital adrenal hyperplasia or congenital hypopituitarism. Since gender assignment usually occurs in the delivery room, it is imperative that the obstetrician or pediatrician avoid mentioning the sex of the child whenever sexual ambiguity exists, however minor it may seem. A frequently recommended phrase is that the baby's genital structures “have not developed completely.” This explanation may allay parental fears, avoid the potentially devastating psychosocial consequences of an erroneous initial sex assignment, and allow time for a rational and expeditious evaluation. In addition to a good history, physical examination should focus on whether gonads are palpable and whether perineal malformations are present. A careful rectal examination is performed to assess whether a uterus is present; the extrusion of mucus from the urogenital sinus when pressure is applied may be a valuable clue. An ultrasound of the abdomen is also frequently helpful in visualizing internal female structures. Karyotype and steroid determinations (initially 17-hydroxyprogesterone, 11-deoxycortisol, 17-hydroxypregnenolone, and testosterone, measured in a laboratory experienced in pediatric endocrinology) will elucidate the chromosomal sex, whether genetic abnormalities are present, and whether the etiology is likely to be congenital adrenal hyperplasia. (Many states include measurement of 17-hydroxyprogesterone in their newborn screening program.) Blood glucose and assessment of pituitary function are performed if hypopituitarism is suspected. Further evaluation is performed as necessary. Because of the rarity of the problem, the complexity of the diagnostic workup, and surgical considerations, involvement of an experienced team, including a pediatric endocrinologist, geneticist, pediatric surgeon, and pediatric radiologist, is recommended for optimal management. Ongoing support for and communication with the family will minimize the stress engendered by the uncertainties of diagnosis, outlook, and management; psychological counseling is a valuable adjunct. In unfortunate cases where sex reassignment and correction of discordant external

genitalia are necessary, these should be done before the age of 18–24 months if unambiguous gender identity is to be achieved.

During the period between birth and the time of *sexual maturation (puberty)*, the pituitary-gonadal axis operates at a low level, with very small amounts of hormones produced. The initiation of puberty is dependent on a disruption of this balance by a decrease in hypothalamic and pituitary sensitivity to circulating levels of gonadal steroids, such that higher levels of androgen or estrogen are required for feedback inhibition of gonadotropin secretion. The factors effecting the "resetting" of the axis and increased activity of the hypothalamic "pulse generator" are not clearly defined, but probably include body mass and degree of skeletal maturation. Adrenal maturation ("adrenarche"), which involves increased secretion of the adrenal androgen dehydroepiandrosterone sulfate (DHEA-S), is a separate process that precedes true puberty by about 2 years.

Sexual maturation at puberty (development of secondary sexual characteristics and the capacity for fertility) normally progresses in an orderly pattern, often described in terms of the "Tanner stages" of growth of pubic hair in both sexes and of breasts in the female, and genitalia in the male. (Tanner stage I is prepubertal; Tanner stage V is mature adult). Testicular enlargement heralds the onset of true puberty in the male; the growth spurt occurs in the middle to end of this process, usually at around 14 years of age. In the female, true puberty begins with the appearance of breast buds and culminates in menarche; the growth spurt occurs early in female puberty, usually at 12 years of age. The average time from beginning to end of puberty is 2 years for females and 3 years for males, although there is considerable individual variation.

Delayed puberty is defined as the absence of secondary sexual characteristics by the age of 13 years in a female or 14 years in a male. Constitutional delay of growth and adolescence, a normal variant of somatic and sexual development, is the most common cause (see Chap. 19, Physical Growth) and is frequently associated with a positive family history. It must be distinguished from a persistent failure of sexual maturation, which can be due to deficient production of gonadotropins (hypogonadotropic hypogonadism) or to primary hypogonadism (hypergonadotropic hypogonadism). In patients with hypogonadotropic hypogonadism, the possibility of a hypothalamic or pituitary abnormality should be considered, particularly if evidence for associated anterior or posterior pituitary hormonal deficits is obtained. The presence of a midline facial defect (e.g., cleft palate) or of pendular nystagmus, due to optic hypoplasia, suggests the possibility of congenital causes of hypopituitarism. Acquired etiologies include a tumor (especially a craniopharyngioma) or damage due to such insults as trauma, infection, granuloma, or irradiation; when hypogonadism is associated with anosmia, the diagnosis of Kallmann syndrome is suggested. Chronic systemic diseases, undernutrition, hypothyroidism, and a prolactin-secreting pituitary tumor may all mimic hypogonadotropic hypogonadism, but are reversible when the underlying condition is treated. Hypergonadotropic hypogonadism is due to gonadal agenesis or dysgenesis, or to a postnatal process (such as viral infection, trauma, irradiation, or chemotherapy) that has destroyed the gonads. The treatment of failure of sexual maturation consists of administration of gonadal hormones to produce and maintain secondary sexual characteristics.

Sexual maturation is considered precocious if secondary sexual characteristics appear before the age of 9 years in males or 8 years in females. True isosexual *precocious puberty* implies early maturation of the hypothalamic-pituitary-gonadal axis. Whereas delayed puberty is more common in males, precocious puberty is more common in females. In 80% of females, but in less than 40% of males, it is idiopathic. Causes of nonidiopathic precocious puberty include certain tumors (in particular, hypothalamic hamartoma, germinoma, optic glioma, craniopharyngioma, and pinealoma); there is an increased incidence of precocious puberty in patients with neurofibromatosis and in patients with congenital brain dysfunction, such as cerebral palsy or hydrocephalus. Rarely, patients with longstanding hypothyroidism present with precocious rather than delayed puberty. True isosexual precocity may also occur in individuals who have received cranial irradiation or in patients with the syndrome of septo-optic hypoplasia; when accompanied by growth hormone deficiency, adult height may be severely compromised.

The precocious appearance of secondary sexual characteristics in the absence of hypothalamic-pituitary maturation is termed *precocious pseudopuberty*, and is usually due to autonomous sex steroid production by the adrenals or gonads, to ectopic secretion of human chorionic gonadotropin (hCG), or to exposure to estrogens or androgens from exogenous sources. Precocious pseudopuberty, rather than true puberty, in males is usually suggested clinically by the absence of bilateral testicular enlargement. Late onset congenital adrenal hyperplasia and gonadotropin-independent precocity due to testicular Leydig cell hyperplasia are important to consider in males; in the latter condition, an autosomal-dominant, male-limited family history may be obtained. The presence of irregular cafe au lait spots and bony lesions suggests McCune-Albright syndrome. Rapid onset and progression are characteristic of a tumor. Pseudoprecocity due to an hCG-secreting tumor may be due to a hypothalamic germinoma or a hepatoma. Exogenous sources of sex steroids include oral contraceptives and even estrogen-contaminated meat in females, and anabolic androgens or testosterone-containing "natural" vitamin preparations in males.

True sexual precocity must be differentiated from *premature adrenarche (pubarche)* and *premature thelarche*, benign variants in which isolated sexual hair growth or breast development, respectively, is found, unassociated with increased linear growth or other evidence of pubertal development. This distinction can usually be made by careful history and physical examination, measurement of growth, and observation for evidence of further sexual development during the ensuing months. Skeletal maturation (i.e., bone age) should be assessed if there is any evidence of accelerated linear growth or pubertal progression.

Diagnosis of true isosexual precocity is confirmed by demonstration of a pubertal gonadotropin response to gonadotropin-releasing hormone (Gn-RH). In contrast, in precocious pseudopuberty, the gonadotropin response to Gn-RH is suppressed because of the presence of increased sex steroids. In adrenarche, serum DHEA-S rises, but the Gn-RH response is prepubertal; in thelarche, both DHEA-S and Gn-RH testing are prepubertal.

Treatment of early sexual development is directed at the cause. In patients with true isosexual precocity, pharmacologic therapy with a long-acting Gn-RH agonist that blocks gonadotropin secretion is indicated to reverse the untoward psychosocial consequences of premature sexual development and to improve adult height prediction. Optimal results are obtained if treatment is started before significant growth potential has been lost irretrievably because of advanced skeletal maturation. Psychological counseling may be helpful in selected cases; it is important to recognize that both the psychosexual orientation and cognitive development of the precociously mature child are age appropriate rather than appropriate for the stage of sexual maturation.

The development of *sexuality*, although usually discussed in the context of adolescence, is a lifelong process, involving the development of gender identity (the experience of one's self as male or female); gender role (gender-specific behavior); adult sexual orientation (the choice of gender of sexual objects); and the desire for parenting. The role of nature versus nurture continues to be controversial. Although gender-specific behavior is probably influenced to some degree by prenatal hormone levels (e.g., prenatally virilized females with congenital adrenal hyperplasia), gender identity is determined by the gender of rearing. The task of the physician in helping patients develop a healthy sexuality involves not only counseling about intercourse and contraception, but also anticipatory guidance and reassurance, especially concerning secondary sexual characteristics, sexual fantasies, sexual orientation, and the importance of nonsexual physical contact in loving human relationships.

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30. ADOLESCENT GYNECOLOGY

Maria T. Britto

Adolescent women frequently present to health care providers with expressed and unexpressed reproductive health concerns. Gynecologic issues must be considered in both preventive care visits and in the evaluation of adolescents with abdominal pain and other nonspecific complaints. Common issues include menstrual irregularities, dysmenorrhea (painful menses), vaginal discharge, contraception, and pregnancy.

History plays a critical role in the evaluation of a young woman with gynecologic concerns. A secure and, in most cases, confidential environment is a prerequisite to obtaining an accurate history. In addition to the details of the primary complaint, the history should include (1) date of menarche (first menstrual period); (2) usual menstrual pattern/frequency, duration of flow, and presence of or change in associated discomfort; (3) date of last normal menstrual period; (4) prior pregnancy; (5) use of contraceptives; (6) presence of vaginal discharge; (7) history of consensual or nonconsensual sexual intercourse; and (8) history of sexually transmitted infections. Most adolescents with gynecologic concerns will require examination of the genitalia. The extent of this examination will depend on the presenting complaint, the physical maturity of the patient, and the history of sexual activity. Tanner staging and evaluation of external anomalies can be done by inspection. In cases where a speculum examination is not possible, the presence of the cervix and uterus can usually be determined by rectal examination. Thorough explanation of the adolescent pelvic examination can be found in the referenced texts.

Menstrual irregularity is perhaps the most common gynecologic concern; 50% of female adolescents report some form of menstrual dysfunction. Some of these concerns reflect developmental processes and normal variation among women. The normal cycle length can vary from 21–45 days; normal menstrual flow may last from 2–7 days. Quantitation of menstrual flow is difficult and does not correlate well with reports of pad or tampon usage. Menarche usually occurs within 3 years of the onset of secondary sexual characteristics, 1 year after the peak of growth velocity (growth spurt), or by the age of 16. Absence of either of these is termed primary amenorrhea. Secondary amenorrhea is conservatively defined as the absence of previously established menses for at least 6 months. Patients with amenorrhea can be categorized according to the presence or absence of other secondary sexual characteristics. The evaluation of patients with absent secondary sexual characteristics is described in Chap. 29. The differential diagnoses for patients with normal secondary sexual characteristics and primary or secondary amenorrhea are similar. The most common causes in general practice are pregnancy and stress. Other common etiologies in this population include exercise, weight loss, medications, chronic illness, and problems with the hypothalamic-pituitary-ovarian axis.

Evaluation includes a thorough history and physical examination with attention to growth parameters, Tanner staging, and pelvic examination. If no abnormalities are found and pregnancy is excluded, a progesterone challenge test can be used to determine the integrity of the hypothalamic-pituitary-ovarian axis. The patient is given oral progesterone for 5–10 days and is then observed for withdrawal bleeding. The presence of withdrawal bleeding indicates adequate estrogen stimulation of the endometrium. This suggests that the amenorrhea is due to hypothalamic dysfunction (usually due to stress, drugs, inadequate nutrition, or reduced body fat proportion) or to an endocrine disturbance (most commonly hypothyroidism, pituitary adenoma, or hyperandrogenism associated with the polycystic ovary syndrome [PCOS]). The PCOS is characterized by chronic anovulation and oligomenorrhea. It may also include obesity, insulin resistance, hirsutism, and infertility. On laboratory testing, a luteinizing hormone–follicle-stimulating hormone (LH/FSH) ratio greater than 3 suggests PCOS. Lack of withdrawal bleeding following progesterone indicates inadequate circulating estrogen to produce a proliferative endometrium. This can be due to a central nervous system lesion in which gonadotropin secretion is suppressed, or to ovarian failure, which is characterized by very high levels of FSH. In addition, some patients with severe weight loss (anorexia nervosa) or severe substance abuse may not have withdrawal bleeding following progesterone. Treatment depends on the underlying cause of amenorrhea. It may range from environmental manipulation, such as decreased exercise and increased calories, to hormonal supplementation to support cyclic endometrial sloughing.

Dysfunctional uterine bleeding (DUB) is irregular, usually painless, profuse bleeding that occurs outside of the normal cycle duration limits and is not due to other identifiable pathology. Thus, a teen with DUB may present with several heavy periods only weeks apart, or she may experience profuse bleeding following a period of amenorrhea. Dysfunctional uterine bleeding is especially common in the first 2 years following menarche, the period of continuing maturation of the hypothalamic-pituitary-ovarian axis. A midcycle surge of LH is often absent; consequently, an ovum is not released and progesterone levels do not rise. Continued estrogen dominance causes continuation of the unstable proliferative endometrium and eventual sloughing with associated heavy bleeding. While 95% of abnormal uterine bleeding in adolescents is related to hypothalamic-pituitary-ovarian immaturity, 5% is due to other pelvic pathology. If the bleeding is severe enough to require hospitalization, the rate of underlying pathology (most commonly platelet dysfunction due to von Willebrand's disease) rises to 19%. Abnormal bleeding associated with the first menstrual period also increases the risk of pathology. The differential diagnosis of abnormal bleeding includes coagulopathy, trauma, pregnancy complications, sexually transmitted infection, endocrine problems such as hypothyroidism and PCOS, systemic disease, and medication effects. Thus, the diagnosis of DUB is one of exclusion. In the presence of a typical history, normal hematocrit, and normal examination, the patient can be reassured and asked to keep a menstrual calendar to document her bleeding pattern. In addition, iron should be prescribed. For bleeding associated with mild-to-moderate anemia, but no clinical instability, the bleeding can be hormonally suppressed, usually with oral contraceptives. Severe anemia or clinical instability necessitates hospitalization for stabilization, hormonal suppression of bleeding, and evaluation for underlying pathology.

Dysmenorrhea is crampy lower abdominal pain associated with menses. Nausea, vomiting, diarrhea, headaches, and lower-extremity cramps are commonly associated complaints. Unlike DUB, dysmenorrhea usually occurs in the setting of ovulatory menstrual cycles. Thus, the prevalence increases throughout adolescence, with 72% of 17-year-old women reporting symptoms. Most dysmenorrhea is not associated with detectable pelvic pathology (*primary dysmenorrhea*) and is believed to be prostaglandin mediated. Among the widespread effects of prostaglandin-F_{2a} and -E_2 are increased myometrial tone. These effects probably require progesterone priming, explaining the higher incidence of dysmenorrhea with ovulatory cycles. Nonsteroidal anti-inflammatory agents provide first-line therapy for primary dysmenorrhea and are effective for 80–85% of women. Patients whose symptoms are unresponsive to nonsteroidal agents can often be treated successfully with combined oral contraceptive pills. These likely work by suppressing ovulation. *Secondary dysmenorrhea* is associated with detectable pelvic pathology. While the differential diagnosis is extensive, common etiologies include infection, endometriosis, and congenital malformations. The risk of underlying pathology rises if significant pain is associated with the first menses, if it is unresponsive to nonsteroidal agents, or if symptoms worsen after a period of regular, presumably ovulatory, cycles.

Premenstrual syndrome (PMS) is a complex of physical and emotional symptoms that occur during the luteal phase of the cycle and resolve with menses. About 5–10% of adult women report symptoms severe enough to interfere with daily functioning. Little is known about the prevalence of the syndrome in adolescents, although most adolescent females report at least some premenstrual symptoms. The pathogenesis is unclear. Serotonin reuptake inhibitors are effective for those with disabling PMS, although they provide more relief of emotional than physical symptoms. The efficacy of other treatments, such as vitamins, dietary modifications, diuretics, and exercise, is less clear.

Vulvovaginitis occurs in both prepubertal and pubertal females. Among sexually active adolescents, vaginal complaints must always raise suspicion of a sexually transmitted infection. Other causes of vaginal discharge include inadequate hygiene, chemical irritation, foreign bodies (such as a retained tampon) and non–sexually transmitted infections. In the pubertal female, estrogen stimulation of the vaginal mucosa induces increased epithelial cell turnover and increased mucus production. This leads to a milky discharge known as leukorrhea, which is often mistaken for a pathologic process by patients and families.

Candida, or *yeast*, is a common cause of an itchy or painful, white, cheesy vaginal discharge. The vulva and vagina may be severely inflamed. The diagnosis can usually be made by identifying typical yeast forms on microscopic examination of the discharge using potassium hydroxide to lyse other cellular elements. Topical treatment with an antifungal agent or a single oral dose of fluconazole is usually successful. Topical treatment is preferred for external and/or severe disease. Severe, unresponsive, or persistent *Candida* infections raise concern of diabetes mellitus or immune deficiency, such as that associated with human immunodeficiency virus

(HIV) infection.

Patients with *bacterial vaginosis* often complain of malodorous (often fishy) vaginal discharge. It may cause itching and, at times, lower abdominal pain. It is felt to result from an alteration in the normal vaginal flora leading to an overgrowth of anaerobes and *Gardnerella vaginalis* and loss of normal lactobacilli. The diagnosis is based on clinical symptoms, vaginal pH ³ 4.5, the presence of ³20% clue cells (epithelial cells coated with gram-negative rods) on wet mount of vaginal secretions, and a positive “whiff” test (a fishlike amine odor that is liberated when vaginal secretions are mixed with potassium hydroxide). Increased white blood cells in the secretions suggest a coinfection such as chlamydia or trichomonas. Women with bacterial vaginosis are generally treated with oral or topical metronidazole or clindamycin. Although bacterial vaginosis was formerly believed to represent a purely nuisance vaginal condition, recent evidence links bacterial vaginosis to pelvic inflammatory disease and pregnancy complications such as preterm delivery. Many now believe that sexual transmission occurs.

Although adolescent sexual activity has finally begun to decline in the United States, more than 70% of American females have had sexual intercourse by age 19. Helping adolescents access *contraception* and finding contraceptive regimens that teens can use effectively represent major challenges to clinicians. A wide array of contraceptive options is available. All sexually active adolescents should be encouraged to use condoms. In addition to an approximately 75% efficacy in preventing pregnancy (when used consistently), condoms are essential for reducing the risk of sexually transmitted infections, including HIV. Other barrier methods of contraception include contraceptive foam; vaginal inserts, sponges, and film; and diaphragms. Aside from diaphragms, which require professional fitting and prescription, barrier methods have the advantage of being available over the counter. For teens, the need to use these agents consistently, and at the time of intercourse, can be a strong disincentive. The most popular hormonal contraceptive is the combined estrogen-progestogen contraceptive pill. Pills are more than 98% effective if used correctly and have the advantage of not requiring action at the time of intercourse. Teens, however, have difficulty remembering to take pills regularly and tend to discontinue them for minor side effects or because a sexual relationship ends. Long-acting contraceptive agents include medroxyprogesterone acetate (DepoProvera), which is given intramuscularly every 3 months; a new monthly injectable combined estrogen/progesterone; and subdermal levonorgestrel implants (Norplant), which can provide effective contraception for up to 5 years. The progesterone-only methods are associated with high rates of menstrual abnormalities, which can be distressing and lead to method discontinuation. The new combined injectable promises less menstrual irregularity but requires more frequent medical visits. Intrauterine devices and sterilization are infrequently utilized by teens.

Sexual activity leads to over one million *teen pregnancies* in the United States each year. Ten percent of American women become pregnant before age 19. Of those who become pregnant, 10–20% miscarry, 30–40% obtain abortions, and 50% give birth. Of those who give birth, 95% parent their children. The pregnancy rate is rising among the youngest teens (those less than 14 years old), but has recently fallen among older adolescents. The causes of, and solutions to, teen pregnancy are complex and well beyond the scope of this discussion. Some basic principles apply to all teens who become pregnant. Supportive, confidential counseling is essential. Federal law guarantees all pregnant women the right to confidential pregnancy services, although state laws regarding parental consent for pregnancy termination vary. All pregnant teens should be informed of their options, which include (1) continuing the pregnancy and keeping the baby, (2) continuing the pregnancy and placing the infant for adoption, and (3) terminating the pregnancy. Most teens will benefit from referral to specialized teen pregnancy programs, which can offer medical, psychological, and social support.

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31. EATING DISORDERS

Maria T. Britto

Dissatisfaction with weight and body image is widespread among American preteens and adolescents. School- and population-based studies have reported that 45% of children in a grade 3–6 sample wanted to be thinner (80% of the girls), and 67% of junior high girls are unhappy with their weight. While many of these youth pursue diets, exercise, and other behaviors in attempts to change their appearances, only a very small proportion go on to develop the intense preoccupation with eating and weight characteristic of anorexia nervosa or bulimia nervosa.

Descriptions consistent with anorexia have been found since antiquity, but it was not until 1888 that Gull described anorexia nervosa as a specific entity. Bulimia nervosa was described in 1977. Diagnostic criteria for these disorders are standardized in the American Psychiatric Association *Diagnostic and Statistical Manual*, 4th ed. (DSM-IV). Anorexia nervosa is characterized by 15% or greater loss of body weight, intense fear of fatness, disturbed body image, and amenorrhea. Anorexia is subcategorized into restricting and binge-purge types. In bulimia nervosa, patients repeatedly consume large quantities of food (binge eating) and then purge themselves with vomiting, laxatives, or diuretics. In addition, patients feel out of control regarding their eating and exhibit overconcern with body shape and weight. The symptoms persist for at least 3 months. A third disorder, binge eating disorder, is similar to bulimia nervosa except that patients do not purge on a regular basis and body dissatisfaction is less intense. These criteria have been criticized for lack of applicability to children and adolescents. For example, they lack developmental considerations in their criteria for weight loss and amenorrhea. In a growing adolescent, failure to gain expected weight may be abnormal, but the criteria do not address this.

Many patients are white and from middle- or upper-middle-class families, although there tends to be more sociodemographic heterogeneity among patients with bulimia than those with anorexia. Some believe that the socioeconomic profile of diagnosed cases represents bias in diagnosis and reporting rather than the true prevalence of the disorders in the population. Both illnesses occur predominantly in females, with a 20:1 female-to-male ratio reported in most case series. Although males are infrequently affected, they tend to have an earlier age of onset and a worse prognosis compared to females. For women, there is a bimodal age of onset for anorexia with peaks at 13–14 years and at 17–18 years. Patients with bulimia tend to be older, with an average age at diagnosis between 17 and 25 years. Bulimia nervosa is more common than anorexia nervosa. Prevalence estimates generally range from 3% to 5% of female high school and college students. The prevalence of anorexia is 0.5–3.0% in the same population. Some authorities believe that this rate is rising, especially among 15- to 19-year-old females. Others believe that the true prevalence is stable and that reported rates are influenced by increased awareness of the illness and changes in diagnostic criteria.

Social changes may also play a role in the changing epidemiology of eating disorders. Most believe that the pathogenesis involves social and cultural norms (how thin is the ideal woman, how important are physical characteristics), combined with biologic, family, and individual factors. The central individual psychological attribute is felt to be a pervasive sense of ineffectiveness, which leads to an attempt to gain self-control by controlling weight. Those who binge and purge often exhibit other impulsive behaviors as well. Once the eating disorder is established, neuropsychological changes associated with malnutrition may perpetuate the symptoms.

Although many exceptions exist, patients with anorexia have been described as high achieving, conforming, and perfectionistic. They often come from apparently intact, high-functioning families. Affected girls tend to deny their illnesses and may come to attention only after severe weight loss. Conversely, most patients with bulimia nervosa are distressed by their symptoms and may seek help on their own. Many women define a binge by the feeling of being out of control about eating rather than by the rate or quantity of food ingested. Bingeing often predates purging by about a year.

Medical evaluation begins with a thorough history and physical examination (including weight for height and, at times, determination of body fat percentage). Other medical and psychiatric causes of weight loss should be excluded. Laboratory tests are often normal, especially in those who do not purge. Those who induce vomiting or abuse laxatives may demonstrate electrolyte abnormalities such as hypokalemia. If sought, many endocrine abnormalities can be identified. The majority of these are due to starvation, but some (e.g., abnormal dexamethasone suppression testing in anorexia) are felt to be directly related to the underlying disorder. Psychological and nutritional assessments complete the initial evaluation. Once a diagnosis is made, a team approach to therapy is usually employed. Team members may include the primary physician, psychotherapist, nutritionist, and social worker. Some mildly affected individuals, especially those with bulimia and little other psychosocial dysfunction, may be adequately managed on a more limited basis. Although there are some similarities, treatment strategies and goals differ for patients with anorexia and those with bulimia.

In anorexia, nutritional and medical stabilization must often precede significant psychological work. Indeed, many of the behaviors evidenced by patients with anorexia are likely the direct result of starvation. In the 1950s, Keys demonstrated similar behaviors in a group of conscientious objectors. These individuals were starved for 3 months and developed the same symptoms of apathy, obsessionality, food preoccupation, hoarding, and depression that are demonstrated by patients with anorexia nervosa. Behavior modification contracts are often used as a method to enhance eating and weight gain. In general, the goal is to achieve a body weight within 10% of ideal body weight and to have the return of reproductive function as evidenced by menses. Failure to attain expected bone density is a major long-term problem, and attention should be paid to ensuring optimal calcium intake. Although outpatient management is often attempted, several situations may warrant hospitalization. These include profound weight loss (generally >25–30% of ideal body weight), medical instability (such as dehydration or unstable vital signs), severe psychiatric dysfunction or family crisis, and inability to comply with outpatient therapy. Once restoration of normal eating patterns and weight gain have begun, attention can be turned to treating the underlying psychosocial and family dysfunction. Medications play a limited role in the treatment of anorexia.

Therapy for bulimia also involves nutritional and psychological counseling. Cognitive behavioral therapy has been shown to reduce bingeing and purging symptoms, especially in the short term. Nutritional interventions include general education as well as planned meals and food diaries. Hospitalization is required for life-threatening medical complications (usually electrolyte imbalance), suicidality, and severe concurrent substance abuse. In contrast to anorexia, where there is no clear evidence of effectiveness, psychopharmacologic agents can play an important role in the therapy of bulimia. In randomized, controlled trials, antidepressants have been shown to reduce binge eating and purging even in the absence of depression. Improvement has been demonstrated for up to 1 year of follow-up. A combination of cognitive behavior therapy and an antidepressant has been shown more efficacious than either alone.

Outcome studies for eating disorders are fraught with methodological problems, but some generalizations can be made. The long-term prognosis for patients with bulimia nervosa remains uncertain. Patients who receive the described therapy typically show a 50–90% reduction in binge eating and purging in the short term. Five to 10 years from presentation, about 50% have fully recovered, 30% relapse into bulimic symptoms, and 20% continue to meet criteria for bulimia nervosa. Deaths are rare and are usually related to electrolyte disturbances or suicide. For anorexia, it appears that about 25–45% of patients do well in the long term, 25–50% show some improvement, and 25% do poorly despite adequate treatment. Poor prognosis is associated with older age at onset, purging, and premorbid personality problems. Mortality estimates range from less than 5% at 4 years to more than 20% at 20-year follow-up. Cardiac arrest and suicide are the most common causes of death. Even for those who are able to maintain a normal weight, eating disorders remain a long-term struggle. Many patients report continued problems with eating, socialization, and sexuality. Given the prevalence and severity of these conditions, efforts to prevent their formation and improve their treatment become important public health challenges.

Reviews and Guidelines

1. American Psychiatric Association. *Diagnostic and Statistical Manual* (4th ed.). Washington, D.C.: American Psychiatric Association, 1994.
   Contains the diagnostic criteria for recognized eating disorders of childhood and adolescence, including the provisional diagnosis, Binge eating disorder.
2. Steinhausen, H. (ed.). *Eating Disorders In Adolescence: Anorexia and Bulimia Nervosa.* New York: DeGruyler, 1995.
   A thorough, useful text.
3. American Psychiatric Association. Practice guideline for the treatment of patients with eating disorders. *Am. J. Psychiatry* 157(Suppl.):1–39, 2000.
   A comprehensive review of the available literature, and guidelines for diagnosis and management; references are ranked according to the quality of data. Aimed at psychiatrists, but contains information on medical complications and therapy as well.

4. Fisher, M., et al. Eating disorders in adolescents: A background paper. *J. Adolesc. Health* 16:420–437, 1995.
Highlights issues specific to adolescents; for adolescent treatment guidelines, see p. 476 of the same journal or the Society for Adolescent Medicine's web site at www.adolescenthealth.org/samfinal/activities/position/eating.html.
5. Yager, J. (ed.). Symposium on eating disorders. *Psychiatr. Clin. North Am.* 19(4), 1996.
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6. Joffe, A. Too little, too much: Eating disorders in adolescents. *Contemp. Pediatr.* 7:114–135, 1990.
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A slim volume detailing theories of pathogenesis and illustrative case histories. For an abbreviated version of some of the same material, see Am. J. Psychiatry *139: 1531–1538, 1982.*
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32. SUBSTANCE USE AND ABUSE

Maria T. Britto

Use and abuse of mood-altering substances is widespread among American youth. Since 1975, Johnson and colleagues at the University of Michigan have surveyed high school seniors annually regarding their drug use. Their data provide the best nationally representative information regarding teen and young adult substance abuse. Alcohol and tobacco are by far the most commonly used substances by American teens, with 90% of seniors reporting having tried alcohol and more than 20% smoking cigarettes daily. Experts disagree as to whether any use of illicit (both cigarettes and alcohol use are illegal for those under age 18) substance by minors constitutes abuse. The American Medical Association defines drug abuse as “any use that causes physical, psychological, economic, legal, or social harm to the individual user or to others affected by the drug user's behavior.” Many argue that experimental use of alcohol and tobacco by teens is normative behavior. Others point to the illegality, to the risks of addiction, and to the serious health consequences that can follow even experimental use. For example, 50% of fatal motor vehicle injuries and homicides are associated with alcohol and other drug use.

Tobacco remains the substance most frequently used by teens on a daily basis and is the substance more frequently used by females than males. Overall, tobacco contributes more than any other preventable factor to death and disability in the United States. Teen smoking rates dropped in the late 1970s but increased in the late 1990s. The majority of smokers acquire their habits as adolescents. Initiation of cigarette use often occurs by the sixth to eighth grade. Cigarette smoking is highly addictive: 85% of adolescents who smoke two or more full cigarettes will become regular smokers. The strongest predictors of adolescent smoking are parental, peer, and sibling smoking. Although the major adverse physiologic consequences of tobacco abuse are not seen for many years, short-term health changes are apparent. Teen smokers display increased cough and dyspnea and decreased athletic performance compared to their nonsmoking peers. About 80% of smokers are physically addicted to nicotine. Smoking one's first cigarette of the day within 30 minutes of arising is a good indicator of addiction. Nicotine replacement therapy and the antidepressant buproprion provide useful adjuncts in assisting addicted smokers who are motivated to quit.

After tobacco, alcohol is the most frequently used substance among high school seniors. Males report binge drinking (5 or more drinks at one time) more than twice as often as females. At low doses, alcohol acts as a behavioral stimulant with disinhibiting effects. At higher doses, however, central nervous system (CNS) depressant effects pre dominate. Teens rarely experience alcohol-related seizures or other withdrawal reactions. They are also unlikely to manifest physiologic consequences of long-term alcohol use such as cirrhosis. More frequently, teens with alcohol problems come to medical attention because of injuries or altered mental status. Alcohol-related motor vehicle accidents are the leading cause of death among 15- to 24-year-olds in the United States.

Although it receives tremendous media and governmental attention, illicit drug use is far less prevalent than alcohol and tobacco use. Progression to illicit drugs and use of multiple drugs is, however, associated with increased risk of drug-related problems in later life. It is rare for an individual to use cocaine or heroin without first experimenting with the so-called gateway substances—tobacco, alcohol, and marijuana. The active ingredient in marijuana is D ^{9}-tetrahydrocannabinol, a substance that has found legitimate medical use for treatment of chemotherapy-related nausea. Acute effects include euphoria, impaired cognition, altered perception, and slowed reaction time. With long-term use, it can lead to impaired problem-solving and an “amotivational” syndrome. Physical dependence does not occur. Panic and paranoia are the most common toxic effects; they tend to occur most frequently in inexperienced users. In addition, those with predispositions can experience seizures or psychosis.

Crack cocaine is a free-base form of cocaine that can be smoked, leading to a much higher blood concentration than is obtained from inhaling the hydrochloride form. Cocaine is a central and peripheral nervous system stimulant, as well as an intense vasoconstrictor and local anesthetic. It works both by stimulating release of neurotransmitters and by inhibiting their reuptake, leading to a sense of euphoria for the user. Other effects are due to generalized sympathetic activation. Cocaine is intensely addicting. Rapid development of tolerance and psychological dependence lead to an ever-increasing need for the drug. Physical and psychological withdrawal syndromes can also occur. In addition to cocaine, stimulants abused by adolescents include amphetamines and over-the-counter stay-awake pills.

Hallucinogens include lysergic acid diethylamide (LSD), mescaline, mushrooms (psilocybin), jimsonweed, and others. LSD is the most potent of these and the most frequently used by high school seniors. It acts by inhibiting serotonin release, leading to a generalized stress response. Both the physiologic effects and the problems related to overdose are related to this autonomic activation. Users seek the perception-altering effect of LSD and other hallucinogens. Depersonalization may also be experienced. So-called bad trips represent a negative emotional response to the drug, often associated with the feeling of going crazy or losing one's mind. Flashbacks, recurrences of the LSD-induced state after the acute effects have worn off, may occur unpredictably for years following use.

Heroin, morphine, and other opiates relieve pain. Side effects include CNS depression, which can lead to death in the acute overdose situation. The use of heroin by high school seniors is below 1%; other opiates combined are reportedly used by 4–6% of seniors.

Chemical dependency is defined as harmful psychological dependence on mood-altering drugs. Stages of use have been described by Macdonald as (1) learning the high—experimental use, where drugs are obtained from friends; (2) seeking the high—the user seeks out his own supply; (3) preoccupation with the high—the user has lost control over his drug use; and (4) burnout. Signs of drug use include isolation from family and a change in the user's peer group. A decline in school performance is one of the most consistent features of frequent drug use. Early onset of use and rapid progression through the stages of use are risk factors for the development of severe substance use disorders. Comorbidity with other psychiatric disorders, particularly conduct disorder, is fairly common and can complicate intervention and treatment.

Pediatricians and other health providers who care for teens should inquire about drug use during health maintenance examinations and when teens present with vague complaints. When possible, the drug history should be obtained from both the patient and the parent. In cases of limited abuse, primary providers may offer counseling if they feel comfortable doing so. In most cases, a seriously drug-abusing teen should be referred to a drug treatment program. Initial treatment of chemical dependency includes cessation of all drug use, maintenance of sobriety, and development of a chemical-free lifestyle. Significant family involvement and peer support (often through Alcoholics Anonymous or similar groups) are typically included in successful programs. Inpatient treatment is usually reserved for those who are unable to become drug free in an outpatient setting, who lack a supportive home environment, or who pose a danger to themselves or others. Chemical dependency is a treatable, but seldom curable disease. Health care providers who are alert to the problems of substance abuse and are able to intervene early can have a significant impact on the course of their patients' lives. Primary prevention of substance abuse is best addressed at the public health level. Effective community-based programs are characterized by being comprehensive and noncategorical. They take an indirect approach to substance abuse prevention by providing alternative activities such as education and recreation. In the school setting, the most effective programs combine resistance and life skills training with strong antidrug social norms.

Collections, Reviews, and Texts

1. Rogers, P., and Werner, M. (eds.). Substance abuse. *Pediatr. Clin. North Am.* 42(2), 1995.
   Entire issue devoted to this topic. Includes epidemiology, prevention, screening, toxicology and treatment. There is a particularly helpful chapter on brief office-based interventions for substance use.
2. Graham, A., Schultz, T., and Wilford, B. (eds.). *Principles of Addiction Medicine* (2nd ed.) Chevy Chase, Md.: American Society of Addiction Medicine, Inc., 1998.
   Encyclopedic reference, including pharmacology, prevention, treatment, and comorbidity.
3. Neinstein, L. *Adolescent Health Care: A Practical Guide* (3rd ed.). Baltimore: Williams & Wilkins, 1996.
   Outline-style textbook with a section devoted to substance use and abuse. The management chapter includes an extensive list of street names for drugs.
4. Macdonald, D. *Drugs, Drinking and Adolescents* (2nd ed.). Chicago: Year Book, 1987.
   Written by the former director of the White House Drug Abuse Policy Office. Somewhat crusading monograph, which details the stages of drug abuse and provides direction for both parents and professionals regarding prevention and treatment options. For a condensed version of much of the same material, see Am. J. Dis. Child. *138:117–125, 1984; or* Curr. Probl. Pediatr. *19:389–444,*

1989.
5. Augenstein, W. (ed.). Symposium on emergency aspects of drug abuse. *Emerg. Med. Clin. North Am.* 8(3), 1990.
Contains information on emergency department management of most substances of abuse, as well as chapters dealing with special situations such as neonatal effects, human immunodeficiency virus, and endocarditis. Especially useful chapter on the reliability and utility of toxicologic testing.

Prevention

5. Belcher, H., and Shinitzky, H. Substance abuse in children: Prediction, protection, and prevention. *Arch. Pediatr. Adolesc. Med.* 152:952–960, 1998.
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For the most recent epidemiology data on adolescent substance use from the Monitoring the Future Study, go to their web site at www.isr.umich.edu/src/mtf/indexz.html. For the Centers for Disease Control and Prevention's most recent data, search M.M.W.R. at www2.cdc.gov/mmwr/mmwrsrch.htm . For an example of the difficulty in distinguishing use from abuse in adolescents, see Am. J. Psychiatry *155:486–492, 1998.*
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For more on the high prevalence of psychiatric comorbidity, see Am. J. Orthopsychiatry *66:52–60, 1996.*

Medical Complications

11. Stein, M. Medical complications of intravenous drug use. *J. Gen. Intern. Med.* 5:249–257, 1990.
Reviews problems related to injection sites as well as organ-specific pathology. See also Postgrad. Med. *92:205–214, 1992. For more on cardiovascular effects, see* J. Adolesc. Health Care *10:332–337, 1989.*
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Take this oldie (but still goodie) with you to the emergency department when you need to manage problems related to sedative-hypnotics, cocaine, phencyclidine hydrochloride (PCP), hallucinogens, inhalants, and marijuana.
13. Graham, C. Emergency care of the substance-abusing adolescent. *Adolesc. Med. State Art Rev.* 4:167–180, 1993.
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Tobacco

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Role of Practitioner

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This and other policy statements are also available on the web at www.aap.org.
23. Adger, H., Macdonald, D., and Wenger, S. Core competencies for involvement of health care providers in the care of children and adolescents in families affected by substance abuse: Report from a conference. *Pediatrics* 103:1083–1084, 1999.
What providers need to know.
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33. SUICIDE

Maria T. Britto

Suicidality requires intent to kill oneself. Understanding of the concept of suicide develops progressively; by age 10, most children understand what suicide means. Younger children, who may lack the cognitive capabilities to fully comprehend the finality of death, still may kill themselves, although such suicide is rare. Depression and self-inflicted injury both increase steeply at puberty. The rate of suicide among teenagers has increased four-fold since 1950, and suicide now ranks among the top three causes of death among American youth. As such, suicide among children and adolescents is a grave public health concern, and an area in which pediatricians must be skilled in both prevention and management techniques. Although females attempt suicide more frequently (ratios range from 3:1 to 9:1), males are much more likely to suffer a fatal outcome since they use more lethal means. Reported male-to-female ratios for completed suicide range from 3:1 to 5:1. The gender differences are most marked for whites, the highest risk group. They are less marked among Hispanics and a little less so among blacks. For Native Americans, the rate varies widely among tribes. Firearms are the most common (67%) method of completed suicide followed by hanging (18%). Although fewer completed suicides occur by self-poisoning (overdoses and toxic gases), it accounts for the vast majority of suicide attempts. Aspirin, cold preparations, tranquilizers, sedatives, antidepressants, and other readily available substances form the bulk of overdoses.

Suicide can be the final response to many psychiatric and social problems. Although predicting suicide is difficult, a variety of risk factors have been associated with attempts and completion. Most who complete suicide have attempted it in the past, and a previous attempt provides the best predictor of a future attempt. The medical seriousness of the initial attempt, however, does not predict reattempt; thus, even minor wrist cutting or ingestion of a few aspirin places the teen at significant risk. A second major contributing factor is the presence of major depression or other affective disorder. Major affective disorder carries with it a 15% lifetime suicide risk. Other psychiatric factors associated with increased suicide risk include character disorders such as borderline personality, psychotic disorders such as schizophrenia, and antisocial and conduct disorders. Substance abuse can act both as an underlying factor and as a trigger for an attempt. Intoxication at the time of death, most often with alcohol, has been reported in approximately half of youth suicides.

Family factors also contribute to suicide risk. Studies of suicidal adolescents have shown high levels of family disruption, including divorce, early parental death, and chaotic or abusive households. Substance abuse is common in family members. The incidence of depression and suicide among family members is elevated compared to the general population. Twin adoption studies have suggested that there is a genetic component to suicide; some feel biologic markers of increased risk will be available soon.

Social factors have also been implicated in the rising rates of teen suicide. Increased family mobility and decreased family cohesiveness have been blamed. Many believe that the increasing availability of handguns has also contributed to a rise in completed suicide. The presence of a gun in the home increases the risk of suicide even after all other known predisposing factors are accounted for. Over half of the suicides in the United States occur by firearm. Finally, suicide rates increase for short periods following nationally televised news reports and movies about suicide. It is believed that this occurs by a “copycat” effect among vulnerable individuals who would not otherwise have acted. Imitative “clusters” of teen suicides have also occurred in communities following deaths from both unintentional injuries and suicides.

While suicide is a rare event, suicidal ideation and depression are common. Rates of major depression include 0.9% of preschool children, 2.5% of school-aged children, and 4.5–6.1% of adolescents. Suicidal ideation occurs among 20–40% of teens. Many adolescents who attempt suicide have seen their physicians shortly before the event. A visit for vague or nonspecific complaints should prompt an inquiry into depressive symptoms and suicidal ideation. Asking patients about suicide does not “put the idea into their heads,” and most teens will respond honestly to direct questioning (especially if the parents are not present in the room). Rating scales for depression (such as the Beck Child Depression Inventory and the Reynolds Adolescent Depression Scale) may be helpful in clarifying a diagnosis. The teen can then be referred for appropriate services. A suicidal incident is often immediately preceded by a traumatic life event. These include a disciplinary crisis at home, a rejection or humiliation (such as failure at school or loss of a romantic relationship), or interaction with a psychotic parent.

Suicide attempts account for 10–15% of adolescent emergency department visits. The first priority is medical stabilization. Once that has been achieved, the history should focus on determining the patient's level of risk for future attempts. Possible questions include “Did you want to die?” “What did you think would happen?” “Do you still want to die?” “Would you tell someone if you felt this way again?” Other important history includes past suicide attempts and other psychiatric diagnoses. In the presence of a low lethality attempt, a supportive family, and available community resources, outpatient management may be possible. In other situations, at least a short-term hospitalization is usually safest, although there is no evidence that hospitalization prevents patients from eventually making another attempt. If the outpatient route is chosen, studies show that follow-up is more likely to be kept if the appointment is made from the emergency department than if just a name and phone number are given.

An estimated 10% of those who make a suicide attempt will repeat it in the first year. The risk increases if the initial attempt led to a psychiatric hospitalization, and is greatest in the first 3 months after the attempt. The rate of completed suicide among those with previous attempts ranges from 0.1% of females followed as outpatients to 11.3% of males who required inpatient psychiatric treatment. Eisenberg has written that following a completed suicide, survivors feel “grief at the loss, rage at desertion, and guilt at having failed.” The social stigma attached to suicide compounds the difficulty. As with other grieving families, the physician should meet with the survivors as soon after the death as possible. Follow-up visits should be offered at about 1 month and thereafter as necessary. Support to close friends of the deceased is appropriate, but schoolwide assemblies or other demonstrations should be avoided. They may prompt other suicides via the copycat effect.

Prevention of youth suicide requires long-term approaches at both the societal and individual levels. From a public health and policy perspective, prevention, identification, and treatment of underlying mental and addictive disorders are crucial. Since suicide is often an impulsive act, increased restriction on access to firearms may reduce the rate of completed suicides. In clinical settings, practitioners should provide routine psychosocial screening to all patients. Early recognition of psychopathological conditions in the child and family may reduce the number of youth who progress to suicide.

Reviews and Texts

1. Blumenthal, S., and Kupfer, D. (eds.). *Suicide Over the Life Cycle: Risk Factors, Assessment and Treatment of Suicidal Patients.* Washington, D.C.: American Psychiatric Press, 1990.
   An encyclopedic reference that provides practical assessment and management advice.
2. Jellinek, M., and Snyder, J. Depression and suicide in children and adolescents. *Pediatr. Rev.* 19:255–264, 1998.
   Thorough but concise review; includes a strong developmental perspective from infancy through young adulthood. For a more detailed developmental approach, including suicide in prepubertal children, see Psychiatr. Clin. North Am. *20: 551–562, 1997.*
3. Rosewater, K., and Burr, B. Epidemiology, risk factors, intervention, and prevention of adolescent suicide. *Curr. Opin. Pediatr.* 10:338–343, 1998.
   Brief and practical; helpful reference list.

Risk Factors

4. Slap, G., et al. Risk factors for attempted suicide during adolescence. *Pediatrics* 84:762–772, 1989.
   A five-item self-administered screen was able to correctly identify 84% of suicidal inpatient adolescents.
5. Moscicki, E. Identification of suicide risk factors using epidemiologic studies. *Psychiatr. Clin. North Am.* 20:499–517, 1997.
   Learn some basic principles of epidemiologic investigation and analysis while exploring risk factors for suicide.
6. Boyd, J., and Moscicki, E. Firearms and youth suicide. *Am. J. Public Health* 76: 1240–1242, 1986.
   Between 1933 and 1982, the firearm suicide rate rose 139%. This was three times the rate of rise for all other suicide methods for 15- to 19-year-olds, and 10 times the rate of rise for 20- to 24-year-olds.
7. Remafedi, G., Farrow, J., and Deisher, R. Risk factors for attempted suicide in gay and bisexual youth. *Pediatrics* 87:869–875, 1991.
   In a study of 137 gay and bisexual males, 30% reported at least one suicide attempt. Adoption of a bisexual or homosexual lifestyle at a young age and having a feminine gender role were

associated with increased risk. For more, see Adv. Pediatr. *45:107–144, 1998; and* Am. J. Public Health *90:573–578, 2000.*

Management

8. Press, B., and Khan, S. Management of the suicidal child or adolescent in the emergency department. *Curr. Opin. Pediatr.* 9:237–241, 1997.
   Practical approach to initial assessment and management. Oriented to the emergency room, but also appropriate for the clinic.
9. Hirschfeld, R., and Russell, J. Assessment and treatment of suicidal patients. *N. Engl. J. Med.* 337:910–915, 1997.
   Brief, with useful algorithm for assessing risk. Good references.

Prevention

10. Ploeg, J., et al. A systematic overview of adolescent suicide prevention programs. *Can. J. Public Health* 87:319–324, 1996.
    School curricular programs may have harmful as well as beneficial effects on attitudes related to suicide. For more on the difficulty in designing and evaluating effective interventions, see Child Care Health Dev. *23:173–185, 1997.*
11. Shaffer, D., et al. Preventing teenage suicide: A critical review. *J. Am. Acad. Child Adolesc. Psychiatry* 27:675–687, 1988.
    Discusses epidemiology and risk factors in the context of those that might be amenable to preventive strategies. Asserts that the greatest preventive impact could come from effective interventions targeted toward teenage boys who have made previous attempts or who are depressed.
12. Miller, H., et al. An analysis of the effects of suicide prevention facilities on suicide rates in the United States. *Am. J. Public Health* 74:340–343, 1984.
    Most callers to crisis centers are young white females. A small reduction (1.7/100,000) in the rate of suicide in this population could be attributed to the presence of a center.

Role of the Practitioner

13. American Academy of Pediatrics. Suicide and suicide attempts in adolescents and young adults. *Pediatrics* 81:322–324, 1988. (Available at: www.aap.org/policy/01954.html.)
    Pediatricians should play a major role in the prevention of youth suicide. This Academy statement provides strategies for approaching, identifying, and treating suicidal adolescents.
14. Hergenroeder, A., et al. The pediatrician's role in adolescent suicide. *Pediatr. Ann.* 15:787–798, 1986.
    Pediatricians have many opportunities to intervene with suicidal adolescents but may be inadequately trained to recognize and treat these patients.
15. Frankenfield, D., et al. Adolescent patients—healthy or hurting? *Arch. Pediatr. Adolesc. Med.* 154:162–168, 2000.
    The subtitle is "Missed opportunities to screen for suicide risk in the primary care setting."
16. Adler, R., and Jellinek, M. After teen suicide: Issues for pediatricians who are asked to consult to schools. *Pediatrics* 86:982, 1990.
    Practical responses to a suicide in the community.

34. DEATH, DYING, AND MOURNING

Kenneth B. Roberts

The popular writings of Dr. Elisabeth Kübler-Ross stimulated much interest in death and dying. Dr. Kübler-Ross identified several important principles, chief among which is our inability (at any age) to conceive of our own death, a psychological limitation reinforced by our death-denying society. She proposed that terminally ill patients know the seriousness of their condition whether or not they are told and would like their physicians to acknowledge the gravity of the disease—but not to remove hope. Above all, she stressed, the fear of abandonment, of being alone, is worse than the fear of death.

Dr. Kübler-Ross also described five psychological “stages” through which dying patients progress: denial, anger, bargaining, depression, and acceptance. The progression is not lock-step, i.e., one stage is not completed before another is entered. In fact, at any given time in the grieving process, many (and probably most) individuals have feelings and behaviors that represent more than one of the stages. Because individuals are “in denial” one minute, does not mean that they won't attempt to “bargain” the next. Feelings may be confusing to the individual experiencing them, and the individual's behaviors may seem unpredictable to the health professionals observing them. Knowledge of the stages allows the feelings and behaviors to be recognized as reflective of the grieving process.

Since grief and mourning are the responses to a major loss, it is important to recognize that the stages described above typify the reaction not only to death, but also to other losses. Thus, the parents of a newborn with Down syndrome mourn the loss of the normal child they expected to have, and the children who learn of intended parental separation mourn the loss of their intact family. Both will go through the five stages in some form. Whether a loss is “major” or not depends solely on the perception of the individual, so the teenager whose loss seems trivial to adults may also grieve and express denial, anger, bargaining, and depression before reaching acceptance.

When a child is seriously ill, it often requires a conscious effort for medical personnel to maintain open and frequent communication with the child and the child's parents. The inability to effect a cure is frustrating and disheartening, and may be personally (professionally) threatening. The child may ask questions that make adults uncomfortable. As with other emotionally charged subjects, it is important to ascertain the child's level of understanding before answering. Just as one needs to know the child's frame of reference to answer appropriately to the question, “Where do babies come from?” one should similarly determine the fantasies of the questioner before responding to, “Is Jimmy going to die?” or, “Am I going to die?” Often, the physician or parent will discover that the child's concern is not death per se, but mutilation, pain, or being left alone, and reassurance about such matters can be both honest and effective. Management of a sick child—whether or not the illness is fatal—includes providing reassurance that pain will be controlled, that a capable adult will provide care, and that the child will not be abandoned.

What children (and adults) understand about death and the coping behaviors they employ are age related. In very young children, separation and death are more or less equivalent—both result in the absence of a loved one on whom the child depends. By age 3–5 years, boys and girls are aware of sex differences and may become concerned about mutilation of their bodies; death is considered a dramatic event that happens to strangers. Preschool children also have a sense of magical omnipotence, which can be the source of much guilt because they believe that all occurrences stem from their own wishes or deeds; for example, the death of a newborn brother or sister may be interpreted as “his fault” because the child wished to remain an only child. In early school years, the few facts that children glean are woven together with rich, often terrifying fantasies. Until age 10, children usually consider death a reversible process; that is, the dead person is able to return to life at will. Adolescents are capable of recognizing that death is both irreversible and universal; it has been demonstrated that they may be able to comprehend the implications of fatal illness and make decisions about the termination of their life. Teenagers struggling for independence view fatal illness as an unjust intrusion into a personal world in which they perceive themselves to be all-powerful; death is a “punishment.” Young adults typically respond to death with feelings of rage. The reaction of middle-aged adults is characterized by intellectual acceptance but emotional denial, in contrast to that of persons of more advanced age, in whom personal assessment leads more naturally to an acceptance of death, although often with a lack of understanding of the appropriate age-related behavior of younger persons.

The popular phrase “death and dying” overlooks consideration of the important areas of mourning and grief. The goal of “grief work” has been defined as “emancipation from the bondage to the deceased,” involving readjustment to life without the loved one and reinvestment of the self in new relationships. The anguish is revealed in a variety of somatic signs, including sighing respirations, digestive symptoms, feelings of being “choked up,” and complaints of exhaustion, coupled with patterns of constant but nonproductive activity. Less well-recognized features, which may cause a mourner to fear he is “losing his mind with grief,” are perceptions that the deceased is still present (“I can still hear the baby crying sometimes”), overwhelming guilt, and hostile reactions to friends who attempt to give comfort. The process of grieving is a slow one. Each season brings its own memories, and special holidays and anniversaries may be difficult for years. All too commonly, parents do not resolve their grief; instead, they may create a “replacement child.”

It is important to recognize that individuals grieve differently; some are overtly emotional, others more stoic. Gender stereotypes may create expectations. Communication between parents can become strained and the sense of isolation deepened. Children usually do not express their sense of loss by overt “grieving” as adults do but may become more demanding of attention; parents may have difficulty accepting such behavior, seeing it as uncaring and self-centered. The physician sensitive to these issues can provide a valuable service to the family by acknowledging different styles and by fostering communication.

Chronic illness provides an opportunity for preparation for death; progression through the five stages usually begins at the time of diagnosis. Although “anticipatory grief” is of benefit to the parents, shortening their period of mourning following the child's death, premature separation may make the child's final days more frightening and more lonely. Moreover, if the child survives a potentially fatal episode, the parents may have difficulty accepting the child as still living (“Lazarus syndrome”), or they may perceive the child as particularly fragile and become excessively protective (“vulnerable child syndrome”). The physician's responsibility is both to ensure the physical and the emotional comfort of the child, and to provide guidance for the grieving parents.

Most infants and children who die do not have chronic diseases, however; rather, they are the victims of accidents or sudden infant death syndrome. Acceptance of the unexpected death is particularly difficult, since there has been no anticipatory grief, no opportunity for the parents to work through the five stages gradually. Incapacitation may be prolonged, and the follow-up visit is of special importance.

Much has been learned from parents' feedback about “breaking bad news,” including the information that their child has died. Whenever possible, if only one parent is present, he or she should have the opportunity to be accompanied by the other parent or another appropriate support person. The setting should be as quiet and private as possible. The news should be direct, without euphemisms or circumlocutions that may be misunderstood; particularly when death is not anticipated, using the word “died” or “dead” may be helpful for the family. The physician should be sympathetic and empathetic, listening as well as speaking; the pace of information should be slow, with time for parents to process the overwhelming news. Parents should be invited to see, touch, and hold their child, even if the circumstances of the death render the body altered in some way (e.g., a motor vehicle accident); the decision to accept or decline the opportunity should belong to the family member, not the physician. In addition to collecting and returning all personal effects, an invitation often appreciated is to inquire about a memento, such as a lock of hair; this may be considered particularly important by parents of very young babies.

The physician's role is to help parents face their loss and to guide them through the many difficult months of grief work. The physician should meet with the family of a deceased child 2–3 months after the death to answer lingering questions (and review autopsy results), to assess the family members' level of functioning, and to assist in the mourning process. The physician's role is to listen, to support, to sanction mourning behavior, and to give assurance that surprising and disturbing feelings are signs not of insanity but of grief.

Reviews

1. Kübler-Ross, E., Wessler, S., and Avioli, L. On death and dying. *J.A.M.A.* 221: 174–179, 1972.
A resume of the 1969 book with same title, discussing why we have so much trouble facing death, and proposing five stages of dying: denial, anger, bargaining, depression, and acceptance.
2. Sahler, O., and Friedman, S. The dying child. *Pediatr. Rev.* 3:159–164, 1981.
A readable review that touches many relevant issues, from child's concepts to management.

Child's Concept of Death

3. Easson, W. Care of the young patient who is dying. *J.A.M.A.* 205:203–207, 1968.
Describes the stages in children and physician (adult). The best descriptions are of the preschool years, adolescence, and beyond. (One of the few reviews that includes "stages" in adulthood. See if you find your "stage" being described.)
4. Green, M. Care of the dying child. *Pediatrics* 40:492–497, 1967.
Emphasizes that a child asking about his own death wonders, "Am I safe?" "Will I be alone?" "Will you make me feel all right?"
5. Yudkin, S. Children and death. *Lancet* 1:37–41, 1967.
A good description of the terrifying mix of fact and fantasy in 3- to 7-year-old children and an expression of concern for the child whose fears are reasonable.
6. Spinetta, J., Rigler, D., and Karon, M. Anxiety in the dying child. *Pediatrics* 52: 841–845, 1973.
The focus is on children 6–10 years old; data are presented to show that hospitalized children with leukemia are more anxious than matched controls with chronic but nonfatal illness (as outpatients, too: Pediatrics *56:1035–1037, 1975).*
7. Childers, P., and Wimmers, M. The concept of death in early childhood. *Child Dev.* 42:1299–1301, 1971.
Discussions with 75 children aged 4–10 revealed an increasing trend toward acceptance of death as universal (100% by age 9), but fewer than one third at ages 4–9 and fewer than two thirds at age 10 believed that death is irreversible (irrevocable).
8. Leikin, S. A proposal concerning decision to forgo life-sustaining treatment for young people. *J. Pediatr.* 115:17–22, 1989.
A thoughtful review of the issues surrounding an adolescent's desire to forgo life-sustaining treatment, including a consideration of the physician's role. (Preceded by a related review on the ability of children to make decisions, pp. 10–11.) Also see Ref. 15 below.

Approach to Fatal Disease

9. Barakat, L., Sills, R., and LaBagnara, S. Management of fatal illness and death in children or their parents. *Pediatr. Rev.* 16:419–423, 1995.
The focus is on the adjustments required in a chronic illness; considers parents and children separately.
10. Krahn, G., Hallum, A., and Kime, C. Are there good ways to give "bad news"? *Pediatrics* 91:578–582, 1993.
The authors propose the answer to be "yes" and offer specific recommendations, based on structured interviews of parents of children with developmental disabilities. (For more on "breaking the news," see Am. J. Dis. Child. *137:572–577, 1983.)*
11. Vernick, J., and Karon, M. Who's afraid of death on a leukemic ward? *Am. J. Dis. Child.* 109:393–397, 1965.
Everybody is. Includes a discussion of the staff's feelings. The authors advocate telling the child the diagnosis, and present an example of "how to."
12. Waller, D., et al. Coping with poor prognosis in the pediatric intensive care unit. The Cassandra prophecy. *Am. J. Dis. Child.* 133:1121–1125, 1979.
Dealing with parental denial; also see companion editorial, pp. 1119–1120. (Remember that denial may have a positive function: J. Pediatr. *99:401–402, 1981.)*
13. Howell, D. A child dies. *J. Pediatr. Surg.* 1:2–7, 1966.
A sensitive presentation of the author's approach: anticipate the child's needs and questions and address them ("the best defense is a good offense").
14. Wessel, M. The primary physician and the death of a child in a specialized hospital setting. *Pediatrics* 71:443–445, 1983.
The role of the primary care provider in a tertiary setting.
15. American Academy of Pediatrics Committee on Bioethics. Guidelines on forgoing life-sustaining medical treatment. *Pediatrics* 93:532–536, 1994.
Principles, guides for decision-making, and a consideration of decision-making for patients (and parents) who lack decision-making capacity.

Grief, Mourning, and Parents

16. Lindemann, E. Symptomatology and management of acute grief. *Am. J. Psychiatry* 101:141–148, 1944.
Five (perhaps six) pathognomonic features of grief and a definition of "grief work" (mourning) are presented. (Poignant illustrations of the principles, elicited from group sessions with parents after their child's death: J. Pediatr. *88:140–146, 1976.)*
17. Cassell, E. The nature of suffering and the goals of medicine. *N. Engl. J. Med.* 306:639–645, 1982.
Distinguishes pain from suffering. This article should be required reading before assuming the responsibilities of a physician.
18. Schulman, J., and Rehm, J. Assisting the bereaved. *J. Pediatr.* 102:992–998, 1983.
Many practical suggestions. (What to do visit by visit: Clin. Pediatr. *20:466–470, 1981.)*
19. Wasserman, A. Helping families get through the holidays after the death of a child. *Am. J. Dis. Child.* 142:1284–1286, 1988.
Excellent general suggestions, as well as specific recommendations regarding holiday times; includes a list of support groups for bereaved parents.
20. Mandell, F., McAnulty, E., and Reece, R. Observations of paternal response to sudden unanticipated infant death. *Pediatrics* 65:221–225, 1980.
A pattern often different than the maternal response.
21. Friedman, S. Psychological aspects of sudden unexpected death in infants and children. *Pediatr. Clin. North Am.* 21:103–111, 1974.
Differences between anticipated loss and unexpected loss are discussed, followed by superb commentary by Bergman (pp. 115–121).
22. Speck, W., and Kennell, J. Management of perinatal death. *Pediatr. Rev.* 2:59–62, 1980.
Review, ranging from stillbirth to follow-up meetings.
23. Poznanski, E. The "replacement child": A saga of unresolved parental grief. *J. Pediatr.* 81:1190–1193, 1972.
A case history to remind us of this entity as representing ineffective coping.
24. Green, M., and Solnit, A. Pediatric management of the dying child. III. Reactions to the threatened loss of a child: A vulnerable child syndrome. *Pediatrics* 34:58–66, 1964.
Overprotection of the child with a fatal illness or of a surviving sibling is discussed.

Bereaved Children

25. American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health. The pediatrician and childhood bereavement. *Pediatrics* 105:445–447, 2000.
A brief review of the issues, with age-specific observations and recommendations for management.
26. American Academy of Pediatrics Committee on Psychosocial Aspects of Child and Family Health. Pediatrician's role in helping children and families deal with separation and divorce. *Pediatrics* 94:119–121, 1994.
Provides a brief description of how children at various ages react to divorce. Reminds us that 1 out of 7 marriages end in divorce, and 61% of children live with a single parent. (For more on the consequences of divorce for children, see Pediatr. Rev. *16:306–310, 1995.)*

Generalizability

27. Butler A. There's something wrong with Michael: A pediatrician-mother's perspective. *Pediatrics* 71:446–448, 1983.
Articulate and sensitive description of feelings and dynamics.
28. Miller, L. Toward a greater understanding of the parents of the mentally retarded. *J. Pediatr.* 73:699–705, 1968.
Parents react to the diagnosis of mental retardation with "grief"; so do parents told of the need to transfer a neonate to a regional center. N. Engl. J. Med. *294:975–978, 1976.*
29. Jellinek, M., and Kearns, M. Separation anxiety. *Pediatr. Rev.* 16:57–61, 1995.
The focus is on separation anxiety disorder.

Physicians

30. Schowalter, J. Death and the pediatric house officer. *J. Pediatr.* 76:706–710, 1970.
A description of 10 house officers through the "period of impact," the "period of battle," and the "period of defeat."
31. Sahler, O., McAnarney, E., and Friedman, S. Factors influencing pediatric interns' relationships with dying children and their parents. *Pediatrics* 67:207–216, 1981.
The child's age, neurologic status, and duration of illness.
32. Wiener, J. Attitudes of pediatricians toward the care of fatally ill children. *J. Pediatr.* 76:700–705, 1970.
Varies with the age of the physician (see Ref. 3).

35. ASSESSMENT OF THE NEWBORN

Robert D. White

The physician's first contact with a neonate is usually in the newborn nursery, after an uneventful labor and delivery, although ideally the relationship with the parents has begun at a prenatal conference. The prenatal visit serves to initiate communication between physician and parents, permits a mutual assessment of child-rearing styles, and affords the physician the opportunity to elicit a personal and family history in an unpressured setting. Parental fears and concerns, if any, can be aired, and the physician can then give specific attention to these when assessing the newborn. Choices regarding breast-feeding and circumcision should be outlined so that these decisions can be made carefully and with confidence.

Evaluation of the neonate properly begins with a review of the pregnancy, labor, delivery, and immediate neonatal period, as well as the mother's medical history and the family history. The physical examination of a newborn requires patience and gentleness, and is most successful when unpleasant procedures such as examining the ears and hips are performed last. While the infant is resting quietly, one should inspect the color, activity, and respiratory effort, then determine the vital signs and listen to the heart sounds. An estimate of gestational age should be made, and the weight, length, and head circumference measured; these can be used to determine whether the physical measurements are appropriate for gestational age. The remainder of the physical examination is directed to detection of congenital malformations or signs and symptoms of potentially serious disease.

The importance of this examination cannot be overemphasized. Many findings, such as the clouded cornea of congenital glaucoma or the hip “click” of congenital hip dislocation, may be the only clue to potentially disabling disorders; if the early, subtle signs are overlooked, the disorders may not to be discovered until permanent damage has occurred.

The neurologic examination of a neonate is largely accomplished during the general physical examination and gestational age assessment, which provide a reasonable impression of muscle tone, alertness, and irritability; the Moro, suck, grasp, and deep tendon reflexes should also be tested.

The data from the history and physical examination are combined to form an initial health profile of the infant: genetic endowment, exposure to potentially harmful factors in utero, and physical well-being. The health profile is not complete, however, until a clear impression of the child's future home environment is obtained. The first postpartum meeting should consist of two-way communication: The parents learn the results of the initial assessment and have an opportunity to ask questions, and the physician learns the mother's plan for feeding the baby and what preparations have been made for the infant's general care.

Occasionally, the physician's first contact with a newborn follows an emergency call to the delivery room. Even then, a history is essential to interpret the infant's physical condition properly. Obstetric complications, maternal medications, and notable events during labor and delivery must rapidly be ascertained. In some cases the situation is so emergent that history-taking is interspersed with the first few minutes of active resuscitation and physical examination, but it cannot be safely omitted.

At the moment of birth, the integrity of a neonate's respiratory, cardiovascular, and neurologic systems must be established to permit a healthy transition from fetal to extrauterine life; therefore, the initial physical examination considers these first. The Apgar score permits rapid assessment by grading the infant's heart rate, respiratory effort, color, tone, and reflex irritability, each on a scale of 0–2 points. Infants whose total score is 4–7 of the possible 10 points at 1 minute of life have generally been depressed in utero by hypoxia or maternal medications and require assistance in the form of oxygen and gentle stimulation. An Apgar score of less than 4 at 1 minute of age indicates that the infant is profoundly depressed and must be given immediate respiratory assistance and, in many cases, cardiovascular and metabolic support as well. A second determination of Apgar score at 5 minutes of age reflects the success of resuscitative efforts and correlates to some extent with the infant's ultimate prognosis. While in the delivery room, an abbreviated physical examination is performed to rule out life-threatening congenital malformations, and the obstetrician and parents are briefly apprised of the infant's condition. The neonate is transferred to an intensive care nursery if seriously ill or at high risk of becoming ill; many initially depressed infants require only a period of observation in a transitional nursery prior to routine care in the healthy newborn nursery.

During the baby's stay in the nursery, further assessments and action on the part of the infant's physician depend largely on whether problems are detected in the initial health profile. A healthy, full-term infant with a good home setting needs only a daily reassessment of feeding, urine and stooling patterns, extent of jaundice, and body weight, and visits with the parents to discuss new questions or problems. A second, abbreviated physical examination prior to discharge is necessary, since heart murmurs, decreased femoral pulses, hip clicks, increasing head circumference, and other signs of significant disease frequently do not become apparent until after the first day of life; in addition, a minor abnormality present on the initial assessment often requires further assessment on following days. With this in mind, infants should be discharged “early” (i.e., on the first day of life) only if appropriate arrangements are made for follow-up, particularly during the critical next few days. All parents should be alerted to signs that require prompt communication with the physician (e.g., marked jaundice, poor feeding, lethargy, fever).

A discharge conference serves several purposes. Arrangements for well-baby care are confirmed. Feeding plans are discussed (if the infant will be breast-fed, vitamin D supplementation should be considered; if bottle-feeding is planned, a formula fortified with iron should be selected). The parents are instructed in umbilical cord, circumcision, and skin care; in normal patterns of sleep, crying, and stooling; and about normal events that might be alarming to new parents, such as transient vaginal bleeding. This is also an appropriate time to emphasize that a significant reduction in accidental injuries (the leading cause of childhood mortality) is possible through early establishment of safety habits such as use of an infant car seat.

Initial Assessment and Resuscitation

1. Neonatal resuscitation. *J.A.M.A.* 268:2276–2281, 1992.
   Contains recommended practices with some physiologic background. The Neonatal Resuscitation Program (available from the American Academy of Pediatrics) presents updated information in a self-learning format.
2. Keener, P. General pediatrician's role in high risk deliveries. *Pediatr. Rev.* 10: 119–128, 1988.
   The importance of planning prior to and team communication during and after the actual resuscitation is emphasized.
3. Jain, L., et al. Cardiopulmonary resuscitation of apparently stillborn infants: Survival and long-term outcome. *J. Pediatr.* 118:778–782, 1991.
   The majority of those who survive the neonatal period do well. Absence of a heartbeat at 10 minutes or of spontaneous respiratory effort by 30 minutes of age (even if a heartbeat is present) portends death or severe disability.

Extensive Assessment and Counseling

4. Brazelton, T., Parker, W., and Zuckerman, B. Importance of behavioral assessment of the neonate. *Curr. Probl. Pediatr.* 7:1–82, 1976.
   Still the best description of the remarkable complexity and capacity of neonatal behavior.
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36. RESPIRATORY DISTRESS SYNDROME

Robert D. White

The respiratory distress syndrome (RDS) is the most common cause of death among premature infants. It is caused by immaturity of the lungs and occurs in approximately 70% of infants weighing less than 1,500 g, but in less than 1% of those whose birth weight is over 2,500 g. Males, infants of diabetic mothers, infants delivered by cesarean section, and infants born to a mother who has had a previous child with RDS have a particularly high incidence of this disorder. Asphyxia during labor or delivery also seems to predispose the neonate to RDS. Conditions that may lessen the risk of RDS include prolonged rupture of membranes, maternal drug addiction, and intrauterine growth retardation.

The primary abnormality in RDS appears to be deficient synthesis or release of pulmonary surfactant. This material lines the alveoli of the mature lung and lowers the surface tension required to keep the alveolus open during expiration. When surfactant is deficient, diffuse alveolar atelectasis ensues, resulting in pulmonary insufficiency. Surfactant production is normally very low in utero until the third trimester of pregnancy; it then increases gradually until 33–36 weeks' gestation, when there is an abrupt rise to near-term levels. Respiratory distress often develops in infants born prior to this “surge” and does not improve until surfactant production “turns on” at 48–72 hours after birth. Those who die during the acute stage of respiratory insufficiency have profound, generalized atelectasis on autopsy. Often, an eosinophilic material composed of fibrin, hemoglobin products, and cellular debris coats the terminal bronchioles; this is the classically described “hyaline membrane,” but it is not present in all cases, nor is it specific for RDS.

Respiratory distress syndrome produces characteristic clinical and radiographic findings. Tachypnea, nasal flaring, and retractions are usually present within the first hour of life and are often noted at birth. As the infant becomes progressively distressed, cyanosis is evident, and an expiratory grunt or cry is audible. Auscultation reveals poor breath sounds throughout the chest, often with fine, scattered crackles. The chest roentgenogram shows a diffuse granular opacification of the lung fields, with prominent air bronchograms; the heart border and diaphragms are often obscured. Blood gas analysis demonstrates hypoxemia and, in severe cases, hypercapnia and acidosis. Signs and symptoms usually worsen through the first 3 days of life, after which improvement and recovery are the rule, unless complications such as patent ductus arteriosus (PDA) or bronchopulmonary dysplasia have developed.

Conditions that must be differentiated from RDS include meconium aspiration, pneumonia, pneumothorax, airway obstruction, congenital heart disease, hypoglycemia, and sepsis. A particularly difficult disease to distinguish from RDS is pneumonia and sepsis due to the group B streptococcus, which clinically and radiographically may be identical to RDS, but runs a rapidly progressive and frequently fatal course (see Chap. 48).

Management of RDS is dependent on the severity of respiratory insufficiency. In milder cases, administration of supplemental oxygen provides adequate respiratory support through the 4- to 5-day course of the disease. When oxygen alone is insufficient, continuous distending pressure may aid in preventing alveolar collapse and thus improve respiratory function; distending pressure during spontaneous breathing may be delivered as continuous positive airway pressure by means of an endotracheal tube, nasal prongs, or face mask. Many infants with RDS require controlled mechanical ventilation during the most severe stage of their illness; this is the group most susceptible to complications of RDS.

Several forms of therapy have recently been added to the armamentarium of the clinician treating an infant whose RDS is severe enough to require ventilatory assistance, and to predispose to complications and death. Synthetic and natural surfactants are now available, and have changed the course and outcome of RDS as greatly as the introduction of mechanical ventilation did a generation ago. Several types of high-frequency ventilators, which facilitate gas exchange in the lung through diffusion as well as ventilation, can improve blood gases and reduce pulmonary interstitial emphysema, a form of air leak that often precedes pneumothorax and chronic lung disease. Extracorporeal membrane oxygenation (ECMO), a form of heart-lung bypass, can provide crucial support to larger infants with life-threatening RDS in whom all other forms of support have failed.

In spite of the best management, however, complications of RDS are common, especially in infants less than 1,000 g birth weight. High arterial oxygen concentrations during therapy can produce retinal damage, while periods of hypoxemia may lead to neurologic damage; the goal of respiratory assistance, therefore, is to maintain arterial PO_2 between 50 and 70 mm Hg, a range that minimizes but does not eliminate these complications. Continuous distending pressure and positive pressure ventilation produce pneumothorax in approximately 5–10% of cases; this complication usually causes sudden deterioration in respiratory function and can be diagnosed clinically by reduction of breath sounds over the affected lung and by transillumination. Use of oxygen and positive pressure ventilation can also cause bronchopulmonary dysplasia (BPD), a form of chronic pulmonary disease that is described more fully in Chap. 37.

Many other problems can complicate the course of RDS. Hypoglycemia, hypocalcemia, anemia, and acidosis may seriously worsen respiratory function if untreated. In severely ill patients, intracranial hemorrhage (ICH), and pulmonary hemorrhage are potentially fatal complications. Respiratory insufficiency can also be exacerbated by hypothermia or hyperthermia, both of which increase oxygen demands in the tissues. Hyperbilirubinemia is often severe in infants with RDS, and is more likely to cause kernicterus when acidosis or hypoxemia is present. Feeding a severely distressed infant is difficult but essential because of high energy requirements and minimal energy reserves. Usually, this necessitates special feeding techniques, such as nasogastric gavage or intravenous alimentation. Renal function is compromised in infants with RDS, and fluid administration must be adjusted accordingly. This is especially true because PDA is also a complication of RDS, and signs and symptoms of heart failure may be exacerbated by excessive fluid administration. Recovery from RDS usually begins on the third or fourth day of life and is complete by 1 week of age. Deviation from this course may be caused by a PDA, BPD, pneumonia, ICH, or apnea of prematurity. The long-term outlook for survivors of uncomplicated RDS is good; permanent pulmonary or neurologic damage is uncommon.

Prevention of RDS in some infants is possible through prenatal administration of steroids to the mother. Several other promising approaches remain in the experimental stage, including newer drugs to inhibit preterm labor or promote lung maturation. Amniocentesis permits analysis of the state of fetal lung maturation through measurement of the concentration of surfactant components in the amniotic fluid, allowing the delay of some semi-elective deliveries until lung maturation is ensured.

Reviews

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Contributing Factors

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Management: Surfactant

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37. CHRONIC LUNG DISEASE

Robert D. White

Respiratory insufficiency is a common complication of prematurity, due to immaturity of the lungs. The course may be acute, as in the respiratory distress syndrome (RDS) (see Chap. 36), or chronic, as in the Wilson-Mikity syndrome. Attempts to support pulmonary function in affected infants produce additional problems, among them bronchopulmonary dysplasia (BPD). The chronic pulmonary diseases that originate in the neonatal period share certain characteristics, the most encouraging of which is that most infants who survive the first year of life avoid any residual symptomatic pulmonary disability.

Bronchopulmonary dysplasia occurs in some infants who have received high concentrations of oxygen for several days. In most cases, an endotracheal tube and intermittent positive pressure ventilation have also been used for at least 24 hours. These observations implicate both oxygen and barotrauma in the pathogenesis of BPD. It is most commonly seen in infants recovering from RDS, since this is by far the most common disease requiring intensive respiratory support.

The clinical course of BPD has been divided into four stages. In the first days of life (stage I), severe respiratory disease is present. Late in the first week of life (stage II), there is clinical improvement, but the infant never becomes totally asymptomatic. In the second week of life (stage III), a clear departure from the natural history of acute respiratory illness occurs: There is clinical deterioration, with increasing hypoxemia, hypercapnia, and acidosis, and additional respiratory support is required. The lungs at this point are usually diffusely opacified on chest roentgenograms; small cystic areas and streaky infiltrates appear shortly thereafter. The clinical picture is often very similar to that of patent ductus arteriosus, which can coexist with BPD in premature infants recovering from RDS. Histologically, there is evidence of intense inflammation, with edema, exudate, and macrophages filling the alveoli. This inflammatory response is strikingly similar to that described in experimental oxygen toxicity of the lung. Frequently, there is also disruption of the bronchiolar tissue, progressing to the cystic lesions noted on x-ray study. Deterioration may continue for several weeks; pneumonia may also supervene and cause additional respiratory compromise.

Stage IV, the chronic healing phase of BPD, occurs after 3–4 weeks of age. Clinically, respiratory distress, cyanosis, and crackles are present; radiographs and histologic examination reveal larger cystic lesions and progression of the fibroplasia. A few infants die during this stage, usually from superimposed infection.

The extent of healing in BPD is evidence of the tremendous regenerative capacity of an infant's lungs. In all but the most severe cases, symptoms usually resolve by 2 years of age, although abnormalities in pulmonary function tests and electrocardiographic evidence of right ventricular hypertrophy may persist for several years.

The Wilson-Mikity syndrome differs from BPD in that RDS is mild or absent at birth, and oxygen requirements initially are minimal. It occurs almost exclusively in premature infants whose birth weight is less than 1,500 g. Many are moderately depressed at birth, but respiratory problems and oxygen administration are minimal. They then usually have an interval of several days with mild symptoms, followed by the insidious onset of respiratory insufficiency. Blood gases reveal hypoxemia, hypercapnia, and acidosis, with severe (30–80%) intrapulmonary shunting of blood. The radiograph demonstrates small cystic lesions scattered throughout the lungs, accompanied by a fine, lacy infiltrate; often, these changes precede clinical symptoms. Respiratory insufficiency may progress for 1–2 months, followed by regression and healing. Survivors usually have no clinical or radiographic evidence of disease at 2 years of age, but exercise tolerance and pulmonary function test abnormalities may persist. The cause of the Wilson-Mikity syndrome is uncertain; histologically, it is characterized by cystic changes and mild scarring, and is distinguished from BPD by the relative absence of inflammation.

A third chronic pulmonary disease of the premature infant has been termed chronic pulmonary insufficiency of prematurity. The clinical syndrome is virtually identical to that of Wilson-Mikity except that radiographic changes, when present, consist of fine generalized opacification without cystic changes. Because mortality is rare, histologic characterization is lacking at present.

Because of the improved survival of extremely premature infants, the incidence of chronic pulmonary disease in infancy is increasing. At present, only supportive therapy is available. Good nutrition is essential to lung healing; infants with chronic lung disease present a challenge because their caloric requirements are increased by the work of breathing, yet fluid tolerance is low due to cor pulmonale. Chest percussion and drainage, diuretics, and bronchodilators may be of acute benefit, but the most effective drug for chronic use appears to be dexamethasone, although serious concerns remain about long-term growth and neurological complications of this therapy. The emotional and developmental needs of the patients and their parents should not be overlooked; the chronic, unstable course of BPD in particular requires close contact with a stable group of sympathetic and helpful caretakers for optimal support. After discharge, efforts to prevent respiratory syncytial virus infection are important, including administration of monoclonal antibody and strategies to minimize exposure to other children.

Reviews

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2. Barrington, K., and Finer, N. Treatment of bronchopulmonary dysplasia: A review. *Clin. Perinatol.* 25:177–202, 1998.
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Bronchopulmonary Dysplasia: Etiology

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   Inflammation, whether induced by infection or oxygen toxicity, is clearly a preceding component of chronic lung disease, and is the basis for the current interest in using steroids and other anti-inflammatory agents in the early stages of disease.
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13. Greenough, A. Gains and losses from dexamethasone for neonatal chronic lung disease. *Lancet* 352:835–836, 1998.
*Brief summary of where we currently stand on the value and complications of dexamethasone therapy for established chronic lung disease. "Pulse" doses, rather than long courses of treatment, may avoid most of the complications (*J. Pediatr. *126:769–776, 1995).*
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Chronic Pulmonary Insufficiency of Prematurity

20. Charadfeddine, L., D'Angio, C., and Phelps, D. Atypical chronic lung disease patterns in neonates. *Pediatrics* 103:759–765, 1999.
Like BPD itself, the other causes of chronic lung disease in premature infants have changed in name and manifestations so much as to be almost unrecognizable in the original, presurfactant descriptions—and prevention remains equally elusive.

38. APNEA IN THE PREMATURE INFANT

Robert D. White

Apnea in the premature infant is a common manifestation of central nervous system (CNS) immaturity, but may also be a symptom of many other neonatal illnesses. Evaluation of the premature infant with apnea therefore begins with exclusion of other potentially dangerous but treatable disorders.

Apnea is defined as cessation of respiration for greater than 15–20 seconds; it is rare beyond 35 weeks' gestation and becomes progressively more common with increasing degrees of prematurity. Before 28 weeks' gestation, apnea of prematurity may be severe enough to require ventilatory assistance, but severe apnea above this age or any degree of apnea beyond 35 weeks' gestation should raise concern about underlying illness.

The differential diagnosis in a child with significant apnea should always include infection, hypoglycemia, and seizures, since these are potentially serious disorders for which early treatment is crucial. Maternal administration of CNS depressants, hypoxemia, hypothermia, anemia, hypocalcemia, and patent ductus arteriosus are additional causes that will usually be apparent from a routine history, physical examination, and laboratory tests, but gastroesophageal reflux, intracranial hemorrhage, and upper airway obstruction are causes that can be missed unless they are considered and explored.

When underlying illnesses have been excluded as the source of apnea in a preterm infant, “apnea of prematurity” becomes the most tenable diagnosis, and a number of treatment options can be considered. Mild, occasional apnea of prematurity does not require treatment and will usually resolve prior to 35 weeks postconceptional age. Severe apnea often requires ventilatory assistance in its early stages but then becomes amenable to less invasive therapy as the infant matures. Theophylline and caffeine are the major standbys; they are stimulants that probably act as competitive inhibitors of adenosine receptor sites in the CNS. Other CNS stimulants (e.g., doxapram), supplemental oxygen, kinesthetic or acoustic stimulation, and continuous positive airway pressure have all shown some value in treatment of apnea, but it is not known whether any of these improve the outcome in this generally self-limited disorder when compared with methylxanthine therapy alone.

Treatment of apnea of prematurity with methylxanthines requires close monitoring of blood levels, since metabolism changes considerably as the infant matures. Careful observation for side effects is also important because these can occur even when blood levels are within the therapeutic range. Sometimes subtle gastroesophageal reflux caused by methylxanthine toxicity actually makes apnea worse; this factor may account for some cases of apparent treatment failures. Metabolism of methylxanthines can also deteriorate rapidly during an acute illness, exacerbating the baby's distress and creating a potentially life-threatening situation.

As the infant matures and apnea resolves, drug and oxygen therapy can be discontinued. In some cases, however, premature infants will be ready for discharge except for their continued need for treatment of apnea; home monitoring may be appropriate in this situation. Parents are frequently interested in obtaining home monitors even when the baby has outgrown the apnea prior to discharge, especially if they are aware of the approximately two-fold increased risk of sudden infant death syndrome (SIDS) that preterm infants carry. There is no evidence, however, that the risk of SIDS in this population is lessened by any treatment modality, so parental reassurance is most appropriate in this situation. It is worth noting, however, that premature infants who appear to have outgrown apnea of prematurity can have recurrence of apnea during severe respiratory infections or after general anesthesia as late as several months following discharge, so short-term monitoring may be indicated in these cases.

Review

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Pathophysiology

2. Ruggins, N. Pathophysiology of apnoea in preterm infants. *Arch. Dis. Child.* 66:70–73, 1991.
   Immaturity of the respiratory center and intermittent airway obstruction are both implicated in apnea of the premature, perhaps explaining the effectiveness of diverse therapies, but also the lack of complete response to any one treatment.
3. Finer, N., et al. Obstructive, mixed, and central apnea in the neonate: Physiologic correlates. *J. Pediatr.* 121:943–950, 1992.
   Not only is the etiology of apnea complex, but the physiologic response is also quite variable. A unifying hypothesis is presented in Arch. Dis. Child. *67:419–424, 1992, in which it is suggested that airway closure occurs as central apnea progresses.*

Therapeutic Interventions

4. Andreasson, B., et al. Effects on respiration of CPAP immediately after extubation in the very preterm infant. *Pediatr. Pulmonol.* 4:213–218, 1988.
   CPAP can reduce the severity of apnea following extubation, sometimes allowing reduced length of mechanical ventilation.
5. Joshi, A., et al. Blood transfusion effect on the respiratory pattern of preterm infants. *Pediatrics* 80:79–84, 1987.
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8. Korner, A., et al. Reduction of sleep apnea and bradycardia in preterm infants on oscillating waterbeds: A controlled polygraphic study. *Pediatrics* 61:528–533, 1978.
   Rhythmic stimulation, whether vestibular, tactile, or auditory, appears to reduce the incidence of apnea, although again the precise mechanism(s) remain unclear.

Discharge Considerations

9. Darnall, R., et al. Margin of safety for discharge after apnea in preterm infants. *Pediatrics* 100:795–801, 1997.
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10. Sanchez, P., et al. Apnea after immunization of preterm infants. *J. Pediatr.* 130: 746–751, 1997.
    Recurrence of apnea occurred in 21% of infants—predominantly those who had previously experienced severe apnea of prematurity or chronic lung disease. Such infants, rather than delaying immunizations, should have their first immunization prior to discharge, if possible, to allow observation through this most susceptible period.

39. CYANOTIC HEART DISEASE

John R. Lane and Kenneth G. Zahka

The introduction of the Blalock-Taussig operation more than 40 years ago for the palliation of cyanotic congenital heart disease opened the modern era of pediatric cardiology and cardiovascular surgery. The subsequent development of cardiopulmonary bypass and further refinements in diagnostic imaging, interventional procedures, and infant heart surgery have dramatically changed the natural history and prognosis for newborns with cyanotic heart disease.

Cyanosis involving the mucous membranes and extremities reflects arterial oxygen desaturation sufficient to produce a desaturated hemoglobin concentration of 3–5 g/dL. Thus, a polycythemic newborn with a hemoglobin of 20 g/dL requires an arterial oxygen saturation below 75–85% (a P_{O_2} of 40–45 mm Hg) before appearing cyanotic. This arterial desaturation may be a result of (1) structural defects, such as transposition of the great arteries, tetralogy of Fallot, total anomalous pulmonary venous return, tricuspid atresia, or truncus arteriosus; (2) intracardiac right-to-left shunting, which occurs at the foramen ovale and ductus arteriosus in newborns with persistence of the fetal circulation due to high pulmonary vascular resistance, but an otherwise structurally and functionally normal heart; or (3) left heart obstructive lesions, such as critical aortic stenosis or coarctation, due to associated pulmonary edema and pulmonary venous oxygen desaturation. As discussed below, primary lung disease, including parenchymal and airway or diaphragmatic abnormalities, must be differentiated from cardiovascular etiologies as a cause of cyanosis.

Differential (upper versus lower body) cyanosis, with normal arterial oxygen saturation in the blood flow to the head and upper extremities but desaturation of the blood supply to the lower half of the body, is characteristic of pulmonary artery–to– descending aorta shunting through a patent ductus arteriosus. This may be observed in newborns with critical coarctation of the aorta or in those with persistence of the fetal circulation and ductal but no atrial level right-to-left shunting. Cyanotic upper extremities with normal lower extremities is diagnostic of the combination of transposition of the great arteries, patent ductus arteriosus, and coarctation of the aorta.

Peripheral cyanosis with normal central color is usually an indication of reduced blood flow to the extremities with normal arterial oxygen saturation but increased oxygen extraction. This may indicate poor cardiac output due to hypovolemia or myocardial dysfunction, or it may reflect hypoglycemia, hypothermia, sepsis, or hyperviscosity due to neonatal polycythemia. Some degree of peripheral cyanosis is normal in healthy newborns, resulting from the combination of vasomotor instability, hypothermia, and polycythemia.

The differentiation of cyanotic heart disease from other forms of structural heart disease and pulmonary disease requires a systematic approach to the history and physical examination. A history of prematurity, prolonged rupture of membranes, meconium-stained amniotic fluid, or perinatal asphyxia favors the diagnosis of lung disease or persistence of the fetal circulation. However, newborns with structural heart disease face the same perinatal risks as other babies, and thus congenital heart disease should never be excluded on the basis of this history alone. A positive family history of congenital heart disease in a parent or sibling increases the likelihood of congenital heart disease.

Cyanosis and tachypnea without dyspnea, but with increased precordial activity, a single second heart sound, and murmurs are reliable bedside clues to the presence of underlying cyanotic congenital heart disease. However, the second heart sound is normally single during the first few hours of life, and remains single in newborns with pulmonary hypertension and persistence of the fetal circulation. Occasionally, newborns with persistence of the fetal circulation will have audible murmurs of tricuspid regurgitation. In contrast, the absence of a murmur does not exclude life-threatening cyanotic heart diseases such as transposition of the great arteries or tetralogy of Fallot with pulmonary atresia.

Hypoxia in a cyanotic-appearing infant can rapidly and noninvasively be confirmed by pulse oximetry. Measurement of the arterial blood gas tensions provides further information about acid-base balance and adequacy of ventilation. A repeat blood gas while the baby is breathing 100% oxygen (the hyperoxia test) helps to further differentiate structural heart disease from pulmonary disease. Lung function with pulmonary disease in the immediate newborn period is usually sufficient to allow an increase in the arterial P_{O_2} to above 150 mm Hg. In contrast, newborns with cyanotic heart disease and intracardiac shunting rarely increase their P_{O_2} above 100 mm Hg. Hyperventilation to achieve a P_{CO_2} below 25 mm Hg and pH above 7.5 will often lower the pulmonary vascular resistance in a newborn with persistence of the fetal circulation at least transiently, resulting in a high arterial P_{O_2}, thereby permitting exclusion of structural heart disease.

A distinctly abnormal cardiothymic silhouette or vascularity on chest x-ray supports the diagnosis of heart disease. The electrocardiogram (ECG) is of limited use in the cyanotic newborn since most of the defects have right ventricular hypertrophy, which is a normal finding in all newborns. An important exception is the newborn with tricuspid atresia, in whom left axis deviation and left ventricular hypertrophy are nearly always present on the ECG due to the underdevelopment of the right ventricle. Two-dimensional and Doppler ECG permit definitive diagnosis of the anatomy and pathophysiology of the cyanotic newborn. Structural defects, including anomalies of the atrial and ventricular septum, semilunar and atrioventricular valves, the systemic and pulmonary venous return, and the great arteries, are now defined with a high degree of reliability. Doppler ECG permits estimation of the severity of semilunar valve stenosis (e.g., in tetralogy of Fallot) and documents the presence of atrioventricular valve regurgitation (e.g., in Ebstein anomaly or single ventricle). Abnormal patterns of blood flow at the ductus arteriosus and foramen ovale documented by Doppler ECG make the differentiation of cyanotic congenital heart disease from persistence of the fetal circulation feasible.

Cardiac catheterization remains a valuable diagnostic tool in selected children with cyanotic heart disease, especially as part of the assessment for surgery. Therapeutic interventional procedures have assumed a much larger role in the cardiac catheterization laboratory. The balloon septostomy for transposition of the great arteries (Rashkind procedure) provides excellent palliation for newborns awaiting surgery. Newborns with cyanosis due to critical pulmonary stenosis may respond dramatically to balloon dilation of the obstruction.

Careful medical management, including attention to the metabolic and thermal needs of a newborn with cyanotic heart disease, is crucial to survival. Defects associated with diminished pulmonary blood flow, including tetralogy of Fallot, tricuspid atresia, and single ventricle with pulmonary stenosis, are likely to be dependent on the patency of the ductus arteriosus for pulmonary blood flow and systemic oxygenation. Newborns with transposition of the great arteries frequently deteriorate when the ductus arteriosus closes, since the increased pulmonary blood flow favors atrial mixing. Any severely cyanotic newborn should be considered to be “ductus dependent” (i.e., dependent on continued patency of the ductus arteriosus) until a definitive diagnosis is established, and prostaglandin E_1 (PGE_1) should be started to maintain or restore patency of the ductus. Mildly cyanotic newborns requiring transport to a tertiary center for diagnosis or treatment are at reduced risk for the sequelae of hypoxia if PGE_1 is administered during transport; however, this advantage must be balanced against the problematic side effect of apnea, which may require mechanical ventilation. Once cardiac disease is excluded or specific therapy is effected, PGE_1 may be discontinued.

The specific surgical management of the most common cyanotic defects, tetralogy of Fallot and transposition of the great arteries, is discussed in Chap. 53 and Chap. 54, respectively. Total anomalous pulmonary venous return, especially when the pulmonary veins return to the inferior vena cava, may present in the newborn period with cyanosis and pulmonary edema and require repair at that time. Newborns with truncus arteriosus have a large ventricular septal defect, common semilunar valve, and an arterial trunk that branches to form the aorta and pulmonary arteries. They usually present with mild cyanosis and congestive heart failure due to complete mixing and the markedly increased pulmonary blood flow at several weeks of age. Associated abnormalities such as truncal valve stenosis or regurgitation, or interrupted aortic arch make infants with this defect symptomatic in the first days of life. Surgical repair is often performed in the first month of life. Palliation rather than definitive repair in infancy remains the usual option for infants with tricuspid atresia and other complex defects, including single ventricle (both atrioventricular valves are present but enter one ventricle with hypoplasia of the other ventricle). In patients with tricuspid atresia or single ventricle, those with diminished pulmonary blood flow require systemic-to-pulmonary shunts to provide adequate pulmonary blood flow. Those without pulmonary stenosis have excessive pulmonary blood flow and pressure, and need pulmonary artery banding to prevent congestive heart failure and the later development of pulmonary vascular disease. The staged modified Fontan procedure is the best current long-term surgical option for these children. Between 3 and 6 months of life, a bidirectional Glenn operation with direct anastomosis of the superior vena cava to the right pulmonary artery and ligation of any shunts is performed. In late infancy or early childhood, the systemic venous

blood is separated from the pulmonary venous blood by baffling of the inferior vena caval blood to the right pulmonary artery.

Advances in the diagnosis, medical treatment, and surgery of newborns with cyanotic heart disease have dramatically altered the prognosis for these infants. Definitive surgery within the first year of life, often within the first month, has minimized much of the physical and emotional impact of chronic cyanosis on the children and their families.

Reviews

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    *Ebstein's anomaly is a broad spectrum, ranging from minimal abnormality of the tricuspid valve to marked displacement of the valve into the right ventricle with severe tricuspid regurgitation, pulmonary stenosis, and cyanosis due to atrial shunting. Symptomatic fetuses and neonates have the worse prognosis (*Am. Heart J. *135:1081–1085, 1998;* Am. J. Cardiol. *81:749–754, 1998). See* Ann. Thorac. Surg. *66:1539–1545, 1998, and* Circulation *80:I197–I202, 1989, for surgical results in older children with Ebstein's anomaly;* Eur. J. Cardiothorac. Surg. *13:280–284, 1998, for neonatal surgery; and* J. Am. Coll. Cardiol. *29:1615–1622, 1997, for exercise tolerance following surgery for Ebstein's anomaly. For the older symptomatic patient, repair of the defect improves not only the hypoxia but also exercise tolerance. Radiofrequency ablation of tachycardia pathways is challenging (*J. Cardiovasc. Electrophysiol. *9:1370–1377, 1998) with acute success tempered by frequent recurrences.*

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40. CONGESTIVE HEART FAILURE IN THE NEONATE

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The congenital cardiovascular defects most likely to cause severe congestive heart failure in the neonate are those with left heart obstruction, atrioventricular and semilunar valve regurgitation, and arteriovenous malformation. In addition to these structural defects, myocarditis, arrhythmias, myocardial tumors, and the hypertrophic cardiomyopathy of the infant of the diabetic mother stress the otherwise normally formed cardiovascular system and result in poor feeding, tachypnea, and poor perfusion or blood pressure. The defects associated with large left-to-right shunts, including ventricular septal defect, patent ductus arteriosus, truncus arteriosus, and total anomalous venous return do not cause symptoms until the pulmonary vascular resistance falls and pulmonary blood flow increases over the first few weeks of life. Hypoglycemia, anemia, and infections can complicate the course of newborns with congestive heart failure, as well as mimic the signs of congestive heart failure. Newborns with urea cycle abnormalities and other rare enzymatic defects may present in shock, initially indistinguishable from a primary cardiovascular etiology.

The left heart obstruction defects presenting in the neonatal period include the hypoplastic left heart syndrome (HLHS), critical aortic stenosis, and critical aortic coarctation or arch interruption. These share the common pathophysiology of severely limited antegrade aortic blood flow. In these children, patency of the ductus arteriosus is essential for survival, and spontaneous closure of the ductus arteriosus after birth results in profound congestive heart failure and shock. Renal, hepatic, and mesenteric ischemia produces multisystem failure mimicking that seen with sepsis; therefore, critical left heart obstruction should be in the differential diagnosis of any newborn with suspected sepsis. A discrepancy in the blood pressure or palpable pulse volume between the upper and lower extremities or variation in the pulse volume over time is an important sign of these defects. A hyperactive precordium, single second heart sound, gallop rhythm, or murmur should prompt further investigation. The absence of a murmur is not reassuring, since, even in severe aortic stenosis, blood flow may be so limited across the obstruction that the turbulence is inaudible. Repeat examinations over several hours are particularly important to detect changes due to closure of the ductus.

A specific echocardiographic or catheterization diagnosis must be made if there is any suspicion of left heart obstruction. An infusion of prostaglandin E_1 should be started when the diagnosis is established or if there is any indication of impaired organ perfusion. Special care must be taken not to lower the pulmonary vascular resistance in newborns with HLHS. Lowering the pulmonary vascular resistance by administering supplemental oxygen or by hyperventilating the baby increases pulmonary blood flow and severely limits systemic blood flow. Problems due to hepatic, renal, and gastrointestinal dysfunction should be anticipated and monitored by clinical and laboratory examinations. Ventricular dysfunction or pulmonary edema may accompany severe aortic stenosis even in the newborn period; diuretics and inotropic drugs are beneficial in these newborns. Infants with left heart obstruction may have other abnormalities and may require further assessment; in particular, aortic stenosis may be a manifestation of Turner syndrome and interrupted arch of DiGeorge syndrome. Timely treatment of acidosis, hypoglycemia, hypocalcemia, and respiratory insufficiency ensures the best possible chance for surgical management.

Surgery for the HLHS, once a uniformly fatal defect, has been pioneered by Norwood, who devised a multiple-stage operation for long-term palliation of these newborns. The first stage consists of an ascending aorta-to-main pulmonary artery anastomosis, transection of the distal pulmonary artery, and creation of a systemic-to-pulmonary shunt. This essentially converts the defect from aortic atresia to pulmonary atresia with a single atrioventricular valve and ventricle. A bidirectional Glenn operation (superior vena cava to right pulmonary artery) is done between 3 and 6 months of life. A modification of the Fontan procedure is performed by 2 years of age to separate the pulmonary and systemic circulations. The long-term results of this approach have dramatically improved with 80–90% survival for the first stage operation and greater than 95% survival for the subsequent stages. The series of operations remains difficult, and meticulous pre- and postoperative care are essential to achieve good results. Cardiac transplantation, despite good intermediate-term results, has become a less frequent alternative for the management of HLHS as the results of staged surgical palliation of HLHS have improved.

Balloon aortic valvuloplasty is the primary initial therapy for newborns with critical aortic stenosis. Surgical valvotomy, either under direct vision or dilation from an apical ventriculotomy, remains an appropriate alternative therapy. Coarctation is repaired either by excision of the coarctation membrane and enlargement of the coarctation site with a synthetic patch, or by mobilizing the left subclavian artery as a flap patch. Aortic arch interruption with ventricular septal defect frequently may be repaired in the neonatal period by direct anastomosis of the proximal and distal aorta and closure of the ventricular septal defect.

Congenital atrioventricular or semilunar valve regurgitation is a rare and difficult-to-treat cause of congestive heart failure in neonates. Absence of the pulmonary valve results in aneurysmal dilatation of the pulmonary arteries and respiratory distress. Congenital mitral regurgitation is either on the basis of a cleft in the mitral valve or a more diffuse maldevelopment of the cusps. Tricuspid regurgitation due to severe Ebstein's anomoly of the valve is complicated by right ventricular dysfunction and outflow tract obstruction, as well as cyanosis due to right-to-left atrial shunting. Medical management of newborns with Ebstein anomaly is the best short-term option, although surgical repair of the valve is feasible in some. Replacement of the valve is deferred unless absolutely necessary until later in the first year of life.

Large arteriovenous malformations produce severe volume overload of both the right and left ventricle. The diagnosis may be made in utero by cranial and cardiac ultrasonography performed because of fetal hydrops or for routine assessment of fetal size. Following delivery, these newborns have a hyperactive precordium, bounding pulses, and continuous murmurs. Cerebral arteriovenous malformations are the most frequent hemodynamically compromising lesions, and they carry a poor prognosis regardless of medical, surgical, or interventional neuroradiology treatments.

Primary myocardial dysfunction secondary to in utero myocarditis or perinatal asphyxia presents with a murmur of mitral or tricuspid regurgitation, with poor perfusion or with ventricular or atrial arrhythmias. Viral cultures may establish the etiologic agent if the infection and inflammatory process are still active. The extent of the myocardial dysfunction, the secondary atrioventricular valve regurgitation, and the nature of the arrhythmias can be documented by echocardiography and electrocardiography. Depending on the extent of the ventricular dysfunction, these newborns require inotropic drugs, mechanical ventilation, afterload reduction, and treatment of the arrhythmias to support them through the perinatal transition.

In utero supraventricular tachycardia can precipitate fetal hydrops and severe congestive heart failure, but can also be an episodic problem that does not impair fetal well-being. The diagnosis of in utero tachycardia is usually made by auscultation or Doppler interrogation of the fetal heart rate. The type of tachycardia and the impact on the fetus may be confirmed by documentation of atrial and ventricular wall motion by fetal echocardiography. Maternal treatment with digoxin or calcium channel blockers has been advocated for the compromised fetus for whom delivery is inadvisable. This must be undertaken with care, since the therapeutic benefit and potential toxicities for mother and fetus are still being defined. Diagnosis and treatment of supraventricular tachycardia postnatally are as in infants and older children (see Chap. 55).

Myocardial tumors, most frequently rhabdomyomas, can occur at any site in the right or left ventricle and be either intracavitary or intramural. Depending on their size, they interfere with ventricular filling, emptying, or wall motion. Their location, size, and hemodynamic impact are best identified by two-dimensional and Doppler echocardiography. Ventricular and atrial arrhythmias are common and poorly tolerated by babies with these tumors. Surgical excision of intracavity tumors has been reported, although no surgery is possible for the large intramural tumors.

The infant of a diabetic mother is subjected to high transplacental glucose loads and develops hyperinsulinemia. Insulin is a potent growth stimulant for the fetal myocardium, and newborns of poorly controlled diabetic mothers have severe biventricular hypertrophy and dramatic septal hypertrophy. The hypertrophy is associated with a variable degree of outflow obstruction, impaired ventricular filling, and atrioventricular valve regurgitation. Congestive heart failure due to these factors and cyanosis due to shunting from the right to left atrial across the foramen ovale usually improve as the hypertrophy regresses over the first month of life. Unless there is evidence of myocardial dysfunction, inotropic drugs are withheld, since they theoretically could worsen the clinical manifestations of this disease by

increasing the obstruction and filling abnormalities.

While the range of defects producing the clinical syndrome of congestive heart failure in the neonate is more limited than that in the older child, special attention must be devoted to the metabolic and infectious etiologies and complications of neonatal congestive heart failure, as well as the types of therapy available for the neonate. Ideally, prenatal diagnosis and possibly treatment can improve the prognosis for these life-threatening conditions.

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27. Goldmuntz, E., et al. Frequency of 22q11 deletions in patients with conotruncal defects. *J. Am. Coll. Cardiol.* 32:492–498, 1998.
    Deletions are found in 50% of patients with interrupted aortic arch. The prevalence is highest with right aortic arch and type B interruption, lowest when the interruption is distal to the left subclavian artery.

Other Etiologies

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    There has been significant progress made in the treatment of cerebral arteriovenous malformations. For babies with large lesions, the neurodevelopmental outcome is not normal.
29. Sallee, D., et al. Primary pediatric cardiac tumors: A 17-year experience. *Cardiol. Young* 9:155–162, 1999.
    Extensive rhabdomyomas and intrapericardial teratomas present in the neonatal period with signs of congestive heart failure.

41. TRANSIENT METABOLIC DISTURBANCES

Robert D. White

Profound metabolic changes may occur at birth when the neonate assumes independent control of homeostasis. The transition from fetal to newborn life does not always proceed smoothly; three of the more common and dramatic examples of transient neonatal metabolic disturbances are discussed in this chapter.

Hypoglycemia (see also Chap. 80) has been defined as blood glucose of less than 30 mg/dL in full-term infants or less than 20 mg/dL in premature infants, but most experts believe higher thresholds are appropriate. It occurs in 0.2–0.5% of newborns and has many causes, including disorders in which inadequate substrate is available (reduced carbohydrate stores in the premature and dysmature infants, galactosemia, glycogen storage disease type I), those in which utilization of glucose is increased (as with virtually any severe neonatal stress), and those in which circulating levels of insulin are increased (maternal diabetes, erythroblastosis fetalis, insulin-producing tumor).

Most infants with hypoglycemia are asymptomatic. In symptomatic patients, the most common sign is jitteriness; some babies, however, present with more serious manifestations, such as convulsions, lethargy, apnea, or cyanosis. Any of these signs should prompt an immediate determination of blood glucose, even if other explanations are available, since hypoglycemia often coexists with sepsis, asphyxia, hypothermia, hypocalcemia, or congenital heart disease.

Hypoglycemia is treated by providing sufficient glucose to the neonate and correcting underlying diseases when possible. Some symptomatic infants require intravenous infusion of more than 10 mg/kg/min of dextrose to maintain a normal blood glucose, but oral feeding of dextrose solution or formula is usually sufficient for asymptomatic infants. Most full-term infants with hypoglycemia due to perinatal asphyxia or intrauterine malnutrition will need glucose supplementation for only 1 or 2 days, but premature infants and those with erythroblastosis or whose mothers are diabetic often require a longer period of therapy. The duration of glucose supplementation needed in infants with sepsis, congestive heart failure, and other similar disorders depends on the severity and outcome of the underlying disease. Rarely, patients have hypoglycemia that persists beyond the first week of life; these infants require an extensive evaluation for endocrine and metabolic disease, and may become normoglycemic only after therapy with adrenocorticotropic hormone or glucocorticoids.

The prognosis is guarded if severe symptoms have occurred, as only 50% of this group develop normally. The outlook for asymptomatic hypoglycemia, or when only jitteriness is present, is much better; 90% or more of these children are normal or have only minimal sequelae on long-term follow-up. Prevention of hypoglycemia is possible in most cases by identification and early feeding of high-risk infants.

Like hypoglycemia, hypocalcemia is a manifestation common to several different diseases. “Early” hypocalcemia, which occurs during the first 72 hours of life, is particularly prevalent in prematures and in infants who have undergone stress, as in asphyxia or maternal toxemia; increasing evidence suggests that immature parathyroid function underlies the hypocalcemia in most of these cases. “Late” hypocalcemia, occurring after several days of cow milk feedings in healthy full-term infants, results from the high renal phosphate load of unmodified cow milk, but has become rare since the resurgence in breast-feeding and the introduction of commercial formulas with lower phosphate concentrations. Other rare causes of neonatal hypocalcemia include maternal hyperparathyroidism, congenital absence of the parathyroid glands, and panhypopituitarism (which can also cause hypoglycemia).

Hypocalcemia is also like hypoglycemia in that most affected neonates are asymptomatic: When signs do appear, twitching and convulsion are most common, although lethargy and apnea also occur. Carpopedal spasm is an infrequent but distinctive manifestation of hypocalcemia. Signs of hypocalcemia are rare unless the total serum calcium is below 6 mg/dL (or the ionized calcium is below 2.5 mg/dL) and the Q-T interval on the electrocardiogram is prolonged. Since hypoxemia, hypoglycemia, infection, or intracerebral hemorrhage frequently coexist, it is not always clear to what extent nonspecific signs can be attributed to hypocalcemia; in these cases, calcium infusion may be both diagnostic and therapeutic. Hypomagnesemia is present in 40–50% of infants with hypocalcemia; it is usually not necessary to administer magnesium, but occasionally hypocalcemia and its symptoms will resolve only after correction of the hypomagnesemia.

The prognosis of hypocalcemia in neonates is similar to that of hypoglycemia. Asymptomatic or jittery infants have essentially normal development, while more than 50% of those with convulsions have permanent neurologic damage. Although it is not yet clear whether this morbidity is related to the hypocalcemia or to the associated disease often present, these figures emphasize the importance of frequent monitoring of high-risk infants to permit treatment prior to clinically apparent hypocalcemia, and make prophylaxis an attractive consideration.

Currently, crack cocaine is responsible for the majority of serious neonatal drug withdrawal reactions, but more than a dozen other drugs are known to be addictive to the fetus, including the widely used barbiturates, antidepressants, narcotics, and alcohol. The severity of fetal addiction and the subsequent withdrawal symptoms are dependent not only on the type of drug and the extent of its use during pregnancy, but also on the timing of the last dose prior to delivery, as well as on coexisting perinatal diseases.

Signs of drug withdrawal characteristically include tremors, irritability, increased muscle tone, diarrhea, and poorly coordinated sucking movements. Sneezing, sweating, and convulsions may also occur. Affected infants are unusually alert and cry frequently, behavior that may be particularly unpleasant to mothers who find it difficult to cope with stress. Symptoms generally appear on the first day of life in cocaine- or heroin-addicted infants but may be delayed 3–4 days or more in infants of methadone users.

Management of an infant with neonatal narcotic withdrawal is primarily supportive. Nursing in a quiet, darkened room and swaddling are often employed to reduce abrasions on the extremities caused by the nearly incessant activity, and feeding requires patience and persistence. In some nurseries, paregoric, phenobarbital, or diazepam are used in symptomatic infants. Even without therapy, however, symptoms are self-limited and, except for the uncommon occurrence of convulsions or severe dehydration from diarrhea, appear to be benign.

Although drug withdrawal is usually the most dramatic manifestation of fetal drug addiction, of equal or greater importance are the associated problems, such as prematurity, intrauterine growth retardation, meconium staining, and perinatal asphyxia. Beyond the neonatal period, sudden infant death, child abuse and neglect, behavioral problems, and developmental delay are all more common in this group of infants than in the general population. Thus, maximal effort is indicated in discharge planning, with provision for regular follow-up of these infants, as few groups have a higher risk for subsequent problems.

Hypoglycemia: Reviews

1. Menon, R., and Sperling, M. Carbohydrate metabolism. *Semin. Perinatol.* 12: 157–162, 1988.
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2. McGowan, J. Neonatal hypoglycemia. Pediatr. Rev. 20:e6, 1999. (Available at: pedsinreview.org/cgi/content/full/20/7/e6 .)
   The two-page introduction to this article is also worthwhile, and makes the case for defining hypoglycemia at less than 50 mg/dL.
3. Halamek, L., and Stevenson, D. Neonatal hypoglycemia, part II: Pathophysiology and treatment. *Clin. Pediatr.* 37:11–16, 1998.
   The treatment algorithm presented here is independent of the definition of hypoglycemia, recognizing that this issue is still in flux.
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5. Cornblath, M., et al. Controversies regarding definition of neonatal hypoglycemia: Suggested operational threshholds. *Pediatrics* 105:1141–1145, 2000.
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6. Cowett, R. Neonatal hypoglycemia: A little goes a long way. *J. Pediatr.* 134: 389–391, 1999.

Reviews the adverse effects of hypoglycemia.

Hypoglycemia: Causes

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9. Milner, R. Nesidioblastosis unravelled. *Arch. Dis. Child.* 74:369–372, 1996.
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    Several endocrine disorders can present with neonatal hypoglycemia and intractable seizures; the former symptom may not be noticed unless specifically sought.
11. Burton, B. Inborn errors of metabolism in infancy: A guide to diagnosis. *Pediatrics* 102:e69, 1998. (Available at: www.pediatrics.org/cgi/content/full/102/6/e69.)
    Many metabolic disorders may also present with hypoglycemia; in some, such as galactosemia, a swift diagnosis (before the routine newborn screening test returns) may be lifesaving.
12. Moore, A., and Perlman, M. Symptomatic hypoglycemia in otherwise healthy, breastfed term infants. *Pediatrics* 103:837–839, 1999.
    Early discharge policies may cause some breast-fed infants to be discharged before adequate feedings are established, with potentially devastating consequences. In two of the three cases described here, jitteriness was noted several hours prior to the onset of seizures, but its significance was missed by medical staff.

Hypocalcemia: Causes

13. Forfar, J. Normal and abnormal calcium, phosphorus and magnesium metabolism in the perinatal period. *Clin. Endocrinol. Metab.* 5:123–148, 1976.
    This extensive review (130 references) investigates the complex biochemistry of calcium metabolism.
14. Alon, U., and Chan, J. Hypocalcemia from deficiency of and resistance to parathyroid hormone. *Adv. Pediatr.* 32:439–468, 1985.
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15. Loughead, J., Mimouni, F., and Tsang, R. Serum ionized calcium concentrations in normal neonates. *Am. J. Dis. Child.* 142:516–518, 1988.
    Norms for ionized and total calcium concentrations are reported for cord blood and specimens obtained at 2 and 24 hours of age.
16. Colleti, R., et al. Detection of hypocalcemia in susceptible neonates: The Q-T_c interval. *N. Engl. J. Med.* 290:931–935, 1974.
    A highly sensitive and simple means of identifying hypocalcemia.

Drug Withdrawal: Reviews

17. American Academy of Pediatrics. Neonatal drug withdrawal. *Pediatrics* 101: 1079–1087, 1998.
    An exhaustive review of the many drugs which produce symptoms of withdrawal or intoxication in the newborn.
18. Lester, B. (ed.). Prenatal drug exposure and child outcome. *Clin. Perinatol.* 26(1), 1999; and Woods, J. (ed.). Substance abuse in pregnancy. *Obstetr. Gynecol. Clin. North Am.* 25(1), 1998.
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Drug Withdrawal: Follow-Up

19. Kandall, S., et al. Relationships of maternal substance abuse to subsequent sudden infant death syndrome in offspring. *J. Pediatr.* 123:120–126, 1993.
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    Of drug-exposed infants, 35% had central nervous system structural lesions; neurotransmitter function may also be affected—see Pediatrics *92:55–60, 1993.*
21. Lipshultz, S., Frassica, J., and Orav, E. Cardiovascular abnormalities in infants prenatally exposed to cocaine. *J. Pediatr.* 118:44–51, 1991.
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42. NEONATAL SEIZURES

Robert D. White

Seizures can be the most dramatic indication of neurologic abnormality in the newborn, yet most neonatal seizures are subtle or even silent. This broad spectrum of clinical presentation is mirrored in the many disease processes that lead to seizures and in the varied electroencephalographic (EEG) patterns found.

The most common forms of clinically apparent seizures in the newborn are the so-called subtle seizures—apnea, brief periods of reduced or absent motor activity associated with staring or eye deviation, or repetitive facial movements such as lip smacking, chewing, or eye blinking. Since these seizures involve brainstem and cranial nerve dysfunction, they indicate significant brain injury, even though the symptoms are much less dramatic than grand mal–type seizures, which are uncommon in newborns. Tonic (sudden stiffening) or clonic seizures (repetitive jerking movements) also occur in newborns and may be focal or generalized; often an infant can manifest more than one type of seizure or may have no clinical evidence of seizures at all, yet an EEG obtained because of other neurologic symptoms (e.g., extreme irritability or lethargy) will demonstrate epileptiform discharges.

Most seizures in full-term newborns are due to ischemic lesions occurring either intrapartum (hypoxic-ischemic encephalopathy) or prenatally (focal cerebral infarctions). In the former case, there is usually a history of fetal distress, followed by lethargy and metabolic acidosis immediately after birth, proceeding to jitteriness and seizures in the first day of life. Seizures may not occur until the second or third day of life with focal cerebral infarction; often there is no contributory history, but seizures and EEG abnormalities are characteristically focal, correlating with the site of the lesion.

A child whose seizures begin on the first day of life, with or without clinical features of asphyxia, should be evaluated for transient metabolic abnormalities (hypoglycemia, hypocalcemia, hypo- or hypernatremia), infection (bacterial, viral, or toxoplasmosis), central nervous system (CNS) malformations or hemorrhage, and familial seizure disorders (pyridoxine dependency and benign familial neonatal convulsions). In those whose seizures begin after the first day of life, one should also consider inborn errors of metabolism and drug withdrawal. Seizures in premature infants most commonly occur after the first day of life and are usually due to intracranial hemorrhage. Subarachnoid hemorrhage is uncommon in prematures, so ultrasound is suitable for diagnostic evaluation, but full-term infants should be studied by computed tomography or magnetic resonance imaging to better visualize the subarachnoid and subdural spaces and the cerebellum and brain stem.

Treatment of seizures in the newborn must usually be initiated concurrent with diagnostic testing. After ruling out hypoglycemia and ensuring that appropriate resuscitation equipment and intravenous access are available, a loading dose of phenobarbital should be given to interrupt an active seizure focus. Continued anticonvulsant therapy is usually accomplished with phenobarbital; phenytoin can be added if necessary to achieve complete cessation of seizures. Since most of the causes of neonatal seizures are self-limited, ongoing therapy is unnecessary for many infants, but the criteria for and timing of discontinuation of anticonvulsant treatment remain largely empiric and therefore controversial.

The prognosis of convulsions in a neonate is determined primarily by the cause of the seizure. Infants with seizures caused by asphyxia, intraventricular hemorrhage, meningitis, or CNS anomalies have less than a 25% chance for normal development, whereas those with subarachnoid hemorrhage, hypoglycemia, or hypocalcemia in the first 3 days of life have a 50% risk of brain damage. The interictal EEG also provides a valuable indication of the prognosis for full-term infants. In this group, a normal tracing is associated with an 80% chance of normal development, grossly abnormal recordings are associated with a 20% chance, and “borderline” or unifocal abnormalities are associated with a 50% likelihood of normal development.

Reviews

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2. Scher, M. Seizures in the newborn infant: Diagnosis, treatment and outcome. *Clin. Perinatol.* 24:735–772, 1997.
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3. Novotny, E. Neonatal seizures. *Semin. Perinatol.* 17:351–356, 1993.
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4. Watkins, A., et al. Significance of seizures in very low-birthweight infants. *Dev. Med. Child Neurol.* 30:162–169, 1988.
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Specific Etiologies

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   This rare condition is lethal if untreated. Rapid alternation between lethargy and irritability and “lightninglike” spasms in a newborn suggest the diagnosis. (See also Arch. Dis. Child. *58:415–418, 1983.)*
6. Leppert, M., et al. Benign familial neonatal convulsions linked to genetic markers on chromosome 20. *Nature* 337:647–648, 1989.
   This autosomal dominant disorder can “skip” generations due to incomplete penetrance, emphasizing again the need for a careful history before embarking on extensive diagnostic testing.
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   More often associated with cerebral ischemic lesions sustained in utero than with withdrawal per se; 50% had persistence of seizures beyond the neonatal period. For a review of seizures due to maternal heroin and methadone use, see J. Pediatr. *91:638–641, 1977.*

Electroencephalography

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9. Connell, J., et al. Continuous EEG monitoring of neonatal seizures: Diagnostic and prognostic considerations. *Arch. Dis. Child.* 64:452–458, 1989.
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Management

10. Hall, R., Hall, F., and Daily, D. High-dose phenobarbital therapy in term newborn infants with severe perinatal asphyxia: A randomized, prospective study with three-year follow-up. *J. Pediatr.* 132:345–348, 1999.
    Higher doses of phenobarbital (40 mg/kg) given early in the course (even before seizures occurred, in this study) appear to improve outcome.
11. Connell, J., et al. Clinical and EEG response to anticonvulsants in neonatal seizures. *Arch. Dis. Child.* 64:459–464, 1989.
    The authors found that good clinical response to anticonvulsants was poorly predictive of EEG response and appeared to improve the prognosis minimally, especially in seizures secondary to ischemic or hemorrhagic lesions.
12. Hellstrom-Westas, L., et al. Low risk of seizure recurrence after early withdrawal of antiepileptic treatment in the neonatal period. *Arch. Dis. Child.* (Fetal Neonatal edition) 72:F97–F101, 1995.
    Median duration of therapy in this series was 5 days, with only an 8% incidence of recurrence.
13. Pruitt, A., et al. Behavioral and cognitive effects of anticonvulsant therapy. *Pediatrics* 76:644–647, 1985.
    Anticonvulsants frequently affect cognitive abilities in children already at risk for difficulties in this area. This article, along with Adv. Pediatr. *33:159–180, 1986, points out factors physicians should be aware of when counseling parents and teachers.*

43. HYPERBILIRUBINEMIA

Robert D. White

Jaundice is a common occurrence in the newborn nursery; about 10% of full-term and over 50% of premature infants become clinically jaundiced during the first week of life. Some of these infants require intervention to prevent more severe jaundice, since high levels of unconjugated bilirubin may exceed the binding capacity of albumin, permitting bilirubin staining of the basal ganglia (kernicterus), which can result in cerebral palsy or death. A mild and transient elevation of serum bilirubin, on the other hand, is benign and occurs in virtually every newborn. Bilirubin is a normal product of catabolism, primarily of hemoglobin, but with a contribution from other body proteins (collectively termed shunt bilirubin). In its unconjugated form (indirect bilirubin), it is fat soluble and carried in the bloodstream bound to albumin. Unconjugated bilirubin is removed from the circulation by the liver, where conjugation into a water-soluble diglucuronide occurs. Hepatic conjugation involves at least three phases: (1) uptake by the hepatocyte, requiring the so-called Y and Z carrier proteins; (2) conjugation, which requires an enzyme (glucuronosyltransferase), a glucuronic acid donor, and an energy source; and (3) excretion into the bile. Conjugated (direct) bilirubin is then carried with the bile to the intestine, where it is excreted from the body, except for a variable portion that is deconjugated by b-glucuronidase in the intestinal mucosa and then reabsorbed (the latter process is referred to as the enterohepatic recirculation of bilirubin).

In the first days of life, a mild degree of jaundice (physiologic jaundice) develops in most infants, probably related to several factors: increased hemolysis from trauma inherent in the birth process; immature uptake, or conjugation in the liver, or both; and enterohepatic recirculation. Unconjugated bilirubin levels usually reach a peak between 2 and 12 mg/dL at 2–3 days of age in healthy full-term infants; this peak is higher and occurs later in the first week of life with increasing degrees of prematurity. The conditions that exaggerate this normal jaundice and predispose an infant to kernicterus constitute an extensive list, involving every step in the metabolic pathway of bilirubin.

The first group of diseases that cause significant hyperbilirubinemia includes those associated with increased red cell hemolysis. Sepsis, polycythemia, and bleeding into an enclosed space (bruising, cephalhematoma, or intracranial hemorrhage) cause hemolysis of normal red cells; congenital red cell abnormalities (congenital spherocytosis, glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, and others) may also increase hemolysis and bilirubin production. Isoimmune hemolytic disorders, were, until recent years, the most common cause of severe jaundice; these have in common the formation and placental transfer of maternal antibodies against specific antigens on the fetal red cell, causing a Coombs-positive hemolytic anemia in the affected infant. Rh isoimmunization, once the major cause of kernicterus, has been virtually eradicated in the 1990s; ABO incompatibilities are now the most common isoimmune disorders requiring treatment for jaundice, although even for these children, late anemia caused by ongoing low-grade hemolysis is often of greater significance than jaundice.

Hyperbilirubinemia can also be caused by impaired hepatic metabolism of bilirubin. Uptake of unconjugated bilirubin by the liver may be decreased by persistent patency of the ductus venosus (caused by hypoxemia or other stress), thus allowing blood to be shunted past the liver, or it may be hindered by organic anions that compete with bilirubin for uptake by the carrier proteins. Conjugation is reduced if the hepatocytes are deficient in glucuronosyltransferase or if they lack an energy source, as in hypoxemia or hypoglycemia. Hepatitis or inhibition of conjugation by factors present in maternal serum or breast milk may also be responsible for reduced clearance of bilirubin from the circulation. Delayed excretion of bilirubin is rarely a problem in the first week of life except with sepsis or hepatitis.

Finally, elevated levels of unconjugated bilirubin may be caused by increased enterohepatic recirculation of bilirubin. Any condition that delays bowel motility and passage of stool (intestinal obstruction, meconium ileus, delayed feedings, hypothyroidism) will allow large amounts of bilirubin to be deconjugated and reabsorbed.

A separate group of disorders causes kernicterus by interfering with the ability of albumin to bind bilirubin. These diseases require particular attention because damage can occur at moderate bilirubin levels that are usually considered safe. Severe acidosis affects albumin binding directly, while many chemicals compete with bilirubin for binding sites on the albumin molecule. Agents responsible for displacement of bilirubin from albumin include drugs (sulfonamides, aspirin, and others), hematin (produced during red cell hemolysis), and free fatty acids, which are found during periods of stress or inadequate caloric intake. Premature infants have an additional disadvantage, in that their normal albumin level may be 1–2 g/dL less than that of full-term infants. Conditions that affect the permeability of the blood-brain barrier to albumin and bilirubin may also be important in producing kernicterus at serum bilirubin levels usually considered safe; however, studies to document this theory are difficult to perform in humans.

In full-term newborns, bilirubin levels less than 20 mg/dL are considered safe, except in infants whose bilirubin-binding capacity is compromised by hypoproteinemia, acidosis, hemolysis, starvation, sepsis, or hypoxia. Jaundice is clinically apparent at much lower levels in white infants, but careful observation is necessary to detect jaundice in black or oriental infants. Premature infants may be at risk at a serum bilirubin concentration of 15 mg/dL or less, because of their lower serum albumin levels; however, they are also frequently hypoxic, acidotic, or otherwise distressed, placing them at risk for kernicterus at even lower bilirubin levels.

Treatment of hyperbilirubinemia is not yet standardized. Most cases of moderate jaundice will resolve with general supportive measures to ensure adequate fluid and caloric intake and bowel function. Severe jaundice, particularly in the presence of a hemolytic process, may require exchange transfusion; this process removes approximately 80% of the fetal red cells and 50% of the serum bilirubin. Phototherapy has been proved effective in reducing the serum bilirubin level and in reducing the necessity for exchange transfusion. Some doubt remains about its safety, since it utilizes an intense form of energy with largely unknown biologic effects. At present, phototherapy is clearly indicated only when there is a significant risk that hyperbilirubinemia will become severe enough to require an exchange transfusion if untreated; it cannot be used as a substitute for the initial exchange in erythroblastosis, whose primary purpose is to remove sensitized red cells and to correct anemia. Jaundice of sufficient degree to require phototherapy must be evaluated to determine the cause of the hyperbilirubinemia, since the jaundice of infection, hemorrhage, hemolysis, or metabolic disorders may respond to phototherapy initially, causing a dangerous delay in reaching the primary diagnosis. Infants receiving phototherapy should be protected from the direct adverse effects of light by shielding their eyes, and from the many indirect effects (e.g., hyperthermia, dehydration) as well.

Reviews

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4. Bifano, E., and Ehrenkranz, R. (eds.). Perinatal hematology. *Clin. Perinatol.* 22(3), 1995.
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Etiologic Factors: Erythroblastosis

5. Duerbeck, N., and Seeds, J. Rhesus immunization in pregnancy: A review. *Obstetr. Gynecol. Surv.* 48:801–810, 1993.
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6. Weinstein, L. Irregular antibodies causing hemolytic disease of the newborn. *Obstet. Gynecol. Surv.* 31:581–591, 1976.
   Isoimmunization by antigens other than Rh(D).

Etiologic Factors: Other

7. Gartner, L., and Lee, K. Jaundice in the breastfed infant. *Clin. Perinatol.* 26: 431–446, 1999.
   This article draws a distinction between breast-feeding jaundice in the first week of life and breast milk jaundice, which has a different mechanism.

8. Monaghan, G., et al. Gilbert's syndrome is a contributory factor in prolonged unconjugated hyperbilirubinemia of the newborn. *J. Pediatr.* 134:441–446, 1999.
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9. Kaplan, M., and Hammerman, C. Severe neonatal hyperbilirubinemia: A potential complication of glucose-6-phosphate dehydrogenase deficiency. *Clin. Perinatol.* 25:575–590, 1998.
Glucose-6-phosphate dehydrogenase deficiency, like Gilbert syndrome, tends to be a benign finding, but when the two coexist, severe disease can result.

Management

10. American Academy of Pediatrics Provisional Committee for Quality Improvement Subcommittee on Hyperbilirubinemia. Practice parameter: Management of hyperbilirubinemia in the healthy term newborn. *Pediatrics* 94:558–565, 1994.
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11. Johnson, L., and Bhutani, V. Guidelines for management of the jaundiced term and near-term infant. *Clin. Perinatol.* 25:555–574, 1998.
This overview of management includes a unique description of risk based on the bilirubin level at any given hour of age, which is most useful in an era of early discharge.
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44. NUTRITION IN THE ILL NEONATE

Robert D. White

The unique metabolic requirements for maintenance and growth of sick infants often create a need for special formulas or feeding techniques. Premature infants are the major group of infants requiring specialized nutritional therapy; their management will be the focus of most of this chapter, with some attention also given to infants with congenital heart disease.

The nutritional needs of prematures are not yet fully defined, largely because of a debate concerning the yardstick by which to measure optimal growth. Many experts believe prematures should be fed so that they continue to grow at intrauterine rates (20–40 g/d), while others point out that this approach has not been proved superior to the more easily attained rate of 10–30 g/d. In spite of this unresolved issue, most agree that for the “normal” growth of healthy prematures, 120–130 cal/kg/d are usually needed; sepsis, respiratory or heart disease, and heat or cold stress may elevate energy demands to as much as 150 cal/kg/d.

The protein need of premature infants is dependent in part on the food source. Human milk has only about 1.8 g protein per deciliter but is highly digestible; recent studies indicate that 1.7–2.0 g/kg/d of human milk protein is adequate for growth in most healthy prematures. Premature infant milk formulas have 2.0–2.4 g protein per deciliter, but the concentrations of cystine and taurine are lower than those of human milk, and 2.5–3.0 g/kg/d of formula protein is needed for optimal growth of premature infants. Higher protein intakes, especially those in excess of 6 g/kg/d, are associated with hyperammonemia, metabolic acidosis, and neurologic damage.

Premature infants do not appear to differ from full-term infants in their need for fat and carbohydrate, except in relation to total caloric requirements. Fat should ideally constitute approximately 40–50% of the caloric intake, with at least 2% of this as linoleic acid. Absorption of fat is somewhat impaired in prematures due to immature bile acid synthesis, but this difficulty can be partially circumvented by the use of medium-chain triglycerides, which are absorbed directly by the intestinal mucosa. Absorption is sometimes a factor in the choice of carbohydrate as well, since many premature are lactase deficient until the second week of life or later, resulting in a higher incidence of diarrhea and metabolic acidosis. Lactose appears to have a salutary effect on calcium absorption and the bacterial flora of the intestine, however, and for this reason it should probably be replaced in the diet only if diarrhea is a problem and then only temporarily until intestinal lactase production matures.

Current formulas designed for premature infants and based on cow milk contain higher concentrations of sodium, calcium, and phosphorus than formulas designed for full-term infants, and breast milk supplements are available that provide these same minerals (as well as protein and vitamins) for prematures. Vitamins contained in these formulas or breast milk supplements for premature infants are usually sufficient for their needs, though some experts recommend additional supplementation of vitamins D, E, or both, and, after the first month of life, iron.

From the preceding discussion, it is apparent that a healthy premature infant fed 150–180 mL/kg/d of supplemented human milk or premature formula receives an adequate quantity of calories, protein, fat, carbohydrate, minerals, and vitamins. This goal is not always easily met, however. Illness may elevate the caloric requirement at the same time that fluid intake must be restricted. The suck and swallow reflexes are immature in prematures, gastric emptying is often slow, and gastric distention is poorly tolerated, especially in infants with respiratory disease. These factors often combine to make adequate intake of calories and nutrients impossible without the use of special formulas, special feeding techniques, or both.

The provision of adequate caloric intake when fluid consumption must be limited may be accomplished by adding a calorie-rich, easily absorbed substance to the feedings (such as medium-chain triglycerides or starch) or by using a more concentrated formula (which provides more calories per unit volume, but also more protein, minerals, and vitamins). Each approach has disadvantages. Medium-chain triglycerides in large quantities can produce diarrhea and may exceed the recommended proportion of calories provided as fat, resulting in sufficient calories but inadequate protein for proper growth. Concentrated formulas have high osmolalities, which may contribute to the development of necrotizing enterocolitis; they also create a high renal solute load. In moderation, however, both approaches have proved useful for large numbers of prematures.

Nipple feedings are often taken poorly by small or ill prematures. Alternatives include feeding by gavage tube, intravenous solution, or both. Gavage feedings, which are usually given into the stomach, permit frequent small feedings (or continuous, if desired) without requiring the infant to expend energy by sucking. An additional advantage is that regurgitation of gastric contents can usually be avoided by leaving the gavage tube in place and open to the air. Occasionally, even gavage feedings are poorly tolerated; in these infants, feedings may often be successfully given through a Silastic tube passed into the duodenum or jejunum.

Parenteral alimentation may be a valuable adjunct to oral feedings, or it may be used as the total food source for weeks or months when oral feedings are impossible, as in infants with catastrophic intestinal disease. Water-soluble preparations of amino acids, carbohydrate, minerals, and vitamins are available, as is a lipid-containing emulsion of vegetable oil; these can be administered by intravenous infusion in amounts necessary to meet the infant's needs for maintenance and growth. Complications are common; most are mild biochemical abnormalities, but serious problems, such as sepsis, liver disease, and rickets, also occur.

Infants with congestive heart failure pose special feeding problems, some of which have been alluded to previously. Tachypnea and tachycardia, cardinal signs of heart failure, cause increased metabolic demands; at the same time, fluid and sodium tolerance are often markedly diminished. Tachypnea also interferes with nipple feedings, resulting in the dilemma of a child with very high energy requirements who can take only limited amounts. Low-sodium formulas that are commercially available can be prepared in concentrated form and supplemented by medium-chain triglycerides to meet these special needs. Occasionally, infants with congestive heart failure also have severe, persistent vomiting induced by digitalis or by heart failure itself and can only be given adequate calories and protein by intravenous alimentation.

Nutrition of ill infants further requires that supportive measures to minimize energy demands be fully utilized. Cold and heat stress should be avoided and underlying diseases treated aggressively. Gavage feedings or oxygen supplementation during feedings may be indicated to diminish the energy expenditure of infants who are sucking poorly. Complications associated with feeding must also be monitored, especially reflux, diarrhea, acidosis, hyponatremia or hypernatremia, and hypocalcemia. The ultimate success of a feeding regimen is measured primarily by weight gain and increases in body length and head circumference; the latter two measures are probably the most useful because they more nearly reflect lean body mass than does weight gain.

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45. NECROTIZING ENTEROCOLITIS

Robert D. White

Necrotizing enterocolitis (NEC) is the most common serious intestinal problem in the neonate. It occurs in approximately 7% of prematures less than 1,500 g and in a much smaller proportion of full-term babies. In a minority of affected infants, necrosis progresses to perforation of the intestine, necessitating emergency surgery; mortality in this group is 20–30%.

The cause of NEC is unclear. The disorder is associated with a large number of conditions and interventions, and has a fluctuating incidence. One hypothesis to account for these observations is that there are two distinct events in the pathogenesis of NEC: The first is hypoxic injury to the intestine; the second is bacterial invasion of the necrotic bowel wall. Considering hypoxic injury a predisposing factor explains why apparently diverse conditions are associated with NEC: They share the complication of reduced oxygen supply to the gastrointestinal tract. Included among these conditions are disorders that cause generalized hypoxemia (e.g., intrauterine asphyxia, respiratory distress syndrome, prolonged apnea), hypoperfusion of the descending aorta (e.g., patent ductus arteriosus, coarctation of the aorta), obstruction or thrombosis of the mesenteric arteries (e.g., umbilical artery catheter), hyperviscosity (e.g., polycythemia), and venous congestion of the portal system causing reduced intestinal capillary perfusion (e.g., exchange transfusion into the portal system). The postulate that bacterial invasion is another common component explains the episodic nature and the sepsislike early symptoms of NEC. Commercial formulas may play a permissive role in the latter event, perhaps by supporting bacterial multiplication; NEC is less common in infants who have not been fed, or in those fed fresh human milk, which contains numerous bacteriostatic factors.

The early signs of NEC are often nonspecific. Apnea, lethargy, poor feeding, lactose malabsorption, and thrombocytopenia all may suggest an infectious disorder. Ileus, abdominal distention, bilious vomiting, erythema of the abdominal wall, and bloody stools are later, more specific signs of NEC, but are highly variable from one case to another. One or more of the latter signs indicate the need for an abdominal radiograph; gas in the bowel wall (pneumatosis intestinalis) or in the portal vein is highly suggestive of NEC, and free air in the abdominal cavity is evidence of perforation of the bowel.

Several regimens have been proposed for medical treatment of NEC in infants whose intestine is not perforated. Most protocols include systemic antibiotics, continuous nasogastric drainage, and frequent monitoring of the physical examination and abdominal radiographs to detect progression of the disease or the development of complications. With aggressive medical treatment of NEC, most cases resolve without perforation. Oral feedings can be restarted several days after symptoms, thrombocytopenia, and radiographic abnormalities have resolved, but relapses can occur, and some infants require prolonged periods of intravenous alimentation before oral feedings are tolerated.

The complications of NEC are perforation of the bowel, generalized sepsis, disseminated intravascular coagulation, and intestinal strictures. Perforation is an indication for surgery; persistent dilatation of an individual loop of bowel may also indicate the presence of nonviable intestine. At surgery, necrotic sections of bowel are removed and the proximal intestinal end usually is brought to the skin as an ostomy. These infants then require parenteral alimentation, and their course is often complicated and prolonged. In most cases, continuity of the intestine can be reestablished by a second operation prior to discharge. Contrast x-ray studies of the bowel may reveal strictures even in infants successfully managed without surgical intervention. A better understanding of NEC is essential for eventual prevention of this disease. Its sporadic nature and the lack of good criteria for early diagnosis have hampered efforts to establish a firm scientific understanding through controlled trials. In the absence of definitive studies, good neonatal care and a high index of suspicion remain the most important means of reducing the mortality and morbidity of this disease.

Reviews

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14. Dorney, S., et al. Improved survival in very short small bowel of infancy with use of long-term parenteral nutrition. *J. Pediatr.* 107:521–525, 1985.
    Improvements in parenteral nutrition have reduced complications, thus permitting more growth of the small bowel and increasing the chances that enteral feedings can finally be established.
15. Vennarecci, G., et al. Intestinal transplantation for short gut syndrome attributable to necrotizing enterocolitis. *Pediatrics* 105:e25, 2000. (Available at www.Pediatrics.org/cgi/content/fall/105/2/e25.)
    The last best hope for those few infants for whom prevention and treatment have failed—usually in combination with liver transplant.

46. SURGICAL EMERGENCIES

Robert D. White

Life-threatening congenital anomalies occur in more than 1% of newborns. Some are extremely complex and incompatible with life, but most are localized to a specific organ system and are surgically remediable. The most common surgical emergencies in the newborn involve the gastrointestinal tract.

Five anatomic variants of *esophageal atresia with tracheoesophageal fistula* exist, but by far the most common (87%) is atresia of the proximal esophagus, with a fistula between the trachea and distal esophagus. This anomaly probably occurs during septation of the trachea and esophagus, which begin embryologically as a single structure. Polyhydramnios and low birth weight commonly accompany esophageal atresia, and there is a high incidence of associated anomalies, including vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia, and cardiac defects (the VATER association). Excessive salivation, regurgitation of feedings with consequent aspiration pneumonia, and gaseous distention of the stomach generally appear in the first day of life. The diagnosis can be established by failure of a nasogastric tube to reach the stomach; a radiograph confirms that the tip of the catheter is in a distended proximal esophageal pouch. The catheter should be connected to suction to remove secretions, and feedings should be discontinued. Until the tracheoesophageal fistula is repaired, the infant should be kept in a semi-upright position, and respiratory assistance, if needed, should be delivered with minimal pressure.

Immediate operative intervention usually consists of gastrostomy and division of the fistula. In some infants, anastomosis of the proximal and distal esophagus is also possible in the first days of life, but in most, the definitive procedure must be delayed for weeks or months. Postoperatively, skilled, constant nursing attention is required; with such care, a survival rate of better than 90% can be anticipated.

Duodenal obstruction is most frequently due to atresia, and less commonly to stenosis, webs, or extrinsic compression by an annular pancreas or peritoneal bands. Low birth weight, Down syndrome, and cardiac defects are frequently associated problems. The characteristic clinical manifestation is bilious vomiting on the first day of life; the diagnosis is supported by the radiographic appearance of the “double bubble” caused by the gas-filled, distended stomach and proximal duodenum. If obstruction or atresia of the duodenum is complete, no air is present in the intestine distal to the double bubble.

Dehydration and electrolyte imbalance secondary to persistent emesis are frequently present at the time of diagnosis and should be corrected prior to operation. Other metabolic problems are common, especially in the premature infant; hyperbilirubinemia is particularly difficult to control, since bile cannot be excreted normally. The operation for duodenal obstruction is usually straightforward; the prognosis depends largely on the presence of associated anomalies.

Jejunoileal atresia probably occurs as the result of a mesenteric vascular accident in utero. Atresia may occur at any point in the small bowel; multiple atresias are not uncommon, but associated nonintestinal anomalies are rare. Bilious vomiting, abdominal distention, and delay or failure in passing meconium are present in most patients. Radiographically, distended loops of small bowel with air-fluid levels are characteristic but not pathognomonic; a barium enema is performed to rule out associated colonic obstruction distal to the atretic area.

Initial supportive management is decompression of the stomach and intravenous replacement of fluid and electrolyte losses from vomiting. Following operative repair, parenteral alimentation is often necessary for prolonged periods until small-bowel function has been restored.

Imperforate anus ranges from a thin membrane obstructing the anus to complete anorectal atresia. For ease of discussion, this spectrum is usually divided into “low” and “high” obstructions: In low obstructions, the colon and rectum are patent distal to the levator sling, whereas in high obstructions, the bowel ends above the sling. In low obstructions other than those caused by a thin membrane, the anus is anteriorly displaced, connected to the rectum by fistula. In high obstructions, a fistula is usually present from the rectum into the lower urinary tract or vagina. The location of the obstruction and the fistula can be determined radiographically. The estimated frequency of associated anomalies (the VATER association previously mentioned) ranges from 25% to 75% of cases.

Low obstructions can usually be corrected primarily; in high obstructions, a colostomy is usually performed initially and definitive repair is delayed until late in the first year of life. Associated anomalies, particularly cardiac and renal anomalies, are responsible for most of the deaths of infants with imperforate anus; the survival rate exceeds 90% in those without associated life-threatening malformations. The most notable morbidity of this anomaly is permanent incontinence; this complication occurs in less than 5% of infants with low obstructions, but it occurs in 25–50% of those with high obstructions.

In *omphalocele and gastroschisis*, the intestines protrude through the abdominal wall. An omphalocele is a protrusion of the bowel through the umbilicus; this has been attributed to an arrest of development in utero when the intestines are still in the yolk sac, outside the abdomen. The bowel in most omphaloceles is covered by a sac of peritoneum, although in some infants the sac ruptures prior to birth. Gastroschisis is herniation of the bowel through a defect in the abdominal musculature next to the umbilicus; there is no covering membrane. A feature helpful in differentiating omphalocele from gastroschisis, besides the presence of a covering membrane, is the point of insertion of the umbilical cord. In omphalocele, the cord inserts into the sac containing the bowel, whereas in gastroschisis, it inserts normally into the abdominal wall. Associated malformations are frequent in omphalocele, particularly intestinal malrotation; renal and cardiac anomalies and low birth weight also may be features.

Initial management is crucial. The exposed intestine must be kept clean, moist, and untraumatized to prevent infection and necrosis. Sterile “bowel bags” are ideal for this purpose. A nasogastric tube is placed to prevent vomiting and aspiration pneumonia. Primary repair of the defect is possible in many patients; in the remainder, the bowel is enclosed in a plastic sheath and gradually returned to the abdominal cavity over a 1- to 2-week period (or longer). Parenteral nutrition is required during this time and usually for several weeks thereafter; infants with gastroschisis and “ruptured” omphalocele are particularly likely to need prolonged therapy, due to thickening and inflammation of the bowel caused by exposure to amniotic fluid in utero.

Malrotation of the bowel may be unsuspected in a healthy neonate for days or weeks, and then cause acute bilious vomiting and abdominal distention. The abnormal position of the intestines is not dangerous per se (many people with malrotation never become symptomatic), but the bowel is poorly fixed to a narrow vascular pedicle, permitting it to twist (volvulus), occluding the superior mesenteric artery and producing extensive bowel necrosis. Volvulus is a true surgical emergency, since the viability of large portions of the bowel is dependent on the prompt return of the blood supply; bloody stools are particularly ominous. Plain x-ray films of the abdomen will often suggest the diagnosis by demonstrating an anomalous position of the cecum, but a barium study is usually necessary for confirmation. Repair consists of mobilization and repositioning of the bowel; if frankly necrotic intestine is present, it must be removed and the proximal end of viable intestine exteriorized as an ostomy, although in some cases an end-to-end anastomosis is possible.

Hirschsprung disease (congenital aganglionic megacolon) produces a spectrum of disability, ranging from acute obstruction in the neonate to chronic constipation in older infants and children. It is caused by an absence of parasympathetic innervation of the internal anal sphincter and varying portions of the colon and terminal ileum. Peristalsis does not occur in the aganglionic segment, which is spastic and contracted, impairing fecal passage. In infants, obstruction and distention often alternate with bouts of diarrhea and periods when the abdominal findings are normal, but virtually all neonates with this anomaly fail to pass meconium in the first 24 hours of life. Diagnostic evaluation consists initially of a barium enema, followed in some centers by anorectal manometrics, electromyographic study, or both; confirmation of Hirschsprung disease requires histologic demonstration that ganglion cells are absent.

In ill newborns, initial surgery is colostomy; unnecessary delay in undertaking this procedure puts the infant at risk for toxic megacolon, a highly dangerous condition. Later, the aganglionic segment of colon may be removed and a more definitive procedure performed (Soave, Swenson, Duhamel). Myectomy, with incision of the internal anal sphincter, may be all that is required in children with involvement limited to a short segment of colon, but colostomy is preferred for severely affected

neonates. Some patients experience significant complications from surgery, including abscess formation, stricture, and damage to the pelvic nerves. However, provided toxic megacolon does not occur, the survival rate is very high (95% or better).

Of infants born with cystic fibrosis, 10–20% have intestinal obstruction due to their extremely thick, almost solid meconium (meconium ileus). This is their first manifestation of abnormal exocrine gland function, and it may be life-threatening if perforation occurs, causing an intense chemical peritonitis. The triad of abdominal distention, bilious vomiting, and failure to pass meconium is common but does not permit distinction from other causes of intestinal obstruction. Radiographic studies are more helpful; intraperitoneal calcifications suggest the diagnosis. The surgical approach to these patients depends on the extent of obstruction and whether an associated perforation, volvulus, or atresia is present. The postoperative course is often difficult because of the predisposition to pneumonia.

Diaphragmatic hernia results from a failure of complete formation of the diaphragm early in fetal life. The defect is usually unilateral and involves the left side in 75% of cases. The presence of abdominal contents in the thorax throughout most of gestation does not permit normal development of the ipsilateral lung and thus is an important cause of respiratory distress following birth.

Successful management of infants with diaphragmatic hernia requires prompt diagnosis and intensive management of respiratory problems. A chest radiograph in the neonate with respiratory distress will establish the diagnosis. Physical findings of a scaphoid abdomen, bowel sounds in the left side of the chest, and prominent heart sounds in the right side of the chest are suggestive, and a chest radiograph will establish the diagnosis. Hypoxia, hypercapnia, and acidosis are generally present, and respiratory assistance is often of only moderate benefit. Severe hypoplasia of a lung may increase pulmonary vascular resistance, promoting extensive right-to-left shunting of blood through the ductus arteriosus and foramen ovale. Prior to operation or transport to a neonatal center, it is important that a nasogastric tube be placed for decompression to minimize respiratory compromise, and acidosis should be vigorously corrected. Intubation is also indicated in any infant with respiratory symptoms, however mild.

Operative repair consists of removing the bowel from the thorax, closing the hernia, and correcting malrotation, if present. Immediately after operation, most patients experience significant improvement in their respiratory status, but deterioration over the next 24 hours often occurs, especially in infants who had severe cyanosis and distress in the first hours of life. In these infants, attempts to reduce pulmonary vascular resistance pharmacologically have been made, with some success. Patients asymptomatic in the first day of life do well following operation, whereas survival in those with distress of earlier onset is only slightly better than 50%. Most of this mortality is due to severe pulmonary hypoplasia, but some deaths may be prevented by implementation of new techniques, such as extracorporeal membrane oxygenation (ECMO), high-frequency ventilation, and nitric oxide inhalation.

Choanal atresia is the persistence of a fetal membrane between the anterior and posterior choanae that results in obstruction of one or both nares. The obstruction may remain membranous but is usually bony (in 85–90%); bilateral atresia is slightly more common than unilateral atresia, and it virtually always causes severe respiratory distress within minutes of birth. Two thirds of affected neonates are female.

Since newborns are obligate nose breathers, bilateral choanal atresia produces cyanosis and severe retractions as the infant attempts to inspire. Not until the mouth is opened to cry can air exchange occur, resulting in a dramatic and characteristic syndrome of intermittent cyanosis relieved by crying. Infants who survive the neonatal period without treatment usually learn to breathe through the mouth, becoming symptomatic only when attempting to nurse. The diagnosis is easily established when a catheter cannot be passed into the pharynx through either nares. Immediate treatment consists of placement of an oropharyngeal airway; feedings are given through an orogastric tube. A palliative operation may then be performed electively, although definitive correction is not usually undertaken until after 6 months of age.

Reviews

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2. Kays, D. Surgical conditions of the neonatal intestinal tract. *Clin. Perinatol.* 23:353–376, 1996.
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3. Filston, H. What's new in pediatric surgery? *Pediatrics* 96:748–757, 1995.
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13. Sherman, J., et al. A 40-year multi-national retrospective study of 880 Swenson procedures. *J. Pediatr. Surg.* 24:833–838, 1989.
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47. CONGENITAL INFECTIONS

Robert D. White

Chronic fetal and neonatal infections by nonbacterial agents compose a clinical spectrum of disease known as the TORCHeS syndrome. The acronym is derived from the most common organisms responsible for this entity: toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis. The incidence of disease caused by this group of agents is uncertain and changing. In the last 2 decades, for example, the incidence of rubella has been reduced by large-scale immunization, but herpes simplex type 2 has become more common, and appreciation of the usually subtle nature of cytomegalovirus infection has altered earlier beliefs that it was relatively uncommon. At present, it is likely that fetal or neonatal infection with one of these organisms occurs in about 1% of all births, with serious disease in perhaps 10% of infected infants.

The classic syndrome of fetal infection by one of the TORCHeS agents was initially characterized as prematurity, intrauterine growth retardation, microcephaly, hepatosplenomegaly with jaundice, thrombocytopenia, hemolytic anemia, chorioretinitis, adenopathy, and rash; the diagnosis was supported by elevated immunoglobulin M (IgM) levels in the neonate and by persistently high antibody titers to the offending organism during early infancy. This generalized picture of congenital infection has been expanded by the recent recognition of specific syndromes, improved diagnostic tests, and a better understanding of the natural history and prognosis of disease caused by each organism.

Toxoplasma is a protozoal parasite common in domestic animals such as cats, swine, and sheep. In the United States, infection is probably most frequently transmitted by oocysts in cat feces. Acute infection is usually unrecognized; symptoms, if present, include a nonspecific lymphadenopathy, malaise, and fever. Antibodies to this organism are present in 20–40% of the adult population in the United States.

Infection occurring in a pregnant woman is transmitted to the fetus in approximately 40% of cases. The severity of fetal disease depends strongly on the time during gestation at which the mother acquires toxoplasmosis; acquisition in the first two trimesters may cause stillbirth, severe neurologic damage, or subclinical disease; infection in the last trimester is usually associated with subclinical symptoms. Overall, only one third of infected infants have clinically apparent disease at birth, and in 40% of these, evidence of involvement is limited to the frequently overlooked but characteristic chorioretinitis. The rest of the affected infants generally have central nervous system (CNS) involvement (hydrocephalus, microcephaly, or intracranial calcifications) in addition to chorioretinitis, while only a few exhibit the classic syndrome of hepatosplenomegaly, lymphadenopathy, and anemia. Some infants with infection that is not apparent at birth may become symptomatic weeks or months later, but most remain apparently normal.

The diagnosis of congenital toxoplasmosis should be suspected in any infant with chorioretinitis or intracranial calcifications, as well as in those with nonspecific symptoms of congenital infection. Persistently elevated antibody titers establish the diagnosis. Sulfadiazine, pyrimethamine, and leucovorin may be useful in controlling toxoplasma infection. The outlook for symptomatic infants is poor. Mental retardation and convulsions occur in most, and cerebral palsy, blindness, deafness, and hydrocephalus are also common; less than half are normal. The prognosis of infants with subclinical disease is less certain; most appear to be normal, but vision and hearing defects, learning disabilities, and epilepsy occur in some.

Rubella is an RNA virus that usually causes mild or inapparent disease in children, but may be devastating to the fetus. Primary infection of susceptible pregnant women results in viremia that persists for 2–3 weeks until maternal antibodies reach appreciable levels. During this time, which is prior to the onset of symptoms in the mother, placental and fetal invasion may occur. Maternal infection during the first 8 weeks of gestation is transmitted to the fetus in more than 50% of cases, whereas infection beginning in the second or third trimester is transmitted to the fetus less frequently.

Fetal infection during the first trimester may cause stillbirth or, more commonly, a constellation of findings that includes growth retardation, cataracts, a characteristic “salt-and-pepper” retinitis, and peripheral pulmonary artery stenosis. The nonspecific signs of adenopathy, hepatosplenomegaly, and thrombocytopenia are also frequent; patent ductus arteriosus, myocardial necrosis, bony radiolucencies, and a “blueberry-muffin” appearance of the skin caused by intradermal erythropoiesis are all less common, but highly suggestive of rubella. Infection later in gestation may cause prematurity or result in mild or no disease in the fetus.

The diagnosis of rubella should be considered in the presence of one or more of the characteristic clinical signs. Antibody titers to rubella in affected infants are persistently elevated, but more immediate evidence is usually available in the form of isolation of virus from the nasopharynx, or occasionally from conjunctival secretions, urine, or feces.

Signs of congenital rubella may also appear after the neonatal period. Pneumonitis, encephalitis, and hypogammaglobulinemia may be progressive during infancy, while sensorineural hearing loss (the single most common manifestation of congenital rubella), dental, renal, and urinary defects, and diabetes are often not appreciated until later in childhood. Mental retardation of mild-to-moderate severity is present in 10–20% of affected patients; learning disabilities or cerebral palsy may also occur.

Although relatively little can be accomplished therapeutically at present in the management of an infant with congenital rubella, eradication of this disease is now conceivable with the introduction of mass immunization; no major epidemics have occurred in the United States since 1964–1965. It is not yet clear, however, whether the immunity conferred by the administration of attenuated viral vaccine to young children will persist through the child-bearing age 20–40 years hence.

Cytomegalovirus belongs to the herpesvirus family of organisms. Transmission to the fetus is usually by contact with infected maternal secretions; 5–10% of pregnant women excrete virus in the urine or cervical secretions. The mother is usually asymptomatic and may harbor the virus for years, even in the presence of “adequate” antibody titers; consequently, it is possible for a woman to infect her offspring in several pregnancies.

Screening programs have demonstrated cytomegalovirus in the urine of 0.5–1.0% of newborns, making it the most common of all perinatal infections. Chronic intrauterine infection classically produces cerebral calcifications (distinguished from those of toxoplasmosis by their periventricular location) and microcephaly, although the nonspecific sign of hepatosplenomegaly is actually more common. Intrauterine transmission of virus appears to be the exception with this organism, however; most infants are infected at the time of birth and are asymptomatic. Infants who have “silent” infection at birth later exhibit sensorineural hearing loss, learning difficulties, or mental retardation in 10% of cases or more.

Virus isolated from the urine or throat of a neonate is diagnostic; antibody titers are also useful, but complement-fixing antibody may disappear within months of birth, even though viral excretion by the infant continues. Prevention of cytomegalovirus disease in the newborn using mass vaccination is currently being investigated but may be hampered by the previously noted ability of women to harbor this organism even in the presence of circulating antibody. Some infants are infected with cytomegalovirus through transfusions; this complication appears to be largely preventable, however, by using blood from cytomegalovirus-negative donors or by maneuvers that remove white blood cells from the transfused blood (washing, irradiating, filtering, or freezing).

Herpes simplex is a DNA virus with two distinct subtypes that produce disease in humans. Herpes simplex type 1, or labial herpesvirus, infects primarily nongenital areas and is the etiologic agent of many cold sores. Herpes simplex type 2, or genital herpes, appears to be venereally transmitted, is present in the cervical secretions of up to 5% of pregnant women and is the predominant cause of neonatal disease. Unlike rubella, but like the related cytomegalovirus, viremia and transplacental transmission of herpesvirus are uncommon, and most fetuses are infected after rupture of the fetal membranes or during vaginal delivery through an infected birth canal. When a primary maternal infection occurs prior to 32 weeks' gestation, the risk to a full-term infant is low; it increases to a 10% risk of infection if

maternal colonization begins after the thirty-second week and to 40% if the virus is present at the time of vaginal delivery.

Neonatal herpesvirus infection may produce systemic or localized disease; asymptomatic patients are thought to be rare. Signs of systemic disease may be present at birth or delayed for as much as 3 weeks; usually, however, signs become apparent late in the first week of life. Lethargy, vomiting, and fever are the most common initial manifestations and suggest neonatal sepsis; with CNS involvement, irritability and convulsions also occur. Hepatomegaly, jaundice, and skin vesicles occur in only a minority of infants with disseminated herpesvirus. Shock, acidosis, and disseminated intravascular coagulation are frequent as terminal events; only 50% survive this illness, one half with permanent sequelae, although this prognosis may be improving with the introduction of vidarabine and acyclovir.

The prognosis is better for the 30–50% of infants with neonatal herpesvirus infection whose disease is localized. Meningoencephalitis, keratoconjunctivitis, and herpetic vesicles of the skin or mouth may occur together or as isolated findings. The CNS disease has a 20% mortality, with permanent sequelae in an additional 40%; disease limited to the eye or skin rarely causes death or morbidity. It should be noted that CNS or disseminated disease subsequently develops in one half of the infants who initially have only skin vesicles, with a marked change in prognosis.

Herpesvirus infection in the neonate is difficult to diagnose in the absence of the characteristic (but uncommon) vesicular eruption, unless suspicion has been raised by the finding of active herpetic lesions in the mother. Rapid confirmation of the presumptive diagnosis is possible by demonstration of multinucleated giant cells and intranuclear inclusions in cell scrapings from mother and infant; subsequent isolation of virus from infected organs is usually possible. Measurements of antibody titers are sometimes helpful, although many infants succumb before results are available. Neonatal herpesvirus infection is, in large part, a preventable disease. Delivery by cesarean section within 4 hours following rupture of the membranes in mothers with active cervical lesions will usually protect the fetus; rules prohibiting medical staff or visitors with cold sores or whitlows from contact with newborns may interrupt another mode of transmission.

Congenital syphilis is a disease with many manifestations that extend from birth to adulthood. It was extensively studied in the early 1900s, then became virtually extinct with the introduction of penicillin. Its resurgence in this decade parallels the increase in sexually transmitted diseases.

Treponema pallidum is a spirochete with almost exclusively venereal transmission. If untreated, maternal disease persists for years, resulting in the birth of many affected infants. The fetus is infected transplacentally; if maternal infection begins or becomes active during pregnancy, virtually 100% of fetuses will be damaged, one half being stillborn or dying in the neonatal period. When the maternal infection is acquired prior to and is latent during pregnancy, the risk of perinatal death falls to 10–20%, but an additional 10–40% of infants bear permanent stigmata of the disease.

The clinical syndrome of congenital syphilis has few specific signs in the neonate. Usually, the infant is considered normal at birth, or prematurity and intrauterine growth retardation are attributed to other causes. Persistent rhinitis (“snuffles”), hepatosplenomegaly, hemolytic anemia, or skin rash appear later in the neonatal period and suggest the diagnosis; a thorough physical examination may also disclose lymphadenopathy and chorioretinitis. Later in childhood, Hutchinson teeth (peg-shaped, notched permanent incisors), “mulberry molars,” interstitial keratitis, saddlenose, rhagades (linear scars around the mouth and nose), CNS involvement, and periostitis (“saber skins”) may become evident, although the natural history is usually altered markedly by early treatment.

Radiography is particularly useful in the early diagnosis of congenital syphilis. Metaphyseal involvement of the long bones is the earliest and most characteristic sign of this disease, progressing to diffuse osteitis in many cases. Serologic identification of antitreponemal antibodies in the neonate confirms maternal infection but is not diagnostic of fetal involvement unless the antibodies are of the IgM class or persist after passively acquired maternal antibodies are no longer present. The spinal fluid should be examined in all infants suspected of having a congenital infection, regardless of the etiologic agent, but is especially important in the evaluation of congenital syphilis, since silent neurosyphilis is not uncommon and, if untreated, may be devastating later in life.

Unlike most of the other forms of congenital infection, congenital syphilis is treatable. Serologic screening of mothers during the first and third trimester of pregnancy and treatment of those found to be infected can minimize fetal damage; affected infants are treated with penicillin and observed carefully during the first year of life to ensure that control of the infection and its sequelae has been achieved.

A number of other infectious agents can be transmitted from mother to baby during labor, delivery, and the neonatal period, including hepatitis B virus, human immunodeficiency virus, *Chlamydia trachomatis*, enteroviruses, parvovirus, and rotavirus. The time and severity of the disease produced by these organisms depend on the incubation period, the magnitude of the inoculum, and the time of infection.

Reviews

1. Stoll, B., and Weisman, L. Infections in perinatology. *Clin. Perinatol.* 24(1), 1997.
   Covers current management of all the major perinatal infections, as well as articles on experimental strategies for both bacterial and viral pathogens.
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9. Boppana, S., et al. Neuroradiographic findings in the newborn period and long-term outcome in children with symptomatic congenital cytomegalovirus infection. *Pediatrics* 99:409–414, 1997.
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11. McIntosh, D., and Isaacs, D. Herpes simplex virus infection in pregnancy. *Arch. Dis. Child.* 67:1137–1138, 1992.
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Syphilis

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A road map to the newer diagnostic assays—but there is still no single definitive test!

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Documented that some newborns may be seronegative at birth and convert weeks or months later when they become symptomatic. Some presented with rash, others with aseptic meningitis, but all had hepatomegaly, anemia, and increased alkaline phosphatase levels, and all had Herxheimer reaction during treatment.

48. NEONATAL SEPSIS

Robert D. White

Infections are a major cause of morbidity and mortality among newborns, and their significance continues to grow as modern neonatal care permits survival of increasing numbers of neonates at high risk. Newborns differ from older children and adults in virtually every aspect of infectious disease. Their immunologic defenses are immature; they are susceptible to a unique spectrum of organisms; symptoms of infection may be subtle and nonspecific; and antibiotic pharmacokinetics differ.

In the first 2 months of gestation, the fetus is virtually defenseless against invading organisms. The placenta and amniotic sac are highly effective barriers to infection, but transplacental passage of certain viruses, such as rubella, can occur. During the third month of gestation, differentiation and maturation of cellular and humoral immune factors begin, and continue up to and after birth.

At birth, the newborn loses the protection afforded in utero and is exposed to a multitude of virulent organisms. Secretory immunoglobulin A (IgA), normally the first line of defense against infection entering through the mucous membranes, is virtually absent at birth. Fresh human milk contains IgA, but appreciable IgA levels do not develop in formula-fed infants until several weeks after birth. Infection may also enter the body through aspiration of infected material, through a break in the skin, or by iatrogenic means (umbilical catheter, endotracheal tube).

With the onset of infection, several immunologic defenses respond. IgG actively transported from mother to fetus in the third trimester of pregnancy provides the newborn with passive immunity against many organisms. The infant can produce IgM and small amounts of IgG, but their effectiveness is limited because opsonization, phagocytosis, and intracellular killing of virulent organisms are not yet mature. Prematures are at greater risk because they are born before receiving the full maternal transfer of IgG, their own immunologic responses are immature, their nutrition may be inadequate for days or weeks following birth, and they are more frequently subjected to invasive procedures. Other factors associated with neonatal sepsis include being male, prolonged rupture of the membranes with active labor, maternal intrapartum infection, and certain congenital anomalies.

In most infants, the onset of neonatal sepsis is heralded by nonspecific signs such as lethargy, apnea, and poor feeding; fever or hypothermia may occur (with the latter more common), but either can be obscured by incubators or warmers that maintain constant body temperature. Because of the newborn's reduced capacity to control infection, any localized signs of infection (e.g., omphalitis, abscess) should be considered part of a systemic infection until proved otherwise.

Laboratory clues to the diagnosis of neonatal infection are often scanty. Cultures are definitive and vital in planning therapy after the infection is brought under control but are not helpful in the initial evaluation. Hematologic studies may show an increased band count, leukocytosis, or occasionally neutropenia (a poor prognostic sign); thrombocytopenia and toxic granulation of the neutrophils may also be seen, but these hematologic changes often do not reach diagnostic significance until several hours after the onset of symptoms. More valuable is examination and Gram's stain of body fluids. Gram's stain of the buffy coat, cerebrospinal fluid, urine, and fluid from any localized area of infection may be diagnostic; a chest radiograph may also help identify the site of infection. Although any of these tests may be extremely useful in an individual case, their yield is relatively low, and the decision to treat a neonate for sepsis is usually based on the nonspecific clinical signs of illness.

Certain pathogens cause identifiable syndromes of disease in neonates. The group B streptococcus (GBS), which is a leading cause of neonatal sepsis, produces two distinct patterns of disease. “Early-onset” disease usually presents in the first 24 hours of life; its incidence is about 2 per 1,000 live births, and is highest in prematures and infants born after prolonged rupture of the membranes. Infants are colonized with GBS during labor or delivery if the organism is present in the maternal vaginal flora; the incidence of maternal colonization varies from 1–30%, depending on the culture technique used and the population studied. Of colonized infants, only 1% become infected. Full-term infants with early-onset GBS infection usually appear healthy at birth, then become lethargic and distressed, with irregular or rapid respirations. Shock, pneumonia, and acidosis occur in most cases; neutropenia is also present in about one half of the infants, and is highly suggestive of GBS sepsis and pneumonia. Premature infants may have a similar course, but often GBS sepsis in this group is indistinguishable from the respiratory distress syndrome (see Chap. 36). Clinically, tachypnea and dyspnea are prominent with both disorders; radiographically, generalized opacification of the lung fields is a consistent finding. Severe apnea in the first 24 hours, relatively good pulmonary compliance in spite of severe hypoxemia, neutropenia, gram-positive cocci in the gastric aspirate, or prolonged rupture of the membranes should suggest GBS sepsis in a premature infant initially believed to have respiratory distress syndrome; differentiating between these two diseases is nevertheless extremely difficult in many cases. The prognosis of early-onset GBS sepsis is guarded; 5–10% of infants die, and some of the survivors have permanent neurologic damage. Prevention of some cases of early-onset disease is now possible through maternal prophylaxis, although there is debate regarding the most desirable screening and treatment regimen.

“Late-onset” GBS infection occurs between 1 and 12 weeks of age. Colonization probably occurs in the newborn nursery, and meningitis is the usual form of infection, with type III serotype responsible for over 90% of cases. The clinical signs are less fulminant and the prognosis better in this group than in early-onset disease; nearly all infants with late-onset GBS infection survive, and only 15–20% sustain neurologic damage.

The choice of antibiotics in the therapy of neonatal infection is usually made in the absence of information about the specific organism responsible and its sensitivities. Drugs that provide coverage against the common pathogens must be chosen, with recognition that an antibiotic regimen to protect against every organism is impractical. Infections that occur shortly after birth are usually by organisms acquired from the mother; GBS and coliforms are the most common pathogens in this group. Infections later in the neonatal period are often due to hospital-acquired organisms; GBS, *Staphylococcus aureus* and *epidermitis,* gram-negative bacilli (sometimes resistant to several antibiotics) and yeast must then be considered. Bacteria of relatively low virulence, such as *Listeria* and anaerobes, and a number of viruses (especially herpes simplex and enteroviruses) can also produce serious infections in neonates.

Intensive supportive care is important for neonates with life-threatening infections. Shock, respiratory failure, hypothermia, hypoglycemia, and disseminated intravascular coagulation are complications of sepsis that must be anticipated and treated vigorously. Renal and hepatic function should be monitored, since impairment in these functions requires adjustment of antibiotic dosage. The duration of treatment must be individualized on the basis of the site of infection and the response to antibiotics; the prognosis also depends on these factors, as well as on the presence of associated diseases and the type of organism responsible for the infection.

Prevention of neonatal infection is possible in many cases through hand-washing by personnel prior to each infant contact, sterilization of equipment, and restraint in the use of invasive procedures.

Reviews and Series

1. Stoll, B., and Weisman, L. Infections in perinatology. *Clin. Perinatol.* 24(1), 1997.
   In addition to the topics typically covered in a compendium, this volume includes articles on neonatal infections in underdeveloped countries, tuberculosis, and novel approaches to prevention and treatment.
2. Quie, P. Antimicrobial defenses in the neonate. *Semin. Perinatol.* 14(Suppl. 1): 2–9, 1990.
   Remainder of this issue is also devoted to neonatal sepsis, with articles on group B streptococcus (GBS), Escherichia coli, *and* Listeria.
3. Stoll, B., et al. Late-onset sepsis in very low birth weight neonates: A report from the National Institute of Child Health and Human Development Neonatal Research Network. *J. Pediatr.* 129:63–71, 1996.

*This report, and its companion on early-onset sepsis (*J. Pediatr. *129:72–80, 1996), constitute by far the largest series available of babies under 1,500 g birthweight, and document that nearly half of all deaths in this group after 2 weeks of age are due to infection.*

The Immune System

4. Cates, K., Rowe, J., and Ballow, M. The premature infant as a compromised host. *Curr. Probl. Pediatr.* 13(8), 1983.
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6. Baley, J. Neonatal sepsis. The potential for immunotherapy. *Clin. Perinatol.* 15:755–771, 1988.
   Evidence supporting the value of exchange transfusion, granulocyte or immunoglobulin infusion, and fibronectin administration is reviewed; each remains experimental with uncertain indications. Updated in J. Perinatol. *13:223–227, 1993.*
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   Outlines the distressing extent of our ignorance about the mechanisms of clinical symptoms of sepsis—and is worth reading for the humor and tantalizing hints of future developments.

Infectious Agents: Group B Streptococcus

8. American Academy of Pediatrics. Revised guidelines for prevention of early-onset group B streptococcal (GBS) infection. *Pediatrics* 99:489–496, 1997.
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10. Nataro, J., et al. Prospective analysis of coagulase-negative staphylococcal infection in hospitalized infants. *J. Pediatr.* 125:798–804, 1994.
    Complete blood cell (CBC) count changes were not helpful in distinguishing infected infants from those with contaminated cultures, so multiple cultures and clinical symptoms become crucial in determining duration of therapy.
11. Butler, K., and Baker, C. *Candida*: An increasingly important pathogen in the nursery. *Pediatr. Clin. North Am.* 35:543–563, 1988.
    A series in Pediatrics *82:211–215, 1988, points out that all infants with systemic disease also had cutaneous involvement, and recommends systemic therapy for cutaneous candidiasis presenting early in the first week of life in infants whose birth weight is less than 1,500 g. Prenatal infection may also occur; see* Acta Obstet. Gynecol. Scand. *72:52–54, 1993.*
12. Waites, K., Crouse, D., and Cassell, G. Antibiotic susceptibilities and therapeutic options for *Ureaplasma urealyticum* infections in neonates. *Pediatr. Infect. Dis. J.* 11:23–29, 1992.
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Sites of Infection: Meningitis

13. Halliday, H. When to do a lumbar puncture in a neonate. *Arch. Dis. Child.* 64:313–316, 1989.
    Reviews not only when, but also why and how.
14. Bale, J., and Murph, J. Infections of the central nervous system in the newborn. *Clin. Perinatol.* 24:787–806, 1997.
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16. Bell, A., et al. *Meningitis in the newborn—A 14-year review. Arch. Dis. Child.* 64:873–874, 1989.
    Long-term sequelae remain common in spite of improvements in neonatal care. Another series can be found in Am. J. Dis. Child. *146:567–571, 1992.*

Sites of Infection: Other

17. Dennehy, P. Respiratory infections in the newborn. *Clin.Perinatol.* 14:667–682, 1987.
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18. Morrissy, R. Bone and joint infection in the neonate. *Pediatr. Ann.* 18:33–44, 1989.
    A difficult diagnosis to make in the early stages of disease. Also see J. Pediatr. *88:621–624, 1976, and* Pediatrics *53:505–510, 1974.*
19. Bergstrom, T., et al. Studies of urinary tract infections in infancy and childhood: XII. Eighty consecutive patients with neonatal infections. *J. Pediatr.* 80:858–866, 1972.
    Congenital anomalies and permanent sequelae were found in less than 5%. Urinary tract infection rarely occurs within the first 24 hours of life; see Pediatr. Infect. Dis. J. *11:764–766, 1992.*
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Diagnostic Aids

21. Manroe, B., et al. The neonatal blood count in health and disease: I. Reference values for neutrophilic cells. *J. Pediatr.* 95:89–98, 1979.
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    Greatly elevated immature-total neutrophil ratio was shown to be good marker for bone marrow depletion and, consequently, for death from sepsis, but the lack of sensitivity of a single determination is emphasized in Pediatr. Infect. Dis. J. *6:429–430, 1987.*
23. Franz, A., et al. Reduction of unnecessary antibiotic therapy in newborn infants using interleukin-8 and C-reactive protein as markers of bacterial infection. *Pediatrics* 104:447–453, 1999.
    Addition of interleukin-8 and C-reactive protein to the diagnostic panel improves the sensitivity and specificity of the CBC, and may reduce the need for or duration of "rule-out" antibiotic therapy.

Management

24. Saez-Llorens, X., and McCracken, G. Sepsis syndrome and septic shock in pediatrics: Current concepts of terminology, pathophysiology, and management. *J. Pediatr.* 123:497–508, 1993.
    Septic shock is presented as the result of overstimulation of the child's immunologic defense mechanisms by specific microbial molecules. Intervening in this process may be as important to recovery as elimination of the invading organism.
25. Goldman, S., et al. Rationale and potential use of cytokines in the prevention and treatment of neonatal sepsis. *Clin. Perinatol.* 25:699–710, 1998.
    One of several promising new therapies for neonatal sepsis currently in clinical trials.

49. INTRACRANIAL HEMORRHAGE IN THE NEWBORN

Robert D. White

Intracranial bleeding is perhaps the most dramatic manifestation of the level of stress, both mechanical and hemodynamic, inherent in the birth process. While intracranial bleeding in the full-term infant most often occurs during labor as the result of mechanical factors, it can occur even prior to labor or as late as the second week of life in the preterm infant, usually as the result of hemodynamic instability. Because these differences in the factors surrounding intracranial hemorrhage in term and preterm infants also extend to clinical symptoms, diagnostic considerations, and treatment, the discussion that follows will separate the two groups according to gestational age.

Intracranial bleeding in the full-term infant can present with any of several diverse symptoms. It is the second leading cause of fever (behind infection) and also the second most common cause of seizures (behind asphyxia). It may lead to “late” jaundice (peaking late in the first week of life), irritability, or abnormalities of muscle tone. Typically, bleeding is subarachnoid, and although forceps delivery can predispose, most cases are found after unassisted vaginal delivery. Subdural hemorrhage is more commonly associated with birth trauma, and intraventricular hemorrhage with severe asphyxia. Intracerebral or cerebellar bleeding in the full-term infant may occur as the result of a vascular accident; usually the etiology of the vascular accident itself is obscure, however.

When symptoms suggestive of intracranial hemorrhage are noted in the term infant, a computed tomography (CT) scan of the head is the preferred diagnostic procedure. Many subarachnoid bleeds will be missed by ultrasound, while magnetic resonance imaging (MRI) is much more expensive; MRI is indicated, however, when posterior fossa hemorrhage is suspected. Usually the CT scan can be performed without contrast, although contrast may be useful if a ruptured aneurysm or other vascular malformation is suggested by the noncontrast CT.

Subarachnoid hemorrhage in the term newborn is usually self-limited, though occasionally a communicating hydrocephalus can develop secondary to obliteration of the arachnoid villi. Subdural, intraventricular, and intracerebral bleeds have greater implications. Subdural hemorrhage occasionally requires surgical intervention, while intraventricular or intracerebellar hemorrhages are often the harbinger of long-term neurologic disability—usually the result of the predisposing condition (e.g., asphyxia), rather than the bleeding itself.

Intracranial hemorrhage in the preterm infant usually follows a different course. While any of the sites of bleeding noted in the full-term infant can also occur in the premature, bleeding in the subependymal region adjacent to the choroid plexus is by far the most common. Whereas hemorrhage in term infants can call attention to itself in a number of ways, subependymal bleeding in the premature is nearly always silent. The etiology of bleeding at this site is not yet clearly established, but it seems likely that variations in blood pressure and flow, poorly regulated by the immature cerebral vasculature of the premature infant, can lead to damage and ultimately rupture of the capillary bed feeding the germinal matrix. When bleeding is confined to the subependymal region, it is classified as grade I; extension into the lateral ventricle(s) is common, however, and is classified as grade II intraventricular hemorrhage. With extensive intraventricular bleeding, hydrocephalus can occur as the result of aqueductal obstruction or subarachnoid obliteration; this is then classified as grade III intraventricular hemorrhage. Grade IV intraventricular hemorrhage is actually not intraventricular but intracerebral; it often occurs concurrently with grade II or III intraventricular hemorrhage, but is probably caused by ischemic infarction of cerebral tissue.

Diagnosis of intracranial hemorrhage in the preterm infant is most accurate with CT scan, but because most bleeding is intra- or periventricular, bedside ultrasound scanning is preferred because it is nearly as accurate and much less stressful for an ill premature infant. Since most cases of intraventricular hemorrhage occur in infants less than 1,500 g birth weight and less than 32 weeks' gestation, diagnostic screening is appropriate in this population during the second week of life (after which further bleeding is uncommon), and sooner if clinical conditions indicate (e.g., unexplained drop in hematocrit, severe apnea or seizures, unexplained respiratory deterioration, bulging fontanelles). When bleeding is found, repeat ultrasound examinations will be necessary to determine whether associated complications (hydrocephalus, periventricular leukomalacia) will occur; some infants with severe grade III or IV hemorrhage will require ventriculoperitoneal shunts to control hydrocephalus, whereas milder degrees of hydrocephalus will often arrest spontaneously.

Intracranial hemorrhage occurs in 25–40% of infants less than 1,500 g birth weight. Most cases involve only grade I or II intraventricular hemorrhage and do not show late sequelae. Infants with grade III or IV hemorrhage have a high incidence of neurologic sequelae; approximately 30% will have severe cerebral palsy or mental retardation. Prevention is therefore a subject of intense interest. Prenatal interventions such as administration of phenobarbital or vitamin K to the mother, delivery by cesarean section, and postnatal interventions such as prophylactic administration of vitamin E, indomethacin, pancuronium, ethamsylate, and phenobarbital have all been studied, but only postnatal indomethacin therapy has gained sufficient evidence to be used prophylactically. Nevertheless, the incidence of grade III or IV intraventricular hemorrhage seems to be declining, perhaps as the result of improving obstetric and neonatal care in general, with the resulting reduction in severe stresses to the premature fetus and newborn.

Reviews

1. du Plessis, A. (ed.). Neurologic disorders in the newborn, part I: Cerebrovascular disease. *Clin. Perinatol.* 24(3), 1997.
   In a disorder where treatment options are limited, most of the current research and much of this volume are devoted to the elucidation of the physiological mechanisms that underlie intracranial bleeding.
2. Vohr, B., and Ment, L. Intraventricular hemorrhage in the preterm infant. *Early Hum. Dev.* 44:1–16, 1996.
   Succinct description of all elements of this disorder, with particular emphasis on follow-up and prevention.
3. Bergman, I., et al. Intracerebral hemorrhage in the full-term neonatal infant. *Pediatrics* 75:488–496, 1985.
   Intracranial bleeding in term infants differs in location, presentation, and outcome from that in preterm infants; bleeding caused by asphyxia or trauma is usually associated with long-term problems, whereas idiopathic bleeding appears to be benign in most term infants.
4. Ravenel, S. Posterior fossa hemorrhage in the term newborn. *Pediatrics* 64:39–42, 1979.
   Posterior fossa hemorrhage is often devastating, and its etiology remains obscure.

Etiologic Factors

5. Thorp, J., et al. Perinatal factors predicting severe intracranial hemorrhage. *Am. J. Perinatol.* 14:631–636, 1997.
   *This study, as well as one focusing on placental pathology (*Pediatr. Res. *43:15–19, 1998), strongly implicates chorioamnionitis as a risk factor for intraventricular hemorrhage (IVH) in premies.*
6. Pape, K. Etiology and pathogenesis of intraventricular hemorrhage in newborns. *Pediatrics* 84:383–385, 1989.
   This brief review focuses on hemodynamic aberrations that might predispose to bleeding in prematures. Additional articles since this review include Early Hum. Dev. *19:103–110, 1989 and* J. Pediatr. *117:607–614, 1990.*

Diagnosis

7. Papile, L., et al. Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 grams. *J. Pediatr.* 92:529–534, 1978.
   This article, which describes the most frequently used classification system for intraventricular hemorrhage, still makes good reading, even though the incidence figures have changed.
8. Pape, K., et al. Diagnostic accuracy of neonatal brain imaging: A postmortem correlation of computed tomography and ultrasound scans. *J. Pediatr.* 102:275–280, 1983.
   Clinical imaging has inherent inaccuracies, as shown by autopsy correlation; even within the same institution, considerable disagreement can exist in the interpretation of clinical studies (see Dev. Med. Child. Neurol. *35:97–101, 1993).*
9. Keeney, S., Adcock, E., and McArdle, C. Prospective observations of 100 high-risk neonates by high-field (1.5 Tesla) magnetic resonance imaging of the central nervous system: I. Intraventricular and extracerebral lesions. *Pediatrics* 87:421–430, 1991.
   Magnetic resonance imaging appears to be more accurate than other imaging techniques for diagnosis of extracerebral hemorrhage and can assist with timing of the bleed as well.

Management

10. Miller, V. Pharmacologic management of neonatal cerebral ischemia and hemorrhage: Old and new directions. *J. Child Neurol.* 8:7–18, 1993.
    The drugs reviewed are primarily used for prevention rather than treatment, but this article also highlights future treatment possibilities.

Follow-Up

11. Van de Bor, M., et al. Outcome of periventricular-intraventricular haemorrhage at five years of age. *Dev. Med. Child Neurol.* 35:33–41, 1993.
    An excellent population-based study with all of the 304 very low-birth-weight survivors available for follow-up at 5 years! Six percent of infants without IVH, 10% of those with grade I–II, IVH, and 24% of those with grade III–IV, IVH had major handicaps.
12. Cooke, R. Determinants of major handicap in post-haemorrhagic hydrocephalus. *Arch. Dis. Child* 62:504–506, 1987.
    Several follow-up studies (see also Dev. Med. Child Neurol. *29:3–11, 623–629, 1987) document that additional ultrasound findings (most commonly periventricular leukomalacia) are important correlates of later developmental problems, some of which may not be apparent in infancy.*

Prevention

13. Thorp, J., et al. Intracranial hemorrhage (ICH) in premature infants: Epidemiology and prevention. *CNS Drugs* 11:421–433, 1999.
    Summarizes the many prevention strategies proposed in recent years, with a special focus on administration of prophylactic drugs to the mother antenatally.
14. Shankaran, S., et al. Prenatal and perinatal risk and protective factors for neonatal intracranial hemorrhage. *Arch. Pediatr. Adolesc. Med.* 150:491–497, 1996.
    Prenatal maternal steroid administration, intended to prevent respiratory distress syndrome, also reduces the incidence of IVH in prematurely born infants.
15. Fowlie, P. Prophylactic indomethacin: Systematic review and meta-analysis. *Arch. Dis. Child.* 74:F81–F87, 1996.
    Prophylactic indomethacin may reduce severe IVH and patent ductus arteriosus, but may increase the risk of necrotizing enterocolitis, so routine use is not yet endorsed.

50. RETINOPATHY OF PREMATURITY

Robert D. White

The fetal retina, like most tissues of the very premature infant, is poorly prepared for extrauterine life. Under ideal circumstances after birth, the final maturational changes in the preterm retina occur normally, but approximately 4% of newborns under 1,500 g birth weight experience retinal scarring and neovascularization in the first months of life sufficient to cause later permanent visual impairment. This condition was formerly known as retrolental fibroplasia, but it is now called retinopathy of prematurity (ROP) due to its strong relationship to preterm birth. Retinopathy of prematurity is rare above 32 weeks' gestation and increases in frequency proportional to the degree of prematurity.

Vascularization of the retina begins in the second trimester and becomes complete at or slightly before term. Conditions that strongly influence retinal homeostasis in the interim may damage the vasculature and adjacent retinal tissue; supranormal arterial concentrations of oxygen have clearly been shown to cause such damage, while sepsis, excessive environmental light, and deficiency of oxygen free-radical scavengers are among other factors that have also been postulated to play causative or permissive roles.

Damage to the retina is described in a staging system ranging from stage I ROP (line of demarcation visible between vascularized retina centrally and avascular retina peripherally) to stage V (complete retinal detachment). In stage II, a ridge of scar tissue forms at the line of demarcation, and in stage III, capillary neovascularization becomes prominent, often with signs of traction on the retina as the scar tissue begins to retract. By stage IV, retinal detachment has begun. A further refinement of this system uses the term plus disease to describe an active inflammatory component that may develop in stage II or III and increases the risk that progression of ROP will occur.

Most premature infants who develop stage I ROP will experience spontaneous regression without intervention, but further progression can occur in 10–20%. These more severe changes (stage II and above, and plus disease) nearly always begin after the fifth week of life, but the rate of progression is less predictable, occurring over many weeks in some infants and changing dramatically in a matter of days in others. For this reason, retinal examination of all infants less than 32 weeks' gestation should be done by a skilled ophthalmologist by 4–6 weeks of age and repeated until vascularization is complete. Infants who have stage III ROP or stage II with extensive plus disease should be considered for cryosurgery or laser photocoagulation; both techniques minimize further neovascularization of the damaged retina, and the former has been shown to reduce the incidence of retinal detachment in this high-risk group of infants from about 40% to 20%.

Infants with stage II or III ROP that spontaneously regresses or is successfully treated are still at risk for myopia, amblyopia, astigmatism, and late retinal detachment, necessitating careful visual screening, and intervention when indicated, throughout childhood.

Prevention of ROP could be achieved by prevention of prematurity and the postnatal complications that attend it, but might also become feasible if the pathophysiology of this disorder were fully delineated. Since the tissue damage of ROP follows a similar time course to certain other complications of prematurity (bronchopulmonary dysplasia, necrotizing enterocolitis, and perhaps periventricular leukomalacia), and since ROP has been postulated to share many of the same risk factors as prematurity, many investigators hope that progress in learning how to intervene in the cellular changes that culminate in ROP will also lead to successful prevention of these other, equally devastating effects of preterm birth.

Reviews

1. Silverman, W. (ed.). *Retrolental Fibroplasia: A Modern Parable.* New York: Grune & Stratton, 1980.
   By perhaps the best writer of parables since Biblical times, this makes fascinating, humbling reading as it traces the many missteps on our road to gaining an understanding of the cause and prevention of retinopathy of prematurity (ROP).
2. Avery, G., and Glass, P. Retinopathy of prematurity. *Clin. Perinatol.* 15:917–928, 1988.
   Also reviewed in Pediatr. Clin. North Am. *40:705–714, 1993, and briefly in* Lancet *337:83–84, 1991.*

Pathophysiology

3. Ng, Y., et al. Epidemiology of retinopathy of prematurity. *Lancet* 2:1235–1238, 1988.
   Large series found only one case of stage III or greater ROP in infants over 32 weeks' gestation; the incidence increases to 2% at 28–31 weeks and 21% at 24–27 weeks.
4. Mittal, M., Dhanireddy, R., and Higgins, R. *Candida* sepsis and association with retinopathy of prematurity. *Pediatrics* 101:654–657, 1998.
   Nearly all infants in this series who had Candida *sepsis developed ROP, with 41% requiring laser surgery, compared to a 9% incidence of surgery in infants of the same cohort who did not get* Candida *sepsis.*
5. Fielder, A., et al. Light and retinopathy of prematurity: Does retinal location offer a clue? *Pediatrics* 89:648–653, 1992.
   An intriguing observation that ROP tends to occur most frequently in those areas of the retina most exposed to environmental lighting.

Screening

6. Fielder, A., and Levene, M. Screening for retinopathy of prematurity. *Arch. Dis. Child.* 67:860–867, 1992.
   This is actually a very comprehensive review of ROP, but the recommendations for screening are especially useful.
7. International Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Pediatrics* 74:127–133, 1984.
   The current staging system is described.

Treatment

8. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryoptherapy for retinopathy of prematurity: One year outcome—Structure and function. *Arch. Ophthalmol.* 108:1408–1416, 1990.
   Cryotherapy increases chances of normal acuity in a randomized trial of treatment for "threshold ROP" from 40% in control infants to 60% in treated infants.
9. Benner, J., et al. A comparison of argon and diode photocoagulation combined with supplemental oxygen for the treatment of retinopathy of prematurity. *Retina* 13:222–229, 1993.
   Laser photocoagulation and supplemental oxygen are two newer forms of treatment for ROP in which use has increased even before the release of definitive studies.
10. Page, J., et al. Ocular sequelae in premature infants. *Pediatrics* 92:787–790, 1993.
    Milder but significant visual problems can occur in premature infants long after their ROP seems to be stable or healed.

51. SYSTOLIC MURMURS

Kenneth G. Zahka

The acceleration and peak velocity of blood flow in the normal heart are greatest during the ejection of blood into the pulmonary artery and aorta during ventricular systole. The transmission of sound to the chest wall as a result of this blood flow (the clinical perception of a murmur) is directly related to the velocity of the blood flow, the turbulence of the blood flow, and the size of the chest. The smaller diameter of the great arteries in children is associated with higher blood flow velocity; this, combined with the smaller chest size, favors the genesis of the systolic murmurs that are frequently detected during the routine physical examination of healthy children.

The differentiation of murmurs associated with underlying cardiovascular abnormalities from normal, functional murmurs requires careful attention to the loudness, quality, type, location, and radiation of the murmur, as well as the characteristics of the precordial activity, the heart sounds, and the peripheral pulses.

The intensity or *loudness* of systolic murmurs conventionally is graded on a 1–6 scale, with 6 being the loudest. The description of the *quality* of a murmur usually reflects the range of frequencies of the sound. A vibratory murmur is a single low frequency (vibration), resembling the sound produced by a single musical note, which, although it varies in intensity, remains the same frequency. Harsh murmurs are characterized by the mixture of many frequencies and intensities of sound simultaneously, resembling static on a radio. Blowing implies a harsh sound with predominantly higher frequencies.

There are two general *types* of systolic murmurs. The systolic ejection murmur is a crescendo-decrescendo murmur that begins after the first heart sound, peaks in intensity in midsystole, and ends with the second heart sound. It is produced by blood flow through the aortic or pulmonary outflow tracts. The characteristic “shape” or change in intensity, as well as the timing relative to the heart sounds of the murmur, is a result of the physiologic events occurring with ejection of blood into the great arteries. The separation between the first heart sound and the onset of the murmur coincides with the period of isovolumic contraction between the closure of the mitral and tricuspid valves, and the opening of the aortic and pulmonary valves. The intensity of the murmur increases as the blood flow reaches its peak velocity in midsystole (crescendo) and then decreases (decrescendo) until the point of aortic or pulmonary valve closure (second heart sound). In contrast, a holosystolic (pansystolic) murmur begins with the first heart sound, is of approximately equal intensity throughout systole, and ends with the second heart sound. The absence of a delay between the first heart sound and the onset of the murmur implies blood flow during the presumed time of isovolumic contraction, such as would occur with mitral or tricuspid regurgitation or a ventricular septal defect. An early systolic murmur is similar to the holosystolic murmur in that it begins with the first heart sound, but then tapers in intensity through the first portion of systole. This murmur is characteristic of muscular ventricular septal defects, which can be obliterated during the muscular contraction of the septum. The late systolic murmur of mitral regurgitation due to mitral valve prolapse does not begin until the mitral valve has become distorted enough during systole to produce the click and the subsequent mitral regurgitation; thus, the murmur extends from a midsystolic click to the second heart sound.

The *location* and *radiation* of murmurs indicate the direction of the blood flow producing them. In a child with normal cardiac and great artery position, murmurs arising from the aortic outflow tract are loudest at the upper right sternal border and radiate to the neck, and murmurs from the pulmonary outflow tract are loudest at the upper left sternal border and radiate to the lungs. Mitral regurgitation is heard best at the lower left sternal border and radiates to the left axilla, whereas the murmur of tricuspid regurgitation is loudest at the lower right sternal border. The intensity of the murmur influences its radiation. A small ventricular septal defect will produce a well-localized murmur at the lower left sternal border, while the murmur from larger defect will be heard more widely.

An accentuated apical impulse is indicative of left ventricular overload, while a prominent substernal impulse suggests right ventricular overload. Left ventricular overload is produced by conditions associated with increased left ventricular pressure (e.g., aortic stenosis) or with increased left ventricular stroke volume (e.g., mitral or aortic regurgitation, ventricular septal defect, patent ductus arteriosus). Similarly, a right ventricular impulse is present in children with increased right ventricular pressure (e.g., pulmonary stenosis) or right ventricular stroke volume (e.g., atrial septal defect). The magnitude of the precordial hyperactivity correlates in general with the degree of abnormal ventricular load.

In some children, abnormalities of the second heart sound are the most conclusive evidence of underlying structural heart disease. For example, the single and accentuated second heart sound in an infant with a ventricular septal defect is indicative of pulmonary hypertension, regardless of the loudness or even the presence of a murmur. The presence of an early systolic click would suggest either a pulmonary or aortic valve abnormality. Midsystolic clicks are most frequently indicative of mitral valve prolapse, although tricuspid valve prolapse can produce a similar finding.

The strength and timing of the peripheral pulses are determined by the stroke volume and vascular resistance. Diminished stroke volume (e.g., severe aortic stenosis or myocardial dysfunction) results in diminished pulses in all extremities. Increased stroke volume, especially when associated with an increased pulse pressure (e.g., patent ductus arteriosus or aortic regurgitation), produces bounding pulses in all extremities. Decreased and delayed pulses in the legs compared to the arms are diagnostic of arterial obstruction (e.g., coarctation of the aorta, interrupted aortic arch, arterial thrombosis).

In general, an acyanotic child with normal precordial activity, normal aortic and pulmonary components of the second heart sound without a click or gallop, normal peripheral pulses, and a *vibratory* systolic ejection murmur has a functional heart murmur, and probably a structurally and functionally normal heart. In contrast, *harsh* quality systolic murmurs are indicative of the turbulent blood flow produced by disordered cardiac structure or function.

Functional or innocent murmurs are produced by either aortic or pulmonic blood flow, although their exact pathogenesis remains controversial. The Still-type functional murmur is a low-to-medium frequency, vibratory or “twangy” crescendo-decrescendo murmur heard along the left sternal border and often radiating to the neck. This murmur probably originates from the left ventricular blood flow, and must be differentiated from the harsh systolic ejection murmur of aortic valve stenosis or subaortic stenosis and the harsh pansystolic murmur of a ventricular septal defect. The vibratory pulmonary systolic ejection murmur is best heard at the upper left sternal border, and may be confused with the harsh murmur of pulmonic stenosis or the pulmonic murmur associated with the increased pulmonary blood flow in a child with an atrial septal defect. The pulmonary vibratory systolic ejection murmur in infants may radiate well to the axillae, in that way resembling the harsh murmur heard in children with discrete branch pulmonary artery stenosis, and thus is referred to as physiologic peripheral pulmonary stenosis.

Fever, anxiety, exercise, or anemia increases cardiac output, generally accentuating functional murmurs, and a repeat examination when the child is well or relaxed helps clarify the etiology of a murmur. Postural maneuvers that transiently diminish systemic venous return, such as standing from the squatting position, often dramatically decrease the intensity of functional murmurs. In contrast, murmurs due to aortic or pulmonary valve stenosis, ventricular septal defects, or mitral regurgitation usually persist regardless of position.

Systolic ejection murmurs arising from aortic or pulmonary stenosis are present at birth. The holosystolic murmur from a ventricular septal defect is not heard until the pulmonary vascular resistance falls over the first few days of life. There are relatively few etiologies for newly developed pathologic murmurs in children. Children with mitral valve prolapse or inflammatory diseases such as rheumatic fever, myocarditis, or endocarditis may develop mitral regurgitation. The murmur arising from the increased blood flow across the pulmonary valve in children with an atrial septal defect is not present in the first few months of life, and is a common presentation of this defect in children and adolescents. While children with congenital aortic valve disease either have a click or a harsh systolic murmur at an early age, subaortic stenosis is often a progressive obstruction, which in its mildest form is difficult to differentiate from Still murmur.

The evaluation of the child with the systolic murmur may be limited to the physical examination alone if the examiner is convinced of the etiology of the murmur. The addition of further tests will confirm the diagnosis and the hemodynamic impact of the defect. The electrocardiogram and chest x-ray are inexpensive and widely available, but are relatively insensitive and nonspecific for the precise confirmation of clinical diagnoses. The two-dimensional and Doppler echocardiogram is both a sensitive and specific tool for the diagnosis of hemodynamically trivial to the most complex defects. It is, however, more expensive and requires special training and

expertise to perform and interpret in children; thus, it is not as widely available.

General Evaluation

1. McCrindle, B., et al. Cardinal clinical signs in the differentiation of heart murmurs in children. *Arch. Pediatr. Adolesc. Med.* 1996;150:169–174.
   Experienced pediatric cardiologists did not miss significant disease that was subsequently found on echocardiogram. This is a relatively small, 200 patient, series. It is possible to miss bicuspid aortic valve.
2. Kuehl, K., Loffredo, C., and Ferencz, C. Failure to diagnose congenital heart disease in infancy. *Pediatrics* 1999;103:743–747.
   Nearly 10% of newborns who died in this population-based study between 1981 and 1989 were only diagnosed with heart disease at autopsy. Left heart disease, truncus arteriosus, and Ebsteins were among the findings.
3. Ferencz, C., et al. Congenital cardiovascular malformations: Questions on inheritance. J. *Am. Coll. Cardiol.* 1989;14:756–763.
   In this cohort of 2100 cases, 26.8% of the infants with heart defects had an associated noncardiac abnormality, while only 3.6% of 2300 control infants had a noncardiac abnormality. Genetic defects, including recognized chromosomal abnormalities and well-defined heritable syndromes, compose a large proportion (369/563) of the associated noncardiac abnormalities.
4. Chang, L. Development and use of the stethoscope in diagnosing cardiac disease. *Am. J. Cardiol.* 1987;60:1378–1382.
   Thorough discussion of the major tool of the trade.
5. Graham, T., Jr., et al. 26th Bethesda conference: Recommendations for determining eligibility for competition in athletes with cardiovascular abnormalities. Task Force 1: Congenital heart disease. *J. Am. Coll. Cardiol.* 1994;24:867–873.
   Recommendations on participation in sports for children with congenital heart disease.

Noninvasive Assessment

6. Sherman, F., and Sahn, D. Pediatric Doppler echocardiography 1987: Major advances in technology. *J. Pediatr.* 110:333–342, 1987.
   A succinct review of color and conventional Doppler. For other reviews, see Am. J. Dis. Child. *138:1003–1009, 1984;* Circulation *71:849–853, 1985; and* Mayo Clin. Proc. *61:725–744, 1986 (particularly thorough). For an excellent study of the estimation of pressure gradients by Doppler echocardiography, see* J. Am. Coll. Cardiol. *7:800–806, 1986.*
7. Higgins, C., and Caputo, G. Role of MR imaging in acquired and congenital cardiovascular disease. *A.J.R.* 161:13–22, 1993.
   Magnetic resonance imaging continues to improve with faster acquisition and increasingly sophisticated analysis of physiology. See Semin. Roentgenol. *33: 228–238, 1998.*

Specific Diagnoses

8. Van Oort, A., et al. The vibratory innocent heart murmur in schoolchildren: A case-control Doppler echocardiographic study. *Pediatr. Cardiol.* 15:275–281, 1994.
   One percent of the normal murmurs were assigned a loudest of grade 3. The authors suggest that the murmurs are more common in children with smaller aortas and higher velocity aortic flow.
9. Rodriguez, R., and Riggs, T. Physiologic peripheral pulmonary stenosis in infancy. *Am. J. Cardiol.* 66:1478–1481, 1990.
   This is an especially common functional murmur in premature infants but can also be heard in full-term infants. It usually resolves by 6 months (Arch. Dis. Child. *[Fetal Neonatal edition] 78:F166–F170, 1998) If it persists, consider atrial septal defect or valve pulmonary stenosis.*
10. Murphy, J., et al. Long-term outcome after surgical repair of isolated atrial septal defect: Follow-up at 27 to 32 years. *N. Engl. J. Med.* 323:1645–1650, 1990.
    The prognosis for children with atrial septal defect repaired in the first two decades is excellent. See Am. Heart J. *109:1327–1333, 1985, for spontaneous closure of isolated secundum atrial septal defects in infants.*
11. Krabill, K., et al. Rest and exercise hemodynamics in pulmonary stenosis: Comparison of children and adults. *Am. J. Cardiol.* 56:360–365, 1985.
    Abnormal exercise hemodynamics were present only in those patients with severe obstruction, indicating that mild and moderate obstruction are well tolerated. See Circulation *87:128–137, 1993, for the report from a large collaborative study on the natural history of pulmonary stenosis.*
12. Nishimura, R., et al. Echocardiographically documented mitral-valve prolapse. *N. Engl. J. Med.* 313:1305–1309, 1985.
    The redundancy and thickening of the valve correlate with the prognosis. See J. Pediatr. *105:885–890, 1984, for a study of ventricular arrhythmias in mitral valve prolapse, and* J. Am. Coll. Cardiol. *5:1173–1177, 1985, for the pitfalls of echocardiographic diagnosis of mitral valve prolapse.*
13. Thoele, D., Muster, A., and Paul, M. Recognition of coarctation of the aorta. *Am. J. Dis. Child.* 141:1201–1204, 1987.
    Stresses the need for careful physical examinations.

Management

14. Mullins, C. History of pediatric interventional catheterization: Pediatric therapeutic cardiac catheterizations. *Pediatr. Cardiol.* 19:3–7, 1998.
    A concise contemporary review. See also Am. J. Cardiol. *61:109G–117G, 1988, for a well-referenced review covering the interventional catheterization of the pulmonary valve, aortic valve, and mitral valve; coarctation of the aorta and branch pulmonary arteries; patent ductus arteriosus; and systemic-pulmonary collaterals.*
15. Rao, P., et al. Five- to nine-year follow-up results of balloon angioplasty of native aortic coarctation in infants and children. *J. Am. Coll. Cardiol.* 27:462–470, 1996.
    Although effective as primary treatment of unoperated coarctation in many older patients, a few are left with aneurysms at the coarctation site. Surgery after failed balloon angioplasty or for aneurysm appears safe: J. Am. Coll. Cardiol. *19:389–393, 1992.*
16. Leenen, F., et al. Postoperative hypertension after repair of coarctation of aorta in children: Protective effect of propranolol? *Am. Heart J.* 113:1164–1173, 1987.
    Discussion of the mechanisms of postoperative hypertension and its treatment. See Circulation *75:1186–1191, 1987.*
17. Neveux, J. Coarctation of the aorta in infants: Which operation? *Ann. Thorac. Surg.* 45:186–191, 1988.
    This article and J. Am. Coll. Cardiol. *8:1406–1411, 1986, suggest that, contrary to the initial hope, subclavian flap angioplasty does not reduce the need for reoperation. The resection with end-to-end anastomosis has become the standard treatment.*
18. Marino, B., et al. Early results of the Ross procedure in simple and complex left heart disease. *Circulation* 100(Suppl. II):162–166, 1999.
    This operation takes the child's pulmonary valve and moves it to the aortic root. The pulmonary valve is replaced by a homograft. It works surprisingly well even in small babies. The long-term issues are the durability of the homograft and possible dilatation of the pulmonary autograft.
19. Chan, K., et al. Transcatheter closure of atrial septal defect and interatrial communications with a new self-expanding nitinol double disc device (Amplatzer septal occluder): Multicentre UK experience. *Heart* 82:300–306, 1999.
    A large series of 100 patients with excellent (99%) closure rates 3 months following the procedure. There were complications including 7 patients who did not have their defect closed, 1 embolized device requiring surgery and 1 transient ischemic attack. See Cardiol. Young *9:65–67, 1999, for a report on bacterial endocarditis after device placement. See* Heart *80:517–521, 1998, for the "angel-wings" device, and* Am. J. Cardiol. *84:1113–1116, 1999, for the newest device, the "STARFlex Occluder."*

52. LEFT-TO-RIGHT SHUNTS: VENTRICULAR SEPTAL DEFECT AND PATENT DUCTUS ARTERIOSUS

Kenneth G. Zahka

The isolated ventricular septal defect is the most common congenital cardiac malformation, comprising 30% of all cardiac defects, with an overall incidence of 3–4 per 1,000 live births. Associated malformations are common and a ventricular septal defect is frequently an integral part of other defects such as Fallot tetralogy. Defects occur most frequently in the fibrous membranous portion of the ventricular septum near the aortic valve. Endocardial cushion or atrioventricular canal defects, common in children with Down syndrome, occur in the inflow portion of the septum adjacent to the tricuspid valve. Defects in the muscular septum may be solitary or multiple. Supracristal ventricular septal defects are located in the outflow portion of the ventricle below the pulmonary valve and tend to be more common in Asian children.

The hemodynamic load resulting from a ventricular septal defect is determined by the size of the defect and the relative systemic and pulmonary vascular resistance, independent of the location of the defect. A large defect with equal ventricular pressures imposes little restriction to flow itself, and blood flow across the defect is determined by vascular resistance. Smaller defects with normal ventricular pressures limit the maximum flow across the defect even with low pulmonary vascular resistance. Small muscular defects can be completely obliterated in late systole, thus limiting blood flow to early systole. The left-to-right shunt across the ventricular septal defect imposes a volume load on the pulmonary artery, pulmonary veins, left atrium, and left ventricle, leading to dilatation and hypertrophy. Large defects associated with pulmonary and right ventricular hypertension have right ventricular hypertrophy as well.

A harsh holosystolic murmur loudest at the left lower sternal border, reflecting the turbulence of blood crossing the defect, is the most common presentation of the child with a ventricular septal defect. The clinical findings depend on the size of the defect and the pulmonary vascular resistance. A small defect is associated with a normally active precordial impulse, normal pulmonary component of the second heart sound, and a well-localized holosystolic murmur. The intensity of the murmur from a small defect is directly related to the blood flow across the defect. In contrast, the intensity of the murmur in the child with a large ventricular septal defect is not as reliable a sign of the increased hemodynamic load as the degree of precordial hyperactivity and the accentuation of the pulmonary component of the second heart sound. A single loud second heart sound implies comparable pulmonary artery and aortic pressures, and thus a large defect. A third heart sound or an apical mid-diastolic murmur reflects increased left ventricular diastolic filling.

Two-dimensional and Doppler echocardiography defines the anatomy and pathophysiology of the ventricular septal defect, including chamber size and an estimation of the pressure gradient between the right and left ventricles. The electrocardiogram is normal in children with small ventricular septal defects. Right ventricular hypertrophy indicates elevated right ventricular pressure and a larger defect, and left ventricular hypertrophy is usually found in children with greater shunts but normal right ventricular pressure. Left axis deviation suggests the presence of an endocardial cushion defect and is particularly valuable in screening children with Down syndrome for heart disease. Cardiac catheterization is rarely performed for diagnosis.

At least 25% of ventricular septal defects, including some large defects, undergo partial or complete spontaneous closure. The mechanisms of closure include adherence of the septal leaflet of the tricuspid valve and buildup of the fibrous tissue on the edge of the defect. Muscular defects may close by continued growth of the muscle around the defect. Children with large ventricular septal defects and pulmonary hypertension are at risk for the development of Eisenmenger syndrome with irreversible pulmonary vascular disease and right-to-left shunting. Occasionally, infundibular or midcavitary right ventricular outflow tract obstruction develops. Aortic regurgitation due to prolapse of a coronary cusp into the ventricular septal defect may occur, particularly in children with supracristal ventricular septal defects.

Congestive heart failure in infancy, most notably manifested by failure to thrive despite adequate caloric and diuretic therapy, and persistent pulmonary hypertension at 6 months of age are the primary indications for repair of the ventricular septal defect in early infancy. Ventricular septal defects, with the exception of apical multiple muscular defects, are primarily patched with very low mortality at any age or weight. Pulmonary artery banding in infancy with subsequent total repair in late childhood is now reserved for those children with apical muscular defects. Complications of total repair are infrequent and include acquired complete heart block and residual defects. Moderate size defects without pulmonary hypertension but with greater than twice normal pulmonary blood flow are usually repaired electively at several years of age. For children with small defects with normal pulmonary artery pressure and less than twice normal pulmonary blood flow, the only long-term risk is that of bacterial endocarditis. With the exception of antibiotic prophylaxis when appropriate, these children need no medications or restrictions.

The ductus arteriosus is an essential structure during fetal life, when more than 90% of the blood ejected by the fetal right ventricle flows through the ductus arteriosus to the descending aorta, bypassing the pulmonary arterial bed. Coincident with the expansion of the lungs and fall in the pulmonary vascular resistance following birth, the ductus arteriosus closes, and the entire right ventricular output is ejected into the pulmonary arterial bed. If the ductus arteriosus remains patent postnatally, blood flow through the ductus will usually be from the aorta to the pulmonary artery. Since the connection is open during both systole and diastole, and pulmonary artery pressure is lower than the respective aortic pressure, blood flows through the patent ductus arteriosus (PDA) in both systole and diastole (continuously). The volume overload and enlargement of the pulmonary artery, pulmonary veins, left atrium, left ventricle, and aorta are directly related to the volume of blood flowing through the PDA, which in turn is determined by the size of the PDA and the relative systemic and pulmonary vascular resistances. Only in those infants with high pulmonary vascular resistance or with restricted left ventricular outflow does blood flow from the pulmonary artery to the aorta through the ductus arteriosus. The ductus arteriosus functionally closes in most full-term infants during the first day of life, but anatomic obliteration of the ductus arteriosus does not occur until after the first week of life. A persistent PDA is uncommon in otherwise normal children. In contrast, 10–20% of premature babies with respiratory distress syndrome have a PDA, possibly as a result of hypoxia and immaturity of the ductal closure mechanisms.

The clinical presentation of the child with an isolated PDA varies with gestational age, postnatal age, the size of the ductus arteriosus, and the relative systemic and pulmonary vascular resistance. In the infant or child, a hyperactive left ventricular impulse, bounding pulses, wide pulse pressure, third heart sound, and continuous “machinery” murmur peaking in intensity at the second heart sound and loudest at the upper left sternal border are the classic physical signs of a PDA. In general, the greater the shunt through the ductus arteriosus, either due to the large caliber of the ductus arteriosus and/or low pulmonary vascular resistance, the more pronounced the physical findings. In the premature baby, the precordial activity, pulses, and third heart sound remain reliable signs of a ductus arteriosus; however, the murmur tends to be a systolic ejection murmur, often varying in intensity throughout systole.

Echocardiography permits an assessment of the hemodynamic impact of the shunt, as reflected by the extent of left atrial and ventricular enlargement, and a careful evaluation is made for other associated defects. Similar physical findings are present in infants with aortic-pulmonary collaterals or aortic-pulmonary windows. Failure to document a PDA by echocardiography should suggest one of these defects.

Spontaneous closure of a PDA after 6 months of age is unusual, and coil occlusion or surgical ligation is recommended to prevent the long-term development of pulmonary vascular disease and to decrease the risk of bacterial endocarditis. In the premature infant, spontaneous closure is more common; however, the congestive heart failure and respiratory distress may require therapy to close the ductus arteriosus. Medical management with fluid restriction and diuretics is occasionally effective. Indomethacin, a prostaglandin synthetase inhibitor, has been shown to close the ductus arteriosus in a large proportion of premature infants. Surgical ligation of the ductus arteriosus carries minimal risk even in the smallest of infants.

Natural History

1. Kidd, L., et al. Second natural history study of congenital heart defects: Results of treatment of patients with ventricular septal defects. *Circulation* 87:138–151, 1993.
   Long-term survival free of symptoms is the rule for young adults with a small unoperated ventricular septal defect or those who have had surgical closure. There was, however, a higher than expected prevalence of arrhythmias even in patients with a small ventricular septal defect.
2. Van Hare, G., et al. Twenty-five-year experience with ventricular septal defect in infants and children. *Am. Heart J.* 114:606–614, 1987.
   Reinforces the favorable natural history of many ventricular septal defects—including some moderate or large defects.
3. Moe, D., and Guntheroth, W. Spontaneous closure of uncomplicated ventricular septal defect. *Am. J. Cardiol.* 60:674–678, 1987.

Of ventricular septal defects diagnosed at birth, 45% closed spontaneously over an average of a 12-month follow-up period. Size of defect or gestational age did not affect chance of closure.

4. Ramaciotti, C., Keren, A., and Silverman, N. Importance of (perimembranous) ventricular septal aneurysm in the natural history of isolated perimembranous ventricular septal defect. *Am. J. Cardiol.* 57:268–272, 1986.
   Patients with ventricular septal defect aneurysm had a higher incidence of spontaneous closure and clinical improvement than those patients without aneurysm, suggesting that this is one mechanism of spontaneous closure. For a different view, see J. Am. Coll. Cardiol. *5:118–123, 1985.*

Diagnosis

5. Danford, D., et al. Children with heart murmurs: Can ventricular septal defect be diagnosed reliably without an echocardiogram? *J. Am. Coll. Cardiol.* 30:243–246, 1997.
   Cardiologists sometimes labeled other defects as a small ventricular septal defect and needed the echocardiogram to make a more accurate diagnosis.
6. Murphy, D., Ludomirsky, A., and Huhta, J. Continuous-wave Doppler in children with ventricular septal defect: Noninvasive estimation of interventricular pressure gradient. *Am. J. Cardiol.* 57:428–432, 1986.
   The velocity of blood flow across the defect correlates directly with the systolic pressure difference between the right and left ventricles.

Surgery and Complications

7. Kitagawa, T., et al. Techniques and results in the management of multiple ventricular septal defects. *J. Thorac. Cardiovasc. Surg.* 115:848–856, 1998.
   Closure of apical muscular ventricular septal defects is very challenging. This paper presents an encouraging surgical approach. See Am. Heart J. *138:339–344 1999, and* J. Am. Coll. Cardiol. *33:1395–1399 1999, for the early experience with catheter device closure of muscular ventricular septal defects.*
8. Hanley, F., et al. Surgical repair of complete atrioventricular canal defects in infancy: Twenty-year trends. *J. Thorac. Cardiovasc. Surg.* 106:387–394, 1993.
   Operative mortality has decreased from 25% to 3%. Long-term morbidity is related to mitral regurgitation.
9. Rhodes, L., et al. Long follow-up (to 43 years) of ventricular septal defect with audible aortic regurgitation. *Am. J. Cardiol.* 66:340–345, 1990.
   Some patients with ventricular septal defect and aortic regurgitation remain asymptomatic. When surgery is done for significant aortic regurgitation and ventricular septal defect, results appear to be best in patients under 10 years of age.
10. Cantor, W., et al. Determinants of survival and length of survival in adults with Eisenmenger syndrome. *Am. J. Cardiol.* 84:677–681, 1999.
    Congestive heart failure, arrhythmias, pregnancy, and surgery are the principal causes of death. Survival into the fourth decade is possible, although patients are often very symptomatic. See J. Thorac. Cardiovasc. Surg. *99:54–59, 1990, for results of heart-lung transplantation, and* J. Thorac. Cardiovasc. Surg. *104:1060–1066, 1992, for single lung transplant.*
11. Gersony, W., et al. Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation* 87:1121–1126, 1993.
    The size of the defect did not alter the risk of endocarditis, and surgery reduced the risk by half.

Patent Ductus Arteriosus

12. Olley, P., and Coceani, F. Lipid mediators in the control of the ductus arteriosus. *Am. Rev. Respir. Dis.* 136:218–219, 1987.
    Succinct review of the mechanism of ductal closure.
13. Reller, M., Rice, M., and McDonald, R. Review of studies evaluating ductal patency in the premature infant. *J. Pediatr.* 122:S59–62, 1993.
    Virtually all closed by 4 days in healthy pre- and full-term babies. Surfactant administration does not increase the prevalence of patent ductus arteriosus. See Am. J. Dis. Child. *145:1017–1020, 1991, and* J. Pediatr. *112:441–446, 1988, for original studies.*
14. Ing, F., and Sommer, R. The snare-assisted technique for transcatheter coil occlusion of moderate to large patent ductus arteriosus: Immediate and intermediate results. *J. Am. Coll. Cardiol.* 33:1710–1718, 1999.
    This is an excellent paper outlining the techniques, risks, and benefits of coil occlusion of patent ductus arteriosus. See Heart *81:160–161, 1999, and* Am. J. Cardiol. *83:1229–1235, 1999, for a discussion about the risk of hemolysis or left pulmonary artery obstruction.*
15. Burke, R., et al. Video-assisted thoracoscopic surgery for patent ductus arteriosus in low birth weight neonates and infants. *Pediatrics* 104:227–230, 1999.
    This is an amazing accomplishment in premature infants.

53. TETRALOGY OF FALLOT

Denver Sallee and Kenneth G. Zahka

Tetralogy of Fallot is the most common cyanotic congenital heart defect presenting after 2 weeks of age. In 1888, Fallot described the association of infundibular (subvalve) and valvar pulmonary stenosis, a large ventricular septal defect, a large aorta overriding the ventricular septum, and right ventricular hypertrophy. A variable degree of pulmonary artery hypoplasia, an atrial septal defect or foramen ovale, patent ductus arteriosus, or systemic-to-pulmonary collaterals are frequently present. The pathogenesis of the defect is unknown, although both genetic and environmental factors are occasionally identified. Extracardiac malformations also constitute an important comorbidity in about 15% of patients with tetralogy of Fallot. Examples include midline defects such as cleft and palatal deformities, genitourinary abnormalities, and skeletal deformities.

The obstruction of the right ventricular outflow reduces pulmonary blood flow and produces systemic arterial desaturation by diverting poorly oxygenated right ventricular blood across the ventricular septal defect into the ascending aorta. The extent of right-to-left shunting is determined by the relative resistance to systemic and pulmonary blood flow. While the systemic resistance is determined by the peripheral arteriolar resistance, the total resistance to pulmonary blood flow is the combination of the pulmonary infundibular, valvar, and arteriolar resistance. Increasing the systemic resistance, for example by squatting, at any given pulmonary resistance will diminish the shunting. In contrast, acutely increasing the pulmonary infundibular obstruction, such as probably occurs with the release of endogenous catecholamine, will exacerbate the shunting. Additional pulmonary blood flow coming through a patent ductus arteriosus or systemic-to-pulmonary collateral vessels will tend to modulate these acute fluctuations due to infundibular contractility as well as the chronic status produced by the overall pulmonary obstruction.

The spectrum of the clinical presentation of tetralogy of Fallot is directly related to the severity of the pulmonary stenosis. The intensely cyanotic newborn generally has very severe pulmonary stenosis or atresia and markedly diminished pulmonary blood flow, while the minimally or even acyanotic child being evaluated for a systolic murmur has just enough pulmonary stenosis to prevent a left-to-right shunt through the ventricular septal defect without producing a right-to-left shunt. Episodic cyanosis is common even in children who are generally acyanotic. These cyanotic spells are frequently seen in the first months to year of life and are characterized by intense cyanosis, hyperpnea, and change in mental status.

There is usually a palpable right ventricular impulse reflecting the right ventricular hypertension, and a single second heart sound with an absent pulmonary component due to the anterior location of the aorta and the marked abnormality of the pulmonary outflow tract. The systolic ejection murmur heard in children with tetralogy of Fallot is produced by turbulent blood flow across the pulmonary stenosis; therefore, the intensity of the murmur is directly related to the amount of pulmonary blood flow and inversely related to the severity of the pulmonary obstruction. Absence of a systolic ejection murmur in children with tetralogy of Fallot implies atresia of the right ventricular outflow tract. In this case, a continuous murmur will indicate blood flow through a patent ductus arteriosus or systemic-to-pulmonary collaterals as the sole source of pulmonary blood flow.

The anatomic diagnosis of tetralogy of Fallot may be established by two-dimensional echocardiography. Of particular importance, in addition to the documentation of the sites of pulmonary obstruction and the ventricular septal defect, is a determination of the size of the main and branch pulmonary arteries and the presence of a patent ductus arteriosus or collaterals. Doppler echocardiography is useful to estimate the right ventricular outflow tract pressure gradient. The electrocardiogram shows right ventricular hypertrophy, and the chest x-ray typically reveals a “boot-shaped” heart and decreased pulmonary vascularity. After the newborn period, polycythemia is a useful sign of the degree of chronic hypoxia. Cardiac catheterization may be performed prior to surgery to define coronary and branch pulmonary artery anatomy.

Newborns with severe cyanosis are stabilized by an infusion of prostaglandin $_1$ to dilate the ductus arteriosus and increase pulmonary blood flow. These newborns often have severely hypoplastic pulmonary arteries and must have a palliative procedure to establish a source of pulmonary blood flow. These include a systemic-to-pulmonary shunt, either a direct connection of the subclavian artery to the pulmonary artery (Blalock-Taussig shunt) or a synthetic tubular graft (Gore-Tex) between the aorta or one of its branches and the pulmonary artery. Alternatively, the right ventricular outflow tract may be widened surgically without closing the ventricular septal defect. Neonatal repair of tetralogy of Fallot is feasible for babies with appropriate pulmonary artery anatomy.

Cyanotic spells must be recognized and treated promptly, since there is a risk of stroke or death if a spell is prolonged. Some infants respond simply to soothing; others require increasing the systemic resistance with the knee-chest position or sedation with morphine. Intravenous propranolol or phenylephrine is a rapid and generally reliable means of terminating a spell.

Surgical repair of tetralogy of Fallot consists of closure of the ventricular septal defect, excision of the pulmonary stenosis, and enlargement of the right ventricular outflow tract with a patch. In the absence of marked pulmonary artery hypoplasia or unfavorable coronary artery anatomy, surgery can be undertaken at virtually any age. The specific indications for surgery are increasing cyanosis, cyanotic spells, or electively by age 1 year. The risk of total repair is low, and the long-term results are excellent. Residual pulmonary stenosis and regurgitation are common but well tolerated. Balloon dilation and stenting of branch pulmonary artery stenoses may improve the distribution of pulmonary blood flow and lower right ventricular pressure. Postoperative ventricular arrhythmias may be symptomatic and require pharmacologic suppression but tend to be less frequent in patients repaired in the first decade of life.

Anatomy and Natural History

1. Anderson, R., et al. Surgical anatomy of tetralogy of Fallot. *J. Thorac. Cardiovasc. Surg.* 81:887–896, 1981.
   A thorough analysis of the anatomy. See Am. J. Cardiol. *26:25–33 1970, for a discussion on the role of the underdevelopment of the infundibulum in the pathogenesis of tetralogy of Fallot.*
2. Kothari, S. Mechanism of cyanotic spells in tetralogy of Fallot—The missing link? *Int. J. Cardiol.* 37:1–5, 1992.
   Spells may be mediated through changes in contractility due to endogenous catecholamines or exacerbated by hypovolemia.
3. Clark, D. Brain abscess in congenital heart disease. *Clin. Neurosurg.* 14:274–87, 1966.
   The differential diagnosis is outlined.

Medical Management

4. Garson, A., Gillette, P., and McNamara, D. Propranolol: The preferred palliation for tetralogy of Fallot. *Am. J. Cardiol.* 47:1098–1102, 1981.
   Surgical repair is the preferred treatment for most infants. Administration of propranolol may permit scheduling of elective repair or palliate the infant for whom early surgery is not feasible.
5. Nudel, D., Berman, M., and Talner, N. Effects of acutely increasing systemic vascular resistance on oxygen tension in tetralogy of Fallot. *Pediatrics* 58:248–251, 1976.
   The pharmacologic equivalent of squatting.

Surgical Management and Follow-up

6. Gladman, G., et al. The modified Blalock-Taussig shunt: Clinical impact and morbidity in Fallot's tetralogy in the current era. *J. Thorac. Cardiovasc. Surg.* 114: 25–30, 1997.
   Distortion of the pulmonary artery was noted in 33% of patients who had undergone a previous modified Blalock-Taussig shunt.
7. Reddy, V., et al. Routine primary repair of tetralogy of Fallot in neonates and infants less than three months of age. *Ann. Thorac. Surg.* 60:S592–596, 1995.
   Current surgical survival, even for symptomatic infants less than 3 months of age, is excellent. Hospital or 1-month survival rates of 100% can be achieved in this patient population. See J. Thorac. Cardiovasc. Surg. *109:332–342, 1995, for another excellent series that found a 25% incidence of second procedures after neonatal repair.*
8. Kreutzer, J., et al. Tetralogy of Fallot with diminutive pulmonary arteries: Preoperative pulmonary valve dilation and transcatheter rehabilitation of pulmonary arteries. *J. Am. Coll. Cardiol.* 27:1741–1747, 1996.
   Improvement in antegrade flow is thought to enhance pulmonary arterial growth by augmenting pulmonary blood flow. This approach avoids any possible surgical complications and/or pulmonary artery distortion that may be seen following a modified Blalock-Taussig shunt. It is usually reserved for infants with poor surgical anatomy or as part of a staged surgical and intervention approach. See J. Am. Coll. Cardiol. *31:661–667, 1998, for the results of stent placement in branch pulmonary arteries.*
9. Zahka, K., et al. Long-term valvular function after total repair of tetralogy of Fallot: Relation to ventricular arrhythmias. *Circulation* 78:III–14, 1988.
   Pulmonary and tricuspid regurgitation are common and usually tolerated well. More serious ventricular arrhythmias are associated with more severe grades of pulmonary regurgitation.

10. Gatzoulis, M., et al. Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Restrictive physiology predicts superior exercise performance. *Circulation* 91:1775–1781, 1995.
Exercise performance and oxygen consumption are better in patients with restrictive right ventricular physiology compared to those without antegrade pulmonary flow during atrial systole.
11. Knott-Craig, C., et al. A 26-year experience with surgical management of tetralogy of Fallot: Risk analysis for mortality or late reintervention. *Ann. Thorac. Surg.* 66:506–511, 1998.
This review demonstrates a long-term favorable outcome for single-stage early repair via a transatrial approach. See J. Thorac. Cardiovasc. Surg. *116:770–779, 1998, for a discussion of the usefulness of this approach in patients with aberrant coronary arteries.*
12. Sullivan, I., et al. Is ventricular arrhythmia in repaired tetralogy of Fallot an effect of operation or a consequence of the course of the disease? A prospective study. *Br. Heart J.* 58:40–44, 1987.
Ventricular arrhythmias following repair were strongly related to age greater than 10 years at the time of repair.
13. Chandar, J., et al. Ventricular arrhythmias in post operative tetralogy of Fallot. *Am. J. Cardiol.* 65:655–661, 1990.
Risk factors for inducible ventricular tachycardia included older age at time of repair, longer follow-up, a history of syncope or presyncope, and high right ventricular pressure.
14. Cullen, S., et al. Prognostic significance of ventricular arrhythmia after repair of tetralogy of Fallot: A 12-year prospective study. *J. Am. Coll. Cardiol.* 23:1151–1155, 1994.
Nonsustained ventricular arrhythmia on ambulatory electrocardiography did not identify patients at high risk for sudden death. They do not recommend long-term antiarrhythmic therapy for asymptomatic postoperative patients. See Heart *81: 650–655, 1999, for a study indicating that QT dispersion is helpful in identifying patients with serious ventricular arrhythmias, and* J. Am. Coll. Cardiol. *2:245–251, 1998, for a population-based study that shows a 4% 25-year risk of sudden death.*
15. Conte, S., et al. Homograft valve insertion for pulmonary regurgitation late after valveless repair of right ventricular outflow tract obstruction. *Eur. J. Cardiothorac. Surg.* 15:143–149, 1999.
This is an important issue for patients with abnormal pulmonary arteries. Early valve placement may preserve right ventricular function.
16. Wessel, H., and Paul M. Exercise studies in tetralogy of Fallot: A review. *Pediatr. Cardiol.* 20:39–47, 1999.
A comprehensive review of exercise testing in patients with tetralogy of Fallot, analyzing data from over 87 studies including 3,000 patients. Maximum oxygen consumption was 81% of normal and work capacity was 85% of normal.

54. TRANSPOSITION OF THE GREAT ARTERIES

Denver Sallee and Kenneth G. Zahka

Transposition of the great arteries is the most common congenital heart defect presenting with severe cyanosis in the first week of life. Although there are frequently associated defects, the anatomic abnormality in transposition of the great arteries is the connection of the aorta to the right ventricle and of the pulmonary artery to the left ventricle. Right ventricular pressure is high due to the high vascular resistance in the aorta and systemic vasculature, and left ventricular pressure is low due to the low pulmonary vascular resistance. In contrast to the blood flow pattern in the normal heart, in which the pulmonary and systemic circulations are in series, in transposition of the great arteries the pulmonary and systemic circulations are in parallel. Thus, venous blood returning to the right atrium flows through the tricuspid valve into the right ventricle and is ejected into the aorta, supplying the body with poorly oxygenated blood, which then returns to the right atrium to repeat the cycle. Fully oxygenated blood from the lungs enters the left atrium, flows through the mitral valve into the left ventricle, and is ejected into the pulmonary artery to perfuse the lungs and return to the left atrium without delivering oxygen to the body. In the absence of shunting across connections between the systemic and pulmonary circulations, this results in profound and lethal systemic hypoxia. The persistence of two fetal connections, the foramen ovale and the ductus arteriosus, provides sites for intracardiac shunting during the first hours and days of life. Following spontaneous closure of the ductus arteriosus, bidirectional shunting at the atrial level is essential for survival.

The intensity of cyanosis and the presence of additional signs of heart disease in infants with transposition of the great arteries are modified by the presence of associated defects. A ventricular septal defect provides an additional site for intracardiac mixing to improve systemic oxygenation. However, large ventricular septal defects in infants with transposition of the great arteries produce excessive pulmonary blood flow and pressure with resultant congestive heart failure. In contrast, pulmonary stenosis with a ventricular septal defect diminishes pulmonary blood flow and intensifies the systemic desaturation. The combination of coarctation of the aorta and transposition of the great arteries produces both hypoxia and poor distal organ perfusion.

The diagnosis of transposition of the great arteries should be considered in any cyanotic newborn. Respiratory symptoms are absent or limited to hyperpnea or tachypnea without dyspnea. Perinatal asphyxia, meconium aspiration, or pneumonia may alter this presentation and produce signs of the secondary process. The second heart sound is persistently single in transposition of the great arteries due to the anterior position of the aorta and the posterior position of the pulmonary artery. A holosystolic murmur suggests an associated ventricular septal defect; a systolic ejection murmur is heard with pulmonary stenosis. In the absence of these associated defects, murmurs are typically not heard. The peripheral pulses are normal unless coarctation of the aorta is present.

The electrocardiogram shows right ventricular hypertrophy, indistinguishable in the first week of life from the right ventricular hypertrophy present in the normal newborn. Similarly the classic “egg-shaped” heart with increased pulmonary vascularity on the chest x-ray may not be seen in the newborn period. Two-dimensional echocardiography provides a definitive diagnosis of transposition of the great arteries and its associated defects. Doppler echocardiography documents patterns of blood flow across the atrial, ventricular, and ductal communications, and the pulmonary valve.

Establishing patency of the ductus arteriosus with prostaglandin $_1$ in newborns with transposition of the great arteries frequently improves arterial oxygenation by increasing shunting from the aorta into the pulmonary artery. This, in turn, increases the pulmonary venous return, distending the left atrium, and facilitating left atrial to right atrial shunting of fully saturated blood across the foramen ovale. If this does not result in adequate systemic oxygenation or if long-term patency of the atrial defect is required, a balloon atrial septostomy is performed. At cardiac catheterization, a balloon tipped catheter is advanced from the inferior vena cava into the right atrium and through the foramen ovale to the left atrium. The balloon is inflated with dilute radio graphic contrast medium. Then the catheter is sharply tugged, rapidly withdrawing the inflated balloon from the left atrium to the junction of the right atrium and in ferior vena cava. This tears the atrial septum, enlarging the foramen ovale into an atrial septal defect and allowing improved mixing of the systemic and pulmonary venous return at the atrial level.

Surgical management of transposition of the great arteries has changed dramatically during the last 50 years and, in particular, during the last 15 years. Surgical creation of an atrial septal defect using the technique described by Blalock and Hanlon in 1950 was eventually replaced by the atrial baffling operations described by Senning in 1959 and Mustard in 1964. In these operations, the arterial and ventricular connections remained transposed and the venous inflow into the atria was redirected. The superior and inferior vena caval blood was tunneled across the atrium to the mitral valve and the pulmonary veins directed to the tricuspid valve. This physiologic repair resulted in fully oxygenated blood in the right ventricle and aorta and poorly oxygenated blood in the left ventricle and pulmonary artery; however, the anatomic ventriculoarterial relationships of the heart remained abnormal. Long-term postoperative problems included atrial arrhythmias, pulmonary and systemic venous obstruction, and right ventricular enlargement and dysfunction.

Jantene and later Yacoub pioneered the anatomic repair of transposition of the great arteries using the arterial switch operation. This operation requires transection of the aorta and pulmonary artery to move the pulmonary artery anteriorly to the right ventricle and the aorta posteriorly to the left ventricle. The coronary arteries are moved from their original position on the aorta to the newly created aorta, and atrial and ventricular septal defects are repaired. The arterial switch operation in infants with transposition of the great arteries with an intact ventricular septum is optimally performed in the first 2 weeks of life. During this time, the left ventricle has sufficient hypertrophy to support systemic blood pressure. After 2 weeks, unless there is a large ventricular septal defect, left ventricular pressure is low, and the left ventricular muscle mass has regressed in a similar fashion to that of the right ventricle in children with normally related great arteries. The follow-up to date for the arterial switch operation is favorable, with evidence of excellent ventricular function, normal rhythm, and a low incidence of obstruction at the pulmonary, aortic, and coronary suture lines.

Natural History

1. Liebman, J., Cullman, L., and Belloc, N. Natural history of transposition of the great arteries: Anatomy and birth and death characteristics. *Circulation* 40: 237–262, 1969.
   Before the introduction of corrective surgery, 90% of infants with this defect died in the first year.
2. Newfeld, E., et al. Pulmonary vascular disease in complete transposition of the great arteries: A study of 200 patients. *Am. J. Cardiol.* 34:75–82, 1974.
   A large ventricular septal defect or patent ductus arteriosus reduces cyanosis but leads to serious pulmonary vascular disease, often in the first year.
3. Becker, T., et al. Occurrence of cardiac malformations in relatives of children with transposition of the great arteries. *Am. J. Med. Genet.* 66:28–32, 1996.
   The overall recurrence risk of cardiac malformations in siblings of transposition of the great arteries probands was 0.82%.
4. Bonnet, D., et al. Detection of transposition of the great arteries in fetuses reduces neonatal morbidity and mortality. *Circulation* 99:916–918, 1999.
   This is one of the few studies that demonstrate the benefit of fetal diagnosis. See J. Am. Coll. Cardiol. *32:753–757, 1998, for an analysis of preoperative mortality.*

Atrial Septostomy

5. Jamjureeruk, V., Sangtawesin, C., and Layangool, T. Balloon atrial septostomy under two-dimensional echocardiographic control: A new outlook. *Pediatr. Cardiol.* 18:197–200, 1997.
   It is safe and feasible, and uses fewer resources. See Circulation *38:453–462, 1968, for the original description of balloon atrial septostomy.*
6. Lee, M., et al. Echocardiographic features of left juxtaposed atrial appendages associated with dextro-transposition of the great arteries. *Pediatr. Cardiol.* 17:63–66, 1996.
   You really donÕt want to blow up the balloon in the wrong place.
7. Satomi, G., et al. Blood flow pattern of the interatrial communication in patients with complete transposition of the great arteries: A pulsed Doppler echocardiographic study. *Circulation* 73:95–99, 1986.
   Bidirectional shunting at the atrial level without patent ductus arteriosus or ventricular septal defect; left-to-right shunt at the atrial level with patent ductus arteriosus or ventricular septal defect.

Atrial Repair and Follow-Up

8. Sarkar, D., et al. Comparison of long-term outcomes of atrial repair of simple transposition with implications for a late arterial switch strategy. *Circulation* 100(Suppl. II):176–181, 1999.
   This study demonstrated that late outcomes after the Senning operation were better than the Mustard operation. Both groups had late sudden deaths that were not in patients with clinical systemic ventricular failure. See J. Am. Coll. Cardiol. *32:758–765, 1998, for another excellent long-term follow-up study.*
9. Hurwitz, R., et al. Right ventricular systolic function in adolescents and young adults after Mustard operation for transposition of the great arteries. *Am. J. Cardiol.* 77:294–297, 1996.
   Right ventricular function was abnormal in only 16% of those followed for more than 10 years. Right ventricular function does appear to deteriorate in about 20% on long-term follow-up.

10. Gelatt, M., et al. Arrhythmia and mortality after the Mustard procedure: A 30-year single-center experience. *J. Am. Coll. Cardiol.* 29:194–201, 1997.
Sinus rhythm was present in 77% at 5 years but only in 40% at 20 years. Atrial flutter was present in 27% at 20 years of age. See Am. J. Cardiol. *77:985–991, 1996, for radiofrequency ablation of atrial flutter in these patients.*
11. Paul, M., and Wessel, H. Exercise studies in patients with transposition of the great arteries after atrial repair operations (Mustard/Senning): A review. *Pediatr. Cardiol.* 20:49–55, 1999.
This paper reviews all the previous work on exercise after the atrial repair and concludes that, despite most patients reporting few symptoms with exercise, there are significant exercise testing abnormalities in many patients compared to control subjects, including diminished exercise performance and a blunted heart rate response.
12. Genoni, M., et al. Pregnancy after atrial repair for transposition of the great arteries. *Heart* 81:276–277, 1999.
Pregnancy was uncomplicated in women with normal cardiac functional status.

Arterial Repair and Follow-Up

13. Serraf, A., et al. Anatomic correction of transposition of the great arteries in neonates. *J. Am. Coll. Cardiol.* 22:193–200, 1993.
A report of more than 400 babies at one center, with 5-year survival 91% in transposition of the great arteries with intact septum. The mortality was 13% for transposition of the great arteries with coarctation. See Pediatr. Cardiol. *19:297–307, 1998, for data from the same group.*
14. Mayer, J., et al. Coronary artery pattern and outcome of arterial switch operation for transposition of the great arteries. *Circulation* 82(Suppl. IV):139–145, 1990.
Single right coronary artery, intramural coronary arteries, and commissural origin of the coronary arteries are risk factors for death or ischemia. See J. Thorac. Cardiovasc. Surg. *104:706–712, 1992.*
15. Lacour-Gayet, F., et al. Biventricular repair of conotruncal anomalies associated with aortic arch obstruction: 103 Patients. *Circulation* 96:II-328–334, 1997.
This experience includes 59 patients with transposition of the great arteries and coarctation or interrupted aortic arch. It is a particularly challenging group of patients with an operative mortality of 10–20% even in the best hands.
16. Nogi, S., et al. Fate of the neopulmonary valve after the arterial switch operation in neonates. *J. Thorac. Cardiovasc. Surg.* 115:557–562, 1998.
One quarter developed supravalvular pulmonary stenosis, and half of those had associated pulmonary valve stenosis. See Eur. J. Pediatr. *157:95–100, 1998, for evidence that the Lecompte maneuver results in flattening of the main pulmonary artery and some degree of branch pulmonary artery hypoplasia.*
17. Massin, M., et al. Results of the Bruce treadmill test in children after arterial switch operation for simple transposition of the great arteries. *Am. J. Cardiol.* 81:56–60, 1998.
Exercise testing is normal if the coronary perfusion is normal.
18. Bellinger, D., et al. Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *Circulation* 100:526–532, 1999.
Circulatory arrest is associated with worse motor coordination and planning, but not with lower IQ or worse overall neurological status in patients assessed at 4 years of age. Look for more data coming out of this important prospective study of the neurologic outcome following the arterial switch operation. See Circulation *97: 773–779, 1998, for a separate analysis of the prognostic risk of postoperative seizures.*

55. ARRHYTHMIAS

Kenneth G. Zahka

The origination of the normal heart beat is at the sinus node, which is located at the junction of the superior vena cava and the right atrium. The cells in the sinus node depolarize spontaneously at the fastest rate of any of the specialized conducting tissue and are the normal pacemaking cells. The impulse is then carried across the atria to the atrioventricular node, into the bundle of His, and across the ventricular myocardium. The coordination of sequential atrial and ventricular contraction is largely the result of delay in conduction of the impulse through the atrioventricular node. On the standard surface electrocardiogram (ECG), the P wave corresponds to the sinus node depolarization, the PR segment to the delay at the atrioventricular node and His-Purkinje system, the QRS complex to the spread of the impulse over the ventricles, and the T wave to repolarization of the ventricles. With advancing age, there is a general slowing of heart rate and prolongation of conduction times; thus, the definition of normal is age dependent.

Arrhythmias are frequently detected during auscultation of the heart but may also be suspected because of palpitations, chest pain, dizziness, syncope, or, in the infant, feeding difficulties. A family history of syncope suggests one of the long QT syndromes, in which prolonged ventricular repolarization is associated with ventricular arrhythmias. Mitral valve prolapse is associated with both ventricular and atrial arrhythmias, and frequently is familial. A history of excessive caffeine intake, sympathomimetic medications, or cocaine abuse not only provides an etiology for arrhythmias, but also suggests appropriate therapy. The temporal association of the symptom caused by the arrhythmia with exercise suggests either tachycardia precipitated by the sympathetic response to exercise or an inadequate heart rate response to exercise.

The frequency and duration of the arrhythmia are particularly important when deciding how to evaluate and treat the child. Examination of the child during the arrhythmia provides the opportunity to assess its hemodynamic impact; at other times, an underlying cardiac etiology such as mitral valve prolapse or myocarditis may be evident from the examination.

Precise diagnosis of arrhythmias requires recording the ECG during the event. This can be accomplished by a routine 12-lead ECG if the arrhythmia is persistent, or 24-hour ambulatory recordings or event monitor recordings if it is episodic. Exercise stress testing is particularly valuable for older children with exercise-induced symptoms. More invasive techniques, including esophageal ECGs and electrophysiologic catheter studies, are available for more complex problems. The echocardiographic assessment of ventricular function is important in children with chronic tachycardia, or those with myocarditis as a possible etiology for their arrhythmia.

The acceleration of heart rate during inspiration is termed *sinus arrhythmia* and is a normal phenomenon in children; it is due to changes in vagal tone with respiration. Occasional premature atrial or ventricular beats are also common and, in a child with an otherwise normal cardiovascular system, are normal. Similarly, bradycardia at rest or during sleep must be interpreted in view of symptoms and the degree of aerobic physical conditioning.

Supraventricular tachycardia (SVT) is the most common rapid rhythm in children from the middle of fetal life through adolescence. The mechanism of the tachycardia is usually a reentry of the electrical impulse back into the conducting system either through an accessory pathway (Wolff-Parkinson-White syndrome) or within the atrioventricular node itself. It occurs in otherwise normal children, in children with congenital heart disease or myocarditis, and in children receiving sympathomimetic medications. For many children, the tachycardia is only an annoyance that happens infrequently and lasts only a few seconds; the appropriate treatment is reassurance that the heart is healthy and that the arrhythmia does not pose a danger. For others, especially infants and children with complex congenital heart defects, SVT can cause severe congestive heart failure. The maximum rate of the tachycardia is 330 beats per minute (bpm) in infants, and 200 bpm in older children. Blood pressure and perfusion are initially normal; however, over a period of hours, the child develops increasing signs of poor cardiac output, with poor perfusion, a gallop rhythm, and hepatomegaly. During the tachycardia, the ECG shows that the heart rate varies little with respiration, the QRS complex is usually normal, and P waves, if present, are superimposed on the T waves. When the child is not in tachycardia, the ECG either is normal or shows the short PR interval and slurred upstroke of the QRS complex typical of Wolff-Parkinson-White syndrome.

Treatment of SVT must be tailored to the childÕs hemodynamic status. If the child is hemodynamically stable or while preparations are being made for other therapy, maneuvers to increase vagal tone, including gagging, Valsalva maneuver, or carotid massage, may be tried. Brief facial stimulation with a cold, wet cloth or ice pack stimulates the “diving reflex” and produces a marked vagal stimulus that is particularly effective in terminating the tachycardia in infants. Intravenous adenosine has become the treatment of choice for the termination of SVT. It is highly effective, and the bradycardia that follows its administration is brief. If this fails or if vascular access is difficult and the child is ill, the SVT should be electrically converted by synchronized direct current countershock. In selected patients, atrial overdrive pacing using an esophageal or transvenous lead is another frequently effective technique for terminating the tachycardia.

Many drugs are effective for the short- and long-term management of SVT. There is extensive clinical experience with digoxin for the treatment of SVT in children. Its major drawback is a relatively slow onset of action, even when given intravenously. It remains useful for the acute treatment of infants without clinical evidence of congestive heart failure and is effective in chronic treatment, with few side effects. It is relatively contraindicated in children with Wolff-Parkinson-White syndrome due to the unpredictable effect of the refractory period of the accessory pathway. There is a risk of rapid ventricular conduction and ventricular fibrillation if the child with Wolff-Parkinson-White syndrome develops atrial fibrillation while taking digoxin. The calcium channel blocker verapamil has more side effects than adenosine and is no longer the intravenous drug of choice for the treatment of acute, symptomatic episodes of SVT. It is not recommended for children younger than age 1 year because of a high incidence of severe hypotension associated with its use, nor should it be given in combination with intravenous propranolol. Phenylephrine increases blood pressure and provokes a reflex increase in vagal tone, while edrophonium is a direct vagal stimulant; bradycardia and hypertension are side effects that limit the use of both drugs. Drugs used for the prevention of recurrences of SVT include propranolol, sotalol, quinidine, and amiodarone. The efficacy and side effects of each drug *must* be carefully considered prior to starting therapy. Serum drug levels should be monitored when applicable during therapy. Radiofrequency catheter ablation is the treatment of choice for most children with persistent supraventricular arrhythmias.

The long-term prognosis of SVT in infancy is good. Many infants, including some with accessory pathways, have only a single episode, and treatment is discontinued by age 1 year. Persistent bouts of tachycardia are more typical when SVT has its onset in older children. Pharmacologic suppression of the arrhythmia is effective but may require multiple drugs and be associated with more side effects. Electrophysiologic testing is particularly useful in these children to define the mechanism of the tachycardia. For those children with either identifiable bypass tracts or with ectopic foci in the atria, radiofrequency catheter ablation of the tract or the ectopic foci frequently provides a long-term solution with freedom from medication and tachycardia.

Ventricular arrhythmias are most frequent in children with myocarditis and following cardiac surgery, although they also occur in normal newborns, infants, and children. Isolated premature ventricular beats, especially those that are unifocal and suppressed by exercise, have a good prognosis and require no treatment. Children with ventricular couplets and nonsustained runs of asymptomatic ventricular tachycardia must be evaluated on an individual basis to determine the best treatment plan. Sustained and symptomatic ventricular tachycardia is treated acutely by electrical cardioversion with 1–2 watt-seconds/kg or by intravenous lidocaine. Phenytoin, quinidine, procainamide, sotalol, or amiodarone is used for chronic suppression.

Abnormalities of ventricular repolarization, manifested by prolongation of the QT interval on the resting or exercise ECG, are a rare but extremely important cause of syncope and ventricular arrhythmias. This syndrome may be sporadic or familial, and in some children is associated with congenital deafness. Syncope or sudden death due to ventricular tachycardia (torsades de pointes) typically occurs with sudden exercise or startling. Some drugs used to treat ventricular arrhythmias, particularly quinidine and procainamide, exacerbate this problem by prolonging repolarization; propranolol is probably the drug of choice in these children. Drugs that

prolong repolarization, such as erythromycin and cisapride, may produce ventricular tachycardia and are contraindicated in these patients.

Bradycardia results from heart block or sinus node dysfunction. Congenital heart block frequently is diagnosed now in utero and confirmed by fetal echocardiography. It is associated with maternal connective tissue disorders. In the absence of congenital heart disease, the ventricular rate is adequate for normal growth and activity through early childhood and adolescence. Acquired complete heart block following cardiac surgery is often transient and is managed by temporary pacing. Sinus node dysfunction occurs in as many as 30% of children following atrial repair of transposition of the great arteries, and in a small number of children as a spontaneous event. Permanent atrial, ventricular, or atrioventricular sequential pacing is indicated for evidence of dizziness or syncope, especially with exercise or congestive heart failure with progressive ventricular dilatation. Implantable pacemakers are now miniaturized, are programmable by telemetry, and respond to increased activity with an increase in heart rate. Pacemaker failure in children is most often due to lead failure or to infection. The prognosis for a child with symptomatic bradycardia requiring a pacemaker is dictated by the associated cardiovascular abnormalities.

Reviews

1. Garson, A. Medicolegal problems in the management of cardiac arrhythmias in children. *Pediatrics* 79:84–88, 1987.
   Remains interesting reading.

Supraventricular Arrhythmias

2. Perry, J., and Garson, A. Supraventricular tachycardia due to Wolff-Parkinson-White syndrome in children: Early disappearance and late recurrence. *J. Am. Coll. Cardiol.* 16:1215–1220, 1990.
   When supraventricular tachycardia (SVT) due to Wolff-Parkinson-White (WPW) syndrome presented at less than 2 months, it persisted in only 7%. If the first presentation was in childhood, over 75% had persistent tachycardia.
3. Deal, B., et al. Wolff-Parkinson-White syndrome and supraventricular tachycardia during infancy: Management and follow-up. *J. Am. Coll. Cardiol.* 5:130–135, 1985.
   Ninety infants presenting in the first 4 months of life. Digoxin is very effective for the acute management of SVT in the WPW syndrome. Propranolol is suggested for chronic therapy. The WPW syndrome disappeared on the surface electrocardiogram (ECG) in 36%, but some still had episodes of tachycardia.
4. Kugler, J., and Danford, D. Management of infants, children, and adolescents with paroxysmal supraventricular tachycardia. *J. Pediatr.* 129:324–338, 1996.
   Outlines a treatment algorithm based on symptoms and natural history. See Am. Heart J. *133:130–131, 1997, for predictors of successful treatment withdrawal, and* Am. J. Cardiol. *82:72–75, 1998, for a reassuring approach.*
5. Losek, J., et al. Adenosine and pediatric supraventricular tachycardia in the emergency department: Multicenter study and review. *Ann. Emerg. Med.* 33:185–191, 1999.
   Doses between 0.1 and 0.3 mg/kg were effective 80% of the time in the emergency department setting.
6. Luedtke, S., Kuhn, R., and McCaffrey, F. Pharmacologic management of supraventricular tachycardias in children. Part 1: Wolff-Parkinson-White and atrioventricular nodal reentry. *Ann. Pharmacother.* 31:1227–1243, 1997; and Luedtke, S., Kuhn, R., and McCaffrey, F. Pharmacologic management of supraventricular tachycardias in children, part 2: Atrial flutter, atrial fibrillation, and junctional and atrial ectopic tachycardia. *Ann. Pharmacother.* 31:1347–1359, 1997.
   These studies comprehensively review the available data for the pharmacologic treatment of children with arrhythmias. They stress the paucity of well-controlled trials to define best therapy.
7. Garson, A., et al. Atrial flutter in the young: A collaborative study of 380 cases. *J. Am. Coll. Cardiol.* 6:871–878, 1985.
   This study reviews clinical presentation, management, and prognosis for these patients. See Pediatrics *75:725–729, 1985, and 75:730–736, 1985, for information about transesophageal atrial pacing for the diagnosis and treatment of atrial flutter.* Am. Heart J. *133:302–306, 1997, reinforces the excellent prognosis of isolated atrial flutter in infancy.*
8. Fishberger, S., et al. Factors that influence the development of atrial flutter after the Fontan operation. *J. Thorac. Cardiovasc. Surg.* 113:80–86, 1997.
   This is a special group of patients who have significant morbidity and mortality from this complication. See Circulation *98:II352–358, 1998, for sick sinus syndrome after the Fontan procedure.*

Ventricular Arrhythmias

9. Van Hare, G., and Stanger, P. Ventricular tachycardia and accelerated ventricular rhythm presenting in the first month of life. *Am. J. Cardiol.* 67:42–45, 1991.
   Hemodynamic compromise does not occur in the very young when the ventricular tachycardia rate is just (12%) greater than the sinus rate. Treatment is not necessarily indicated.
10. Wiles, H., et al. Cardiomyopathy and myocarditis in children with ventricular ectopic rhythm. *J. Am. Coll. Cardiol.* 20:359–362, 1992.
    Abnormal histologic findings, including myocarditis, were found in 42% of children with ventricular tachycardia. Prior to biopsy, they were thought to have normal hearts.
11. Noh, C., et al. Clinical and electrophysiological characteristics of ventricular tachycardia in children with normal hearts. *Am. Heart J.* 120:1326–1333, 1990.
    Paced ventricular extrastimuli and isoproterenol infusion could provoke ventricular tachycardia in a large proportion of patients with negative exercise tests and baseline pacing studies. See J. Am. Coll. Cardiol. *16:681–685, 1990, for treatment of incessant ventricular tachycardia.*
12. Driscoll, D., and Edwards, W. Sudden and unexpected death in children and adolescents. *J. Am. Coll. Cardiol.* 5:118B-121B, 1985.
    See J. Am. Coll. Cardiol. *5:122B-129B, 130B-133B, 134B-137B, and 138B-140B, 1985. This is a group of articles analyzing the relationship between ventricular and atrial arrhythmias in children and sudden death. They stress the importance of not overtreating the child with a fundamentally healthy heart, and review management for children with heart disease at high risk. See* Circulation *85:I64-69, 1992.*
13. Bricker, J., et al. Exercise-related ventricular tachycardia in children. *Am. Heart J.* 112:186–188, 1986.
    Twenty-two children with a variety of diagnoses (including five with normal hearts) had ventricular tachycardia either during or following exercise tests.

Complete Congenital Heart Block

14. Buyon, J., et al. Autoimmune-associated congenital heart block: Demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J. Am. Coll. Cardiol.* 31:1658–1666, 1998.
    This analysis of over 100 infants demonstrated a 20% mortality in the first 3 months. Many infants and young children were paced, but few had structural heart disease. The recurrence risk for subsequent pregnancies is up to three-fold higher in mothers who are antibody positive and have had an affected child. Most mothers without clinical disease stay well (Am. J. Med. *100:328–332, 1996).*
15. Saleeb, S., et al. Comparison of treatment with fluorinated glucocorticoids to the natural history of autoantibody-associated congenital heart block: Retrospective review of the research registry for neonatal lupus. *Arthritis Rheum.* 42:2335–2345, 1999.
    It may help prevent progression of incomplete block or prevent cardiomyopathy and hydrops.
16. Michaelsson, M., Riesenfeld, T., and Jonzon, A. Natural history of congenital complete atrioventricular block. *Pacing Clin. Electrophysiol.* 20:2098–2101, 1997.
    Stresses the variability of the disease and makes specific recommendations for pacing based on clinical and ECG criteria.

Fetal Arrhythmias

17. Naheed, Z., et al. Fetal tachycardia: Mechanisms and predictors of hydrops fetalis. *J. Am. Coll. Cardiol.* 27:1736–1740, 1996.
    Hydrops was most common with sustained tachycardia in young fetuses.
18. Simpson, J., et al. Outcome of intermittent tachyarrhythmias in the fetus. *Pediatr. Cardiol.* 18:78–82, 1997.
    This study suggests that even in some fetuses where the tachycardia is intermittent, hydrops can develop. They recommend and have considerable success with maternal treatment.

Long QT Syndrome

19. Garson, A., et al. The long QT syndrome in children: An international study of 287 patients. *Circulation* 87:1866–1872, 1993.
    *These children are at risk for ventricular tachycardia with torsades de pointes. In this study, 9% presented with cardiac arrest and no preceding symptoms. Long QT is an unusual cause for seizures (*Am. J. Dis. Child. *140:659–661, 1986).*
20. Maron, B., et al. Impact of laboratory molecular diagnosis on contemporary diagnostic criteria for genetically transmitted cardiovascular diseases: Hypertrophic cardiomyopathy, long-QT syndrome, and Marfan syndrome. A statement for healthcare professionals from the Councils on Clinical Cardiology, Cardiovascular Disease in the Young, and Basic Science, American Heart Association. *Circulation* 98:1460–1471, 1998.
    Ideally, genetic diagnosis with clear genotype-phenotype correlation would define prognosis and guide therapy.
21. Schwartz, P., et al. Prolongation of the QT interval and the sudden infant death syndrome. *N. Engl. J. Med.* 338:1709–1714, 1998.
    This study created considerable controversy by suggesting that neonatal prolongation of the QT interval was associated with sudden infant death syndrome. See N. Engl. J. Med. *338:1760–1761, 1998.*
22. Dorostkar, P., et al. Long-term follow-up of patients with long-QT syndrome treated with beta-blockers and continuous pacing. *Circulation* 100:2431–2436, 1999.
    Aggressive treatment can alter prognosis.

Syncope

23. Driscoll, D., et al. Syncope in children and adolescents. *J. Am. Coll. Cardiol.* 29:1039–1045, 1997.
    Syncope in children is usually benign unless it is associated with exertion or a positive family history.
24. Younoszai, A., et al. Oral fluid therapy. A promising treatment for vasodepressor syncope. *Arch. Pediatr. Adolesc. Med.* 152:165–168, 1998.
    A logical first line of therapy.
25. Bloomfield, D., et al. Putting it together: A new treatment algorithm for vasovagal syncope and related disorders. *Am. J. Cardiol.* 84:33Q-39Q, 1999.
    An excellent consensus approach based on adult data for the treatment of vasodepressor syncope. See Am. J. Cardiol. *84:20Q-25Q, 1999, and* Circulation *100:1242–1248, 1999.*
26. McLeod, K., et al. Cardiac pacing for severe childhood neurally mediated syncope with reflex anoxic seizures. *Heart* 82:721–725, 1999.
    In most centers, this is the treatment of last resort.

Pharmacologic and Interventional Therapy

27. Wilbur, S., and Marchlinski, F. Adenosine as an antiarrhythmic agent. *Am. J. Cardiol.* 79:30–37, 1997.
    This drug is remarkably safe and effective for the diagnosis and treatment of arrhythmias.
28. Perry, J., et al. Pediatric use of intravenous amiodarone: Efficacy and safety in critically ill patients from a multicenter protocol. *J. Am. Coll. Cardiol.* 27:1246–1250, 1996.

Particularly in the immediate postoperative period intravenous amiodarone can be useful for the management of refractory atrial and ventricular tachycardias. It must be given slowly to prevent severe hypotension, and may cause bradycardia.

29. Beaufort-Krol, G., and Bink-Boelkens, M. Sotalol for atrial tachycardias after surgery for congenital heart disease. *Pacing Clin. Electrophysiol.* 20:2125–2129, 1997.
Although it can be proarrhythmic, especially in patients with hypokalemia, sotalol has been effective for the chronic treatment of atrial tachycardias. See Pediatr. Cardiol. *18:28–34, 1997.*
30. Janousek, J., et al. Safety of oral propafenone in the treatment of arrhythmias in infants and children (European retrospective multicenter study). Working Group on Pediatric Arrhythmias and Electrophysiology of the Association of European Pediatric Cardiologists. *Am. J. Cardiol.* 81:1121–1124, 1998.
Propafenone may be proarrhythmic in patients with structural heart disease.
31. Fish, F., et al. Proarrhythmia, cardiac arrest and death in young patients receiving encainide and flecainide: The Pediatric Electrophysiology Group. *J. Am. Coll. Cardiol.* 18:356–365, 1991.
These drugs are effective (60–70%) for the treatment of atrial and ventricular arrhythmias; however, they have a high association with death or cardiac arrest (encainide, 7%; flecainide, 3%). Poor ventricular function is a risk factor, but proarrhythmia occurred in children with apparently normal hearts.
32. Kugler, J., et al. Radiofrequency catheter ablation for paroxysmal supraventricular tachycardia in children and adolescents without structural heart disease. Pediatric EP Society, Radiofrequency Catheter Ablation Registry. *Am. J. Cardiol.* 80:1438–1443, 1997.
This technique has dramatically changed the management, prognosis, and quality of life for children with supraventricular tachycardia. The recurrence risk in most cases is low, and for most pathways the risk of complete atrioventricular block is neglible.
33. Wilson, W., Greer, G., and Grubb, B. Implantable cardioverter-defibrillators in children: A single-institutional experience. *Ann. Thorac. Surg.* 65:775–778, 1998.
It is likely that this device will find increasing application in childhood as the size decreases and the pediatric experience evolves.
34. Byrd, C., et al. Intravascular extraction of problematic or infected permanent pacemaker leads: 1994–1996. U.S. Extraction Database, MED Institute. *Pacing Clin. Electrophysiol.* 22:1348–1357, 1999.
Extraction of the old hardware is particularly attractive in children. The newer laser techniques have markedly improved safety over previous approaches. The articles analyze the relationship between ventricular and atrial arrhythmias in children and sudden death. They stress the importance of not overtreating the child with a fundamentally healthy heart, and review management for children with heart disease at high risk. See Circulation *85:I64, 1992.*

56. MYOPERICARDITIS AND CARDIOMYOPATHY

Kenneth G. Zahka

Myocardial and pericardial diseases comprise a diverse group of conditions that affect cardiac structure and function. In some conditions, myocardial involvement may be only a limited feature of a complex metabolic or systemic disease. At one time, many of these diseases were of unknown or presumed metabolic or infectious etiology. With the tools of molecular biology, the understanding of the etiology and pathogenesis of these diseases is rapidly improving.

The clinical recognition of inflammatory diseases of the heart and pericardium is relatively uncommon in childhood. Moreover, the etiologies responsible for myocardial inflammation in children have changed over the last several decades. Rheumatic carditis is rare and typically occurs in isolated outbreaks. Diphtheria is virtually unknown in the modern era of immunization. Viral infections continue to be linked to myocarditis. Coxsackie group B viruses are most often linked to myocarditis. Cases of myocarditis associated with mumps, measles, varicella, influenza, human immunodeficiency virus, Epstein-Barr virus, and *Chlamydia* infection have been reported. Lyme disease, due to infection with *Borrelia burgdorferi*, is a tick-borne disease found in the northeastern and midwestern United States, with a 5–10% prevalence of rhythm abnormalities or myocarditis. Myocarditis is an early feature of the inflammatory process in Kawasaki disease. Chagas disease, caused by parasitic infection with *Trypanosoma cruzi*, is common in South America and may have devastating myocardial involvement. Bacterial pericarditis occurs with staphylococcal, pneumococcal, meningococcal, and *Haemophilus influenzae* type b infections. Chronic renal failure produces uremic pericarditis, and systemic diseases, most notably lupus erythematosus and rheumatoid arthritis, may involve pericardial effusion or myocarditis.

The clinical spectrum of myocardial inflammation is considerable. Acute, severe congestive heart failure accompanying a viral illness is unusual. More subtle symptoms such as fatigue, dyspnea, exercise intolerance, and chest pain are common and are usually initially attributed to the systemic viremia. Abdominal pain may be caused by hepatic congestion. The physical findings of tachycardia, gallop rhythm, and hepatomegaly should suggest the diagnosis of myocarditis. Pulsus paradoxus, a fall in systolic blood pressure during inspiration, increases with pericardial effusion and tamponade. A pericardial friction rub indicates pericardial inflammation. Mitral regurgitation due to myocardial and mitral valve papillary muscle dysfunction is present in more severe cases of myocarditis. In many instances, the myocardial involvement is subclinical and either resolves without sequelae or leads to chronic dilated cardiomyopathy.

The diagnosis of myopericarditis is supported by electrocardiographic (ECG) findings of low voltage, abnormal T waves, and ST segment depression. Echocardiography is extremely helpful for documentation of ventricular dilatation and dysfunction, pericardial effusion, and mitral regurgitation. In children with acute congestive heart failure and elevated left atrial pressures, pulmonary edema will be evident by chest radiograph. Viral serology and cultures are necessary to document the etiology of the infection. Myocardial biopsy is usually not necessary during the acute phase, although genetic identification of the virus using hybridization studies and polymerase chain reaction techniques may be done from myocardial biopsies. Pericardiocentesis is essential if there is any clinical suspicion of bacterial origin of pericardial effusion.

The acute treatment of myopericarditis in the asymptomatic child consists of supportive care through a self-limited disease. Symptoms and signs of myocardial dysfunction require careful monitoring for progression of heart failure and arrhythmias. Digoxin has limited benefit and potential risk in myocarditis. Immunosuppression with prednisone or cyclosporine remains of uncertain benefit. Children with acute, profound cardiac failure require multisystem support. Support with ventricular assist devices may be required until myocardial function improves, or as a bridge to cardiac transplantation. Bacterial pericarditis is treated with catheter or surgical drainage and prolonged intravenous antibiotics.

The prognosis of myopericarditis is variable. Children with inflammation largely limited to the pericardium recover with no sequelae. Myocardial dysfunction, even when severe, is reversible, and complete recovery is possible. Some children continue to have clinical or echocardiographic evidence of myocardial dysfunction and can be successfully managed with oral medications. Large multicenter studies in adults suggest that the combination of digoxin and captopril or enalapril offers the best outcome. Chronic heart failure, refractory to medical management, is the primary indication for cardiac transplantation in these children.

Myocardial disease may become evident at any time from fetal life through adolescence. Some children may be identified simply based on the family history of myopathy or sudden death. If they have a systemic metabolic disease or are receiving cardiotoxic medications, a screening echocardiogram may reveal a myopathy in the absence of symptoms or signs. Symptoms related to impaired systolic and diastolic function include poor exercise tolerance or dyspnea. Clinical findings are often subtle. Precordial activity may be increased, and a third or fourth heart sound may be heard. Murmurs of left ventricular outflow tract obstruction can be heard in children with hypertrophic cardiomyopathy, or mitral regurgitation may be heard in children with dilated cardiomyopathy with poor ventricular function.

Cardiovascular investigations are usually limited to an ECG and echocardiogram. Ambulatory ECG can be added if there is a clinical concern about arrhythmia. Cardiovascular reserve can be determined either from exercise testing or dobutamine stress echocardiography. Cardiac catheterization is indicated usually either as part of a transplant assessment or if a myocardial biopsy is needed. The extent of metabolic and genetic investigation must be guided by the clinical situation.

Treatment of an underlying systemic or metabolic disease may resolve the myopathy. Examples of this include the dietary carnitine for carnitine deficiency, and treatment of hypertension in a patient with acute renal failure. There is considerable evidence from clinical trials to guide therapy in the adult population. These include the use of afterload reduction, spironolactone and b blockers for congestive heart failure, and b blockers and antiarrhythmics for hypertrophic cardiomyopathy. There is limited evidence to guide similar treatments in children; however, it is common for treatments developed for adult congestive heart failure to be applied to children. Cardiac transplantation has been successful in children for 20 years and remains an option for children who have failed maximal medical therapy.

Reviews

1. Sole, M., and Liu, P. Viral myocarditis: A paradigm for understanding the pathogenesis and treatment of dilated cardiomyopathy. *J. Am. Coll. Cardiol.* 22: 99A–105A, 1993.
   This is a superb, well-referenced review that outlines the evidence linking myocarditis to dilated cardiomyopathy, and presents the data on the pathogenesis of myocardial damage. See J. Am. Coll. Cardiol. *22:1385–1388, 1993, for an editorial that summarizes autoimmunity in dilated cardiomyopathy.*
2. Schwartz, M., et al. Clinical approach to genetic cardiomyopathy in children. *Circulation* 94:2021–2038, 1996.
   This is a thorough review that provides an excellent approach to the diagnosis of genetic cardiomyopathy. See also Curr. Opin. Cardiol. *14:250–262, 1999.*
3. Gajarski, R., and Towbin, J. Recent advances in the etiology, diagnosis, and treatment of myocarditis and cardiomyopathies in children. *Curr. Opin. Pediatr.* 7:587–594, 1995.
   Covers all aspects of myocardial disease.

Specific Etiologies

4. Bowles, N., et al. The detection of viral genomes by polymerase chain reaction in the myocardium of pediatric patients with advanced HIV disease. *J. Am. Coll. Cardiol.* 34:857–865, 1999.
   Other viruses in human immunodeficiency virus-infected children may lead to cardiomyopathy or heart failure.
5. Cox, J., and Krajden, M. Cardiovascular manifestations of Lyme disease. *Am. Heart J.* 122:1449–1455, 1991.
   Atrioventricular block is the most common manifestation. A small proportion of patients have myocarditis.
6. Goldenberg, J., et al. Symptomatic cardiac involvement in juvenile rheumatoid arthritis. *Int. J. Cardiol.* 34:57–62, 1992.
   Pericarditis or myocarditis occurred in 7%. Pericardial involvement was sufficient to cause tamponade.
7. Lipshultz, S., et al. Left ventricular structure and function in children infected with human immunodeficiency virus: The prospective P2C2 HIV Multicenter Study. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group. *Circulation* 97:1246–1256, 1998.

Subclinical findings, including pericardial effusion and dilated cardiomyopathy, can be seen and may be progressive.

Diagnosis

8. Bonnet, D., et al. Efficiency of metabolic screening in childhood cardiomyopathies. *Eur. Heart J.* 19:790–793, 1998.
   *Screening is particularly important in the newborn period and early infancy when the yield can be high. This group also suggests that arrhythmias can be frequent and a sign of fatty acid metabolism disorders (*Circulation *100:2248–2253, 1999).*
9. Pophal, S., et al. Complications of endomyocardial biopsy in children. *J. Am. Coll. Cardiol.* 34:2105–2110, 1999.
   The greatest risk of perforation is in infants with myocarditis on significant support.

Pericarditis

10. Spodick, D. The normal and diseased pericardium: Current concepts of pericardial physiology, diagnosis and treatment. *J. Am. Coll. Cardiol.* 1:240–251, 1983.
    Still a terrific review of pericardial disease.
11. Shabetai, R. Acute pericarditis. *Cardiol. Clin.* 8:639–644, 1990.
    This is one of a number of articles in a monograph on pericarditis. See Cardiol. Clin. *8:709–16, 1990, for systemic diseases;* Cardiol. Clin. *8:697–699, 1990, for acquired immunodeficiency syndrome;* Cardiol. Clin. *8:683–696, 1990, for surgical management; and* Cardiol. Clin. *8:621–626, 1990, for recurrent pericarditis.*
12. Sinzobahamvya, N., and Ikeogu, M. Purulent pericarditis. *Arch. Dis. Child.* 62: 696–699, 1987.
    Staphylococcal pericarditis was usually the consequence of an extracardiac focus. Despite surgical drainage, two of 11 patients died. See J. Thorac. Cardiovasc. Surg. *85:527–531, 1983, for a management strategy using pericardiectomy.*
13. Byrd, B., and Linden, R. Superior vena caval Doppler flow velocity patterns in pericardial disease. *Am. J. Cardiol.* 65:1464–1470, 1990.
    Diastolic superior vena cava is blunted during expiration in patients with tamponade. Doppler evaluation and the presence of atrial or ventricular diastolic collapse are a helpful complement to the physical examination in patients with tamponade. See Am. J. Cardiol. *66:1487–1491, 1990, for an excellent discussion of the hemodynamics of tamponade.*

Myocarditis

14. Lee, K., et al. Clinical outcomes of acute myocarditis in childhood. *Heart* 82:226–233, 1999.
    All had documented lymphocytic myocarditis. Survival was 80% at 2 years. A few children required extracorporeal membrane oxygenation or transplant. Immunosuppression was used in 34 of 36. Nearly all had left ventricular function return to normal and were free of arrhythmias. Nearly all deaths were during the acute phase.

Metabolic Cardiomyopathy

15. Marin-Garcia, J., et al. Mitochondrial dysfunction in skeletal muscle of children with cardiomyopathy. *Pediatrics* 103:456–459, 1999.
    Of eight skeletal muscle biopsies, six showed mitochondrial abnormalities.
16. Pauly, D., et al. Complete correction of acid alpha-glucosidase deficiency in Pompe disease fibroblasts in vitro, and lysosomally targeted expression in neonatal rat cardiac and skeletal muscle. *Gene Ther.* 5:473–480, 1998.
    This is one of the myopathies with a hope for gene therapy.

Dilated Cardiomyopathy

17. Crispell, K., et al. Clinical profiles of four large pedigrees with familial dilated cardiomyopathy: Preliminary recommendations for clinical practice. *J. Am. Coll. Cardiol.* 34:837–847, 1999.
    The authors uncovered a huge number of individuals in four families. They stress the importance of screening first-degree relatives and make recommendations for counseling of family members.
18. Lewis, A. Late recovery of ventricular function in children with idiopathic dilated cardiomyopathy. *Am. Heart J.* 138:334–338, 1999.
    Recovery may take over 1 year.

Hypertrophic Cardiomyopathy

19. Maron, B., et al. Impact of laboratory molecular diagnosis on contemporary diagnostic criteria for genetically transmitted cardiovascular diseases: Hypertrophic cardiomyopathy, long-QT syndrome, and Marfan syndrome. A statement for healthcare professionals from the Councils on Clinical Cardiology, Cardiovascular Disease in the Young, and Basic Science, American Heart Association. *Circulation* 98:1460–1471, 1998.
    The goal is a molecular diagnosis that defines prognosis and therapy.
20. Maron, B., et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation* 92: 785–789, 1995.
    Hypertrophy not explained by hypertension was found in 0.2%. Most were asymptomatic. The electrocardiogram (ECG) was abnormal in only five of seven.
21. Maron, B., et al. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *J.A.M.A.* 281:650–655, 1999.
    The prognosis for most patients is better than previously inferred from patients referred to tertiary centers. See N. Engl. J. Med. *336:775–785, 1997, for discussion of management issues.*
22. Cecchi, F., et al. Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy: Assessment in an unselected non-referral based patient population. *Heart* 79: 331–336, 1998.
    Nonrepetitive bursts of nonsustained ventricular tachycardia (VT) were not associated with morbidity or mortality and do not justify treatment. Amiodarone may still be justified in patients with repetitive burst of VT.
23. Yetman, A., et al. Long-term outcome and prognostic determinants in children with hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* 32:1943–1950, 1998.
    QT dispersion on ECG and myocardial bridging of coronary arteries (N. Engl. J. Med. *339:1201–1209, 1998*) *increased the risk of sudden death.*
24. Fritz, K., and Bhat, A. Effect of beta-blockade on symptomatic dexamethasone-induced hypertrophic obstructive cardiomyopathy in premature infants: Three case reports and literature review. *J. Perinatol.* 18:38–44, 1998.
    They were treated and got better; however, the natural course is for improvement once the steroids are stopped.
25. Marino, B., et al. Congenital heart diseases in children with Noonan syndrome: An expanded cardiac spectrum with high prevalence of atrioventricular canal. *J. Pediatr.* 135:703–706, 1999.
    A small proportion also have hypertrophic cardiomyopathy.
26. Ichida, F., et al. Clinical features of isolated noncompaction of the ventricular myocardium: Long-term clinical course, hemodynamic properties, and genetic background. *J. Am. Coll. Cardiol.* 34:233–240, 1999.
    This is a heterogeneous familial myopathy that is characterized by dense apical trabeculations that are present at birth There is a gradual deterioration in function over decades.

Medical Treatment of Heart Failure

27. Di Lenarda, A., et al. Long-term effects of carvedilol in idiopathic dilated cardiomyopathy with persistent left ventricular dysfunction despite chronic metoprolol. The Heart-Muscle Disease Study Group. *J. Am. Coll. Cardiol.* 33:1926–1934, 1999.
    In adult dilated cardiomyopathy patients who did not respond to metoprolol, carvedilol treatment resulted in improved LV systolic function and improved arrhythmias. See J. Am. Coll. Cardiol. *34:1522–1528, 1999, which says they are about the same.*
28. Macdonald, P., et al. Tolerability and efficacy of carvedilol in patients with New York Heart Association class IV heart failure. *J. Am. Coll. Cardiol.* 33:924–931, 1999.
    This drug must be used with extraordinary care in this group of patients. They have frequent side effects while initiating therapy, but they can be helped in the long run.
29. Pitt, B., et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N. Engl. J. Med.* 341:709–717, 1999.
    This study enrolled over 1,600 patients and showed that blocking aldosterone receptors with spironolactone decreased morbidity and mortality in adult heart failure patients.

Athlete's Heart

30. Maron, B., Pelliccia, A., and Spirito, P. Cardiac disease in young trained athletes. Insights into methods for distinguishing athlete's heart from structural heart disease, with particular emphasis on hypertrophic cardiomyopathy. *Circulation* 91:1596–1601, 1995.
    It is essential not to overdiagnose cardiomyopathy in the athlete. Many have LV dilatation with approprite wall thickness that resolves with deconditioning. It is not thought to be associated with arrhythmia or sudden death. See Ann. Intern. Med. *130:23–31, 1999.*

Heart Transplant

31. Boucek, M., et al. The Registry of the International Society of Heart and Lung Transplantation: Second Official Pediatric Report—1998. *J. Heart Lung Transplant.* 17:1141–1160, 1998.
    Excellent statistical data on indications and outcome.
32. Kanter, K., et al. Current results with pediatric heart transplantation. *Ann. Thorac. Surg.* 68:527–530, 1999.
    Five-year survival was 70%, with rejection accounting for the majority of deaths.

57. BACTERIAL ENDOCARDITIS

Kenneth G. Zahka

Untreated, bacterial endocarditis is a fatal disease; however, its initial indolent course is not always easily recognized. Bacterial endocarditis is most common in children with structural heart disease, especially aortic stenosis. Children with secundum atrial septal defect are at no increased risk for endocarditis. Moreover, the early surgical repair of patent ductus arteriosus, ventricular septal defect, and tetralogy of Fallot has substantially lowered the risk of endocarditis in children with these congenital heart diseases. Additionally, the dramatic decrease in the prevalence of rheumatic carditis has reduced the number of children with acquired heart disease at risk of endocarditis. Endocarditis is rare in the first 2 years of life, although postoperative endocarditis and endovascular infections due to infected mural thrombi at the site of intravenous lines are recognized. Endocarditis of the tricuspid valve is prevalent in intravenous drug abusers.

Platelet-fibrin thrombi on damaged valves or endocardial surfaces damaged by high-velocity jets are integral to the pathogenesis of bacterial endocarditis. Asymptomatic episodes of transient bacteremia, which may be associated with dental procedures, create a condition where bacteria infect these thrombi. During the bacteremia, the organisms aggregate platelets, host antibody agglutinates the bacteria and the entrapped bacteria, and platelets adhere to the thrombus. The clinical and laboratory findings in bacterial endocarditis are related to immune complex deposition and emboli.

Acute bacterial endocarditis (ABE) is a fulminant, devastating disease typically due to an aggressive infection with *Staphylococcus aureus*. Sepsis with congestive heart failure, secondary to valve destruction and myocardial dysfunction, occurs with ABE. Subacute bacterial endocarditis (SBE) evolves over several weeks to months and is caused by less invasive organisms, such as *Streptococcus viridans*. The presentation of SBE is with fever, lethargy, fatigue, and malaise. Many strains of bacteria can cause endocarditis, including the enterococcus, gonococcus, and pneumococcus. In addition to bacteria, rickettsiae and fungi can also cause endocarditis, leading many to prefer the term *infective endocarditis.*

The early diagnosis of SBE is a clinical challenge. Regurgitant murmurs, due to valve destruction or systemic embolization of vegetations, are late findings and indicate well-established infection. Fever, malaise, and weight loss should raise concern in any child with heart disease. Careful examination for splenomegaly, splinter hemorrhages, petechiae, Janeway's lesions (painless red nodules on the hands), and Osler's nodes (tender nodules) may support the diagnosis. Mild anemia and an increased sedimentation rate suggest chronic infection. The white blood cell count is typically normal. Echocardiographic evidence of valve, endocardial, or endovascular vegetations is usually diagnostic of SBE.

Positive blood cultures with supporting clinical or laboratory evidence establish the diagnosis of bacterial endocarditis. Transient culture-proven bacteremia in a child with pneumonia or other focal infection does not constitute the diagnosis of SBE. Conversely, if the clinical evidence indicates SBE, blood cultures may not reveal the pathogen if the bacterial load is low. The child who has been treated with prolonged oral antibiotics is most problematic. As many as six blood cultures may be needed to grow the organism. No organism can be isolated in approximately 20% of patients with clinical evidence of SBE.

Antibiotic treatment of SBE is clearly facilitated by the identification of the organism. Prolonged therapy, 4–6 weeks, is essential to eradicate the infection. Even for organisms sensitive to a single antibiotic, an initial course of antibiotics with known synergy for the organism is helpful. Culture-negative endocarditis is treated for 6 weeks with broad-spectrum antibiotics. Surgery for ABE or SBE is indicated for persistent bacteremia with echocardiographic evidence of myocardial abscess, intractable congestive heart failure due to valve regurgitation, and cerebral embolization.

Antibiotic prophylaxis for children with congenital heart disease has become a ritual. Well-established recommendations from the American Heart Association and the American Dental Association provide excellent, but not all-inclusive, guidelines for prophylaxis. The efficacy of prophylaxis is not uniform. Good dental care is probably as important as antibiotic prophylaxis to avoid gingival disease and unrecognized dental abscess. Recognition of the higher risk and morbidity of endocarditis in patients with prosthetic valves, and a diligent approach to prophylaxis and recognition of SBE in this group are essential.

Reviews and Collections

1. Lukes, A., et al. Diagnosis of infective endocarditis. *Infect. Dis. Clin. North Am.* 7:1–8, 1993.
   *The authors stress the importance of echocardiography for the diagnosis of endocarditis. This is the first article in a collection that covers many aspects of endocarditis. Echocardiography (*Infect. Dis. Clin. North Am. *7:877–898, 1993), risk factors (*Infect. Dis. Clin. North Am. *7:9–19, 1993), coagulase-negative and positive staphylococcal endocarditis* Infect. Dis. Clin. North Am. *7:53–68, 1993;* Infect. Dis. Clin. North Am. *7:81–96, 1993), aminoglycoside-resistant enterococcal endocarditis* Infect. Dis. Clin. North Am. *7:117–133, 1993), short-course, outpatient, and oral therapies (*Infect. Dis. Clin. North Am. *7:69–80, 1993;* Infect. Dis. Clin. North Am. *7:97–115, 1993), and management of complications (*Infect. Dis. Clin. North Am. *7:153–165, 1993) are among the topics of the well-referenced articles. For a discussion of acute bacterial endocarditis, see* Infect. Dis. Clin. North Am. *10:811–834, 1996.*
2. Baltimore, R. Infective endocarditis in children. *Pediatr. Infect. Dis. J.* 11:907–912, 1992.
   Reviews the nosocomial catheter-related subacute bacterial endocarditis (SBE), as well as the classic cases, and makes recommendations for therapy.
3. Saiman, L., et al. Pediatric infective endocarditis in the modern era. *J. Pediatr.* 122:847–853, 1993.
   Complex heart disease and ventricular septal defect constituted one third of cases. One third had normal anatomy. The last 2 decades showed an increase in catheter-related and fungal endocarditis. Mortality was 11%, and SBE was diagnosed only at autopsy in 7 of 62.
4. Awadallah, S., et al. The changing pattern of infective endocarditis in childhood. *Am. J. Cardiol.* 68:90–94, 1991.
   Half of their cases were postoperative, with many infected prosthetic valves.

Etiology

5. Baddour, L., et al. Polymicrobial infective endocarditis in the 1980s. *Rev. Infect. Dis.* 13:963–970, 1991.
   Seventy percent were intravenous drug abusers.
6. Chan, P., et al. Tricuspid valve endocarditis. *Am. Heart J.* 117:1140–1146, 1989.
   Most were intravenous drug abusers, and 25% required valve excision. See also Am. Heart J. *111:128–135, 1986. (Transesophageal echocardiography does not improve the diagnostic accuracy of right-sided endocarditis:* J. Am. Coll. Cardiol. *21:1226–1230, 1993.)*
7. Pongratz, G., et al. Risk of endocarditis in transesophageal echocardiography. *Am. Heart J.* 125:190–193, 1993.
   Most studies agree that endocarditis prophylaxis is not required for uncomplicated endoscopy.
8. Jackman, J., and Glamann, D. Gonococcal endocarditis: Twenty-five year experience. *Am. J. Med. Sci.* 301:221–230, 1991.
   Occurs in the absence of underlying heart disease.
9. Marks, A., et al. Identification of high-risk and low-risk subgroups of patients with mitral-valve prolapse. *N. Engl. J. Med.* 320:1031–1036, 1989.
   The thick, redundant mitral valves, especially the ones that leak, are at the highest risk for SBE.
10. Danchin, N., et al. Mitral valve prolapse as a risk factor for infective endocarditis. *Lancet* 1:743–745, 1989.
    The risk of SBE is increased three-fold in individuals who have mitral valve prolapse with mitral regurgitation.
11. Gersony, W., et al. Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation* 87:I121–126, 1993.
    The prevalence of SBE was highest in aortic stenosis and related to severity of obstruction. Subacute bacterial endocarditis in pulmonary stenosis was very low. Surgical closure of ventricular septal defect reduced but did not eliminate the risk of SBE.

Diagnosis

12. Stockheim, J., et al. Are the Duke criteria superior to the Beth Israel criteria for the diagnosis of infective endocarditis in children? *Clin. Infect. Dis.* 27:1451–1456, 1998.
    The Duke criteria were substantially better. See Am. J. Med. *96:200–209, 1994, for the Duke criteria.*
13. Aly, A., et al. The role of transthoracic echocardiography in the diagnosis of infective endocarditis in children. *Arch. Pediatr. Adolesc. Med.* 153:950–954, 1999.
    This study showed that the echocardiogram was most likely to show vegetations in patients with malaise, congestive heart failure, new or changing heart murmur, leukocytosis, hematuria, and two or more positive blood cultures. Simply having an indwelling catheter or immunocompromised status was not predictive of vegetation or infective endocarditis, despite the presence of fever.
14. Jaffe, W., et al. Infective endocarditis, 1983–1988: Echocardiographic findings and factors influencing morbidity and mortality. *J. Am. Coll. Cardiol.* 15:1227–1233, 1990.
    Vegetations were identified in 78% of patients with SBE. Large vegetations tended to embolize. Risk factors for death were prosthetic valves, systemic embolization, and staphylococcal

infection.
15. Karalis, D., et al. Transesophageal echocardiographic recognition of subaortic complications in aortic valve endocarditis: Clinical and surgical implications. *Circulation* 86:353–362, 1992.
Transesophageal echocardiography identified involvement (abscess, perforations, aneurysms) of the subaortic structures in 44% of adults with endocarditis. Half were not seen by transthoracic echocardiography. Great review of anatomy.

Treatment

16. Francioli, P., et al. Treatment of streptococcal endocarditis with a single daily dose of ceftriaxone sodium for 4 weeks: Efficacy and outpatient treatment feasibility. *J.A.M.A.* 267:264–267, 1992.
This treatment was effective in all 55 patients (an additional 4 patients had drug allergy) who completed the course. Ten patients eventually had valve replacement, but none for persistent bacteremia. There were no recurrences.
17. Zenker, P., et al. Successful medical treatment of presumed *Candida endocarditis* in critically ill infants. *J. Pediatr.* 119:472–427, 1991.
Positive Candida *blood cultures and right atrial vegetations were successfully treated in three infants with amphotericin and 5-flucytosine.*
18. Citak, M., et al. Surgical management of infective endocarditis in children. *Ann. Thorac. Surg.* 54:755–760, 1992.
Recommends aggressive surgical approach to vegetations, but there was a 25% surgical mortality.
19. Dreyfus, G., et al. Valve repair in acute endocarditis. *Ann. Thorac. Surg.* 49: 706–711, 1990.
This group has excellent results with valve repairs in all settings. See Ann. Thorac. Surg. *49:619–624, 1990, for homograft replacement for SBE.*

Complications

20. Hart, R., et al. Stroke in infective endocarditis. *Stroke* 21:695–700, 1990.
Neurologic complications in patients with staphylococcal endocarditis can be particularly devastating. This series found a 21% prevalence of strokes in adults. See Medicine *57:329–343, 1978, for a detailed analysis of the neurologic complications of SBE.*
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58. HYPERTENSION

Kenneth G. Zahka

Hypertension is a recognized risk factor for long-term cardiovascular morbidity and mortality in adults. Essential hypertension may begin in late childhood and adolescence, and has the same prognostic significance as hypertension that begins in the third or fourth decade. In contrast to the indolent course of essential hypertension in childhood, renal or renal vascular hypertension in childhood may not be a mild, benign asymptomatic disease. Seizures, stroke, and congestive heart failure from uncontrolled hypertension are recognized at all ages, including the neonate.

Blood pressure, like heart rate, changes with age and activity. It is also a continuous variable with no clear break between normal and abnormal. Blood pressure varies with each cardiac cycle. While the systolic and diastolic pressures may track with each other, changes in cardiac output, vascular resistance, and the properties of the large arteries may produce independent changes in the systolic and diastolic pressures. A number of careful studies have documented the normal range for systolic and diastolic blood pressure from birth to early adulthood, and they provide the basis for the definition of hypertension. These data show that blood pressure increases with age, that larger children have higher blood pressure at any age than smaller children, and that obese children have higher blood pressure at any age than lean children. The 1987 Task Force report recommends that blood pressures between the 90th and 95th percentiles be labeled high normal, and that hypertension be reserved for children with average systolic or diastolic readings above the 95th percentile.

The measurement of the arterial blood pressure by cuff occlusion of the arm blood flow and a mercury manometer is well-validated in adults and children. The cuff should be snug-fitting, and the bladder should nearly encircle the arm and cover two thirds of the distance between the elbow and the axilla. The subject should be comfortable and quiet, and the arm and manometer should be level with the heart. The cuff is rapidly inflated to at least 20 mm Hg above the systolic pressure, and with gentle auscultation over the brachial artery the manometer pressure at which the appearance, muffling, and disappearance of the Korotkoff's sounds are heard is noted. Blood pressure measurement in infants is facilitated by automated blood pressure machines using plethysmography or Doppler technology. Routine blood pressure measurement is recommended for all children after age 2 years and for infants at risk. The latter group includes neonates who had umbilical catheters or renal disease. Central to the diagnosis of hypertension is the documentation of multiple recordings over time. Automated blood pressure machines are a convenient means to record hourly blood pressures over a several-day period. Alternatively, home blood pressure monitors can be used by the patients or their families to establish a database of blood pressure data. These data are essential to establish a diagnosis and to assess the response to intervention.

The cardiovascular short-term sequela of hypertension is compensatory left ventricular hypertrophy. Hypertrophy normalizes wall stress and is the result of increased left ventricular afterload. Long-term sequelae are not adaptive responses, however; these include retinal, renal, cerebral, and coronary arterial vascular changes, which eventually impair organ function.

The pathogenesis of hypertension in the very young child is rarely similar to essential hypertension in the adult. Coarctation of the aorta is the most common cardiovascular cause of upper-extremity hypertension. Every child with hypertension requires careful measurement of upper- and lower-extremity blood pressures to exclude coarctation of the aorta. Rare hormonal causes include adrenal hyperplasia, primary hyperaldosteronism, pheochromocytoma, and hyperthyroidism. The majority of secondary hypertension in children is renal in origin, including inflammatory renal diseases, cystic renal disease, chronic infection, obstructive uropathy, and renovascular disease. Adolescents have a higher likelihood of essential hypertension, especially when they are obese and have a family history of hypertension.

The evaluation of the child with hypertension begins with a careful family and medical history to explore the possible etiologies of hypertension. A diet history should focus on salt intake and cholesterol as another cardiovascular risk factor. Over-the-counter and prescription drug use should be specifically documented, including antihistamines, oral contraceptives, and asthma and allergy medications. The physical examination must specifically address the renal, endocrine, and cardiovascular etiologies and sequelae. The chest radiograph and electrocardiogram are insensitive measures of ventricular hypertrophy. An echocardiogram is useful to document left ventricular mass as a measure of the average afterload on a day-by-day basis. Measurement of electrolytes and renal function and a urinalysis may help exclude renal disease. If the blood pressure is significantly elevated, especially in a young slender child with a negative family history, further evaluation is important. Renal ultrasound is particularly useful for the evaluation for cystic renal disease and obstructive uropathy. Alternatively, renal cortical dimercaptosuccinic acid scan may be used. Renal arteriography and selective renal vein renin sampling are usually reserved for young children with significant hypertension and high peripheral renin levels. It is the most effective means of excluding renovascular hypertension, especially in the distal branch renal arteries.

Management of mild hypertension begins with lifestyle modifications and interventions, including dietary salt reduction, weight reduction, and physical conditioning. Other cardiovascular risk factors, including smoking and high-cholesterol foods, should also be avoided. Sustained hypertension is treated with angiotensin-converting enzyme inhibitors, calcium channel blockers, or cardioselective b-blockers. Consistent follow-up is essential for both blood pressure moderation and side effects. Continued efforts to identify the etiology and to provide trials off therapy are warranted. Severe hypertension is a medical emergency, and intravenous treatment with nitroprusside, hydralazine, or diazoxide is essential to prevent neurologic and cardiac sequelae.

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59. UPPER RESPIRATORY INFECTION

Kenneth B. Roberts and Conrad J. Clemens

The upper respiratory tract is the most frequent site of infection in children. Children in the first 5 years of life have between seven and nine upper respiratory tract infections (URIs) per year. Clinical illness after exposure is 2–3 times more likely to develop in infants than in older children or adults; illness occurs once per 1–2 exposures in infants, and once per 4–5 exposures in older children and adults. Infants in daycare are at increased risk compared to those cared for at home. The increased susceptibility of infants is only partly explained by lack of previous exposure and immunity. An additional factor may be the way individuals (particularly preschoolers) relate to babies, placing young infants' faces close to their own and facilitating the transfer of infectious secretions. Despite folklore to the contrary (and the designation of the illness as a “cold”), chilling does not predispose to the development of disease. What is important is contact with infected persons, specifically with their contaminated nasopharyngeal secretions.

It is difficult to identify the onset of a URI. The first symptom is often just a feeling of congestion or tightness in the upper part of the nose or a sensation of rawness in the nasopharynx. At this early stage, many people are convinced that a favorite home remedy can abort a full-blown cold (lactose capsules used as placebos are so touted by 35% of experimental subjects). The infection is more easily recognized when sneezing and rhinorrhea become prominent. The volume of nasal secretions increases and may reach 100 times the normal quantity. The nasal secretions thicken, and the patient experiences malaise and often shivering, despite the absence of significant fever. Most people shed a large amount of virus early in the disease; symptoms persist, however, until the damaged nasal mucosa is “healed” by regeneration of cells.

The laboratory is of no help in establishing the diagnosis of URI acutely. Even identifying the responsible organism is difficult because there are many strains of rhinovirus, and multiple agents other than rhinovirus may produce URI signs and symptoms, including viruses (e.g., respiratory syncytial virus), bacteria (e.g., Bordetella pertussis), and *Mycoplasma pneumoniae*. The single most dependable indicator of URI is the presence of nasal discharge. In clinical practice, it is often difficult to differentiate URI from allergy; the pattern of illness over time rather than the symptoms during any particular episode may help distinguish the two conditions. If rhinorrhea becomes purulent or prolonged, the possibility of sinusitis should be considered (see Chap. 61).

Treatment is empiric—and inadequate—and folk remedies abound. In fact, in the United States, over $1 billion is spent on hundreds of medications, each promising to cure or alleviate the symptoms of the common cold. Antihistamines, decongestants, antitussives, and expectorants have not been shown to be effective in young children. In addition, concerns regarding overdosing and toxicity make the use of these over-the-counter medications probably more harmful than helpful in young children. In older children, decongestants may have some effect on nasal symptoms. In adolescents and adults, decongestants and combination products do provide symptomatic relief. Antibiotics are not of value in the uncomplicated viral URI, either as treatment or to prevent common complications; antiviral and immunologic approaches remain under investigation. Unfortunately, many health care providers continue to prescribe antibiotics for uncomplicated URIs, causing increased bacterial resistance. Vitamin C and zinc lozenges, as well as a variety of homeopathic medications, have not shown to be effective in children, either prophylactically or therapeutically. Until better treatments are available, chicken soup may still be the best treatment available!

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60. OTITIS MEDIA

Kenneth B. Roberts and Conrad J. Clemens

Otitis media (OM) is one of the most common infections in infants and children. Although suppurative complications, such as mastoiditis and brain abscess, are no longer frequent, chronic middle ear disease with attendant hearing loss is a problem of considerable magnitude and importance.

The functional state of the eustachian tube appears central in the development and resolution of middle ear disease. Normally, the eustachian tube (1) protects the middle ear from infected nasopharyngeal secretions; (2) permits drainage of fluid into the nasopharynx; and (3) ventilates and equilibrates pressure in the middle ear. If edema or perhaps lymphoid hyperplasia occludes the patency of the eustachian tube, negative pressure in the middle ear produces a transudation of fluid, resulting in serous OM. Organisms in the nasopharynx that colonize the medial portion of the eustachian tube but do not normally reach the middle ear may be “trapped” distal to the obstruction. If an organism is able to proliferate in the transudate, acute suppurative OM results. Although the organisms originate in the nasopharynx, studies have failed to demonstrate a precise correlation between routine nasopharyngeal cultures and middle ear aspirates.

The pathogen most frequently responsible for acute suppurative OM after the neonatal period is the pneumococcus, accounting for 30–40% of cases. Currently, as many as 25% of the pneumococci cultured from the ear are highly resistant to penicillin, and another 25% have intermediate resistance. In children younger than 5 years of age, the second most common pathogen is untypeable *Haemophilus influenzae* (not to be confused with *Haemophilus influenzae* type b [Hib], which causes invasive disease and is preventable by immunization). *H. influenzae* less frequently causes otitis in school-aged children, but it remains a consideration when selecting treatment. The third most frequent organism is *Moraxella catarrhalis.* In school-aged children, the group A streptococcus is another cause of acute OM. One third of the aspirates of middle ear exudates do not grow bacteria and are thought to be viral. Of the viruses that are cultured, respiratory syncytial virus is the most common, followed by parainfluenza and influenza viruses.

The symptoms of acute suppurative OM are nonspecific. Fever and ear pain suggest the diagnosis but are present in fewer than 50% of patients. Older children may complain of a sense of fullness rather than, or in addition to, pain. The most frequent symptoms, irritability and rhinorrhea, are also the most nonspecific, and examination of the tympanic membranes is required to establish the diagnosis. Injection of the eardrum by itself is not a valid sign of OM; more valuable findings are the loss of the light reflex and landmarks, bulging of the pars tensa and pars flaccida, and, most importantly, impaired mobility of the tympanic membrane. Subjective impairment of mobility perceived by pneumatic otoscopy can be confirmed by tympanometry, an objective mechanical means of recording data about the compliance of the tympanic membrane and pressure in the middle ear.

The goals of treatment of acute suppurative OM are (1) to provide clinical “cure” of symptomatic disease; (2) to eradicate organisms and prevent suppurative complications; and (3) to clear the fluid from the middle ear and prevent secretory OM (also known as chronic otitus media with effusion). Clinical improvement within 48 hours may occur even without treatment, and therefore many countries around the world do not automatically treat acute OM with antibiotics. In the United States, however, antibiotic therapy is usually given. Amoxicillin remains the preferred drug for initial treatment. However, in addition to the increasing resistance of pneumococcus to penicillin, approximately 40% of strains of *H. influenzae* and 90% or more of *M. catarrhalis* strains produce b-lactamase. Given this, use of amoxicillin with clavulinic acid, high dose amoxicillin (80–100 mg/kg), or a combination of these two should be considered as second line therapy. A single intramuscular injection of ceftriaxone has also shown to be effective, but should be reserved for those children for whom compliance is an issue. Extending the duration of treatment beyond 7–10 days does not appear to be beneficial, and shorter courses continue to be studied.

Most children still have fluid in the middle ear after antibiotic treatment: 70% at 2 weeks, 40% at 1 month, 20% at 2 months, and 10% at 3 months. In the majority of children, this fluid spontaneously clears, but some retain the fluid chronically. Regimens that include decongestants, antihistamines, myringotomy, or a combination of these treatments have all been advocated, but none has been demonstrated consistently to reduce the incidence of “residual” secretory otitis.

Frequent recurrences of acute suppurative OM develop in certain children. Groups at high risk include Eskimos; American Indians; premature and low-birth-weight infants; and infants with cleft palate, allergy, or a bout of pneumococcal otitis in the first year of life. Prophylactic daily amoxicillin or sulfonamides may decrease the frequency of recurrences in the otitis-prone patient.

Secretory OM may develop with or without (recognized) antecedent suppuration; it is particularly common in children with allergies. It appears that secretory OM may cause sufficient hearing loss or distortion of sound (or both) to interfere with the development of receptive language skills in infants, though the effects do not appear to be long-lasting; in older children, fluctuating hearing loss may cause difficulties in school. The evaluation of children with secretory OM includes quantification of hearing loss. A single determination may not be a valid assessment of impairment, however, since the deficit characteristically fluctuates. The role of antibiotics, decongestants, antihistamines, corticosteroids, or combinations of these drugs in the treatment of secretory OM remains uncertain. If the disorder persists beyond 4 months and is associated with a significant hearing deficit, tympanostomy tubes are commonly inserted, and adenoidectomy may be performed. Chronic middle ear disease develops in almost 100% of children with cleft palate, and most centers advocate early insertion of tympanostomy tubes for these patients. Adenoidectomy is contraindicated in these children, since they have velopalatine incompetence and need the “extra” nasopharyngeal tissue to assist in articulation. Secretory OM is not a valid indication for combined adenotonsillectomy in any child.

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   Another well-done prospective study finding, among other things, that repeated exposure to other children is one of the strongest risk factors for OM. See also Pediatrics *103:15–19, 1999, and 1158–1166 for two other studies on the epidemiology of OM.*
6. Owen, M., et al. Relation of infant feeding practices, cigarette smoke exposure, and group child care to the onset and duration of otitis media with effusion in the first two years of life. *J. Pediatr.* 123:702–711, 1993.
   Supine feeding position and early initiation of group child care were associated with earlier onset of OME; shorter duration of breast-feeding, increased packs of cigarettes smoked per day in the home, and increased hours per week in group child care were associated with an increase in the amount of time with OME. See also Arch. Otolaryngol. Head Neck Surg. *125:758–762, 1999, for more on passive smoking and OM.*
7. Fireman, P. Otitis media and eustachian tube dysfunction: Connection to allergic rhinitis. *J. Allergy Clin. Immunol.* 99:S787–S797, 1997.
   A clear discussion of the pathophysiology of OM with emphasis on the role of the eustachian tube. For a good discussion on the role of inflammatory mediators in OM, see Pediatr Ann. *27:76–81, 1998.*
8. Heikkinen, T., Thint, M., and Chonmaitree, T. Prevalence of various respiratory viruses in the middle ear during acute otitis media. *N. Engl. J. Med.* 340:260–264, 1999.
   Implicates respiratory syncytial virus (RSV) as a frequent invader of the middle ear during OM. This and a nice accompanying editorial (p. 312) suggest that an effective RSV vaccination will decrease OM dramatically. For corroboration of these findings, see Pediatrics *101:617–619, 1998, and* J. Pediatr. *133:390–394, 1998.*

9. Isaacson, G. The natural history of a treated episode of acute otitis media. *Pediatrics* 98:968–971, 1996.
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Diagnosis

10. Pelton, S. Otoscopy for the diagnosis of otitis media. *Pediatr. Infect. Dis. J.* 17:540–543, 1998.
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11. Brookhauser, P. Use of tympanometry in office practice for diagnosis of otitis media. *Pediatr. Infect. Dis. J.* 17:544–551, 1998.
A primer on the technique and interpretation of this underused modality.
12. Hoberman, A., Paradise, J., and Wald E. Tympanocentesis technique revisited. *Pediatr. Infect. Dis. J.* 16:S25–S26, 1997.
This is a procedure that may be making a come-back as the identification of the causative organisms in OM becomes more important.

Treatment of Acute Suppurative Otitis Media

13. Marchant, C., et al. Measuring the comparative efficacy of antibacterial agents for acute otitis media: The "Polyanna phenomenon." *J. Pediatr.* 120:72–77, 1992.
A must read! Especially read this before succumbing to the next detail man's data regarding his new Wonder Drug for OM.
14. Dowell, S., et al. Otitis media—Principles of judicious use of antimicrobial agents. *Pediatrics* 101:165–170, 1998.
If you read only two articles on the treatment of OM, read this one and the one above.
15. Klein, J., and Bluestone, C. Management of otitis media in the era of managed care. *Adv. Pediatr. Infect. Dis.* 12:351–386, 1997.
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16. Eden, A., Fireman, P., and Stool, S. Managing acute otitis: A fresh look at a familiar problem. *Contemp. Pediatr.* 13(3):64–80, 1996.
Well written and clear, with good illustrations.
17. Rosenfeld, R. An evidence-based approach to treating otitis media. *Pediatr. Clin. North Am.* 43:1165–1181, 1996.
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18. Del Mar, C., Glasziou, P., and Hayem, M. Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis. *B.M.J.* 314:1526–1529, 1997.
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19. Hoberman, A., et al. Efficacy of Auralgan for the treating of ear pain in children with acute otitis media. *Arch. Pediatr. Adolesc. Med.* 151:675–678, 1997.
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20. Kozyrskyj, A., et al. Treatment of acute otitis media with a shortened course of antibiotics. *J.A.M.A.* 279:1736–1742, 1998.
Five days is as effective as 10 for uncomplicated acute OM. See accompanying editorial on p. 1748. (For the opposing view, see Pediatr. Infect. Dis. J. *19:971–973, 2000.)*
21. Uhari, M., Kontiokari, T., and Niemela, M. A novel use of xylitol sugar in preventing acute otitis media. *Pediatrics* 102:879–884, 1998.
A fascinating study showing that this sugar, which inhibits the growth of pneumococci, can prevent acute OM if taken as a syrup or a gum at least five times a day.

Prevention of Recurrent Acute Suppurative Otitis Media

22. Paradise, J. Antimicrobial prophylaxis for recurrent acute otitis media. *Ann. Otol. Rhinol. Laryngol.* 155(Suppl.):33–36, 1992.
Though questions remain about the optimal regimen, antimicrobial prophylaxis appears to be the "most logical first approach in the management of the child with recurrent OM."
23. Casselbrant, M., et al. Efficacy of antimicrobial prophylaxis and of tympanostomy tube insertion for prevention of recurrent acute otitis media: Results of a randomized clinical trial. *Pediatr. Infect. Dis. J.* 11:278–286, 1992.
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24. Bluestone, C. Role of surgery for otitis media in the era of resistant bacteria. *Pediatr. Infect. Dis. J.* 17:1090–1098, 1998.
Suggests that surgery may now be preferred to prophylactic antibiotics due to the increase in antibiotic resistance. For a review of the randomized clinical trials between these treatment options see Adv. Otorhinolaryngol. *47:319–324, 1992.*

Complications/Sequelae

25. Paradise, J. Otitis media and child development: Should we worry? *Pediatr. Infect. Dis. J.* 17:1076–1083, 1998.
Discusses the controversies, the paucity of evidence, and the need for good studies in this area.
26. Roberts, J., et al. Otitis media, the care-giving environment, and language and cognitive outcomes at 2 years. *Pediatrics* 102:346–354, 1998.
A well-done and provocative study suggesting that the correlation between poor language development and hearing loss secondary to OME becomes less significant when the quality of the home and child-care environment is controlled for.
27. Fliss, D., Leiberman, A., and Dagan, R. Acute and chronic mastoiditis in children. *Adv. Pediatr. Infect. Dis.* 13:165–185, 1997.
An in-depth discussion of this now-rare complication of OM. Discusses other causes of mastoiditis as well. See also Clin. Pediatr. *35:391–396, 1996.*
28. Bluestone, C., et al. Consensus: Management of the child with a chronic draining ear. *Pediatr. Infect. Dis.* 4:607–611, 1985.
What the experts recommend, with an editorial comment on the ideal versus the actual.

Secretory Otitis Media (Otitis Media with Effusion)

29. Daly, K., Hunter, L., and Giebink, G. Chronic otitis media with effusion. *Pediatr. Rev.* 20:85–94, 1999.
A clear overview with a good table on the various audiologic tests for children with chronic OME. For another good overview, see Pediatr. Ann. *27:96–100, 1998.*
30. Stool, S., et al. *Otitis Media With Effusion in Young Children. Clinical Practice Guideline.* Washington, D.C.: Agency for Health Care Policy and Research Publication 94–0622, 1994.
Literature review–based recommendations on diagnosis and management from an expert panel convened by the American Academy of Pediatrics. (Copies available from the Agency for Health Care Policy: 1-800-358-9295.)
31. Williams, R., et al. Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion: A meta-analytic attempt to resolve the brouhaha. *J.A.M.A.* 270:1344–1351, 1993.
The authors set out to answer seven questions regarding the short- and long-term effectiveness of antibiotic treatment in the prophylaxis and treatment of OME. "Antibiotics appear to have a beneficial but limited effect on recurrent otitis media and short-term resolution of OME; a longer-term benefit for OME has not been shown."
32. Brown, D., et al. Drugs affecting clearance of middle ear secretions: A perspective for the management of otitis media with effusion. *Ann. Otol. Rhinol. Laryngol.* 117(Suppl.):3–15, 1985.
A review of the effect on physicochemical properties of secretions of anti-inflammatory drugs, decongestants, antihistamines, antibiotics, and mucolytics.
33. Macklin, M. Steroid treatment for otitis media effusion. *Clin. Pediatr.* 30:178–182, 1991.
The author reviews 15 studies and finds steroids by themselves not to be "convincingly effective"; steroids with antibiotics may offer a temporary beneficial effect. Tables summarizing the studies are provided.
34. Gates, G., et al. Effectiveness of adenoidectomy and tympanostomy tubes in the treatment of chronic otitis media with effusion. *N. Engl. J. Med.* 317:1444–1451, 1987.
Adenoidectomy with myringotomy or tubes was better than myringotomy or tubes alone. Tonsillectomy added to adenoidectomy does not add benefit: Lancet *1:1399–1402, 1986.*

61. SINUSITIS AND PERIORBITAL CELLULITIS

Kenneth B. Roberts and Conrad J. Clemens

The four paranasal sinuses are the maxillary, ethmoid, frontal, and sphenoid. The maxillary are slitlike at birth, growing to contain approximately 15 mL by adulthood. They are located between the floor of the orbits and the maxilla. The ethmoids, by contrast, are not single sinus cavities but are collections of small air cells, located between the nose and the medial walls of the orbits. Like the maxillary sinuses, the ethmoid sinuses are present at birth. The frontal sinuses do not appear until between 6 and 10 years of age, when they develop from the ethmoid air cells and assume their position above the orbits. The sphenoid sinuses are intracranial and are the least frequently infected.

The mucosal lining of the nose is continuous with the mucosa of the sinuses, explaining the frequent involvement of the sinuses with upper respiratory infections (URIs). Sinusitis, like otitis media, develops when bacteria become “trapped” in the normally sterile environment, generally as a result of obstruction to sinus drainage. This obstruction is the result of blockage of sinus ostia by thick secretions or the failure of the mucociliary apparatus or both. In young children, the caliber of the ostia is small, contributing to the ease with which secretions can cause obstruction; moreover, the ostia of the maxillary sinuses are located superiorly, making drainage an “uphill” process.

Because the normally sterile sinuses and the nose share the same mucosal lining, differentiating sinusitis from rhinitis is often difficult. Both cause symptoms such as rhinorrhea and cough. The secretions are often more purulent appearing with sinusitis, particularly after several days of illness, by which time the secretions of an uncomplicated URI have become clear. Nighttime cough, commonly thought to be the hallmark of sinusitis, frequently occurs with uncomplicated URIs and is not a very specific indicator of sinus infection. However, of greater value in differentiating sinusitis from uncomplicated URI is the persistence of daytime as well as nighttime cough beyond 10 days. Facial pain and headache are unusual complaints in small children with sinusitis, and sinus tenderness is generally also not present or is difficult to ascertain. For these reasons, the diagnosis of sinusitis is reserved for infants and children whose URIs are either prolonged or unusually severe. Prolonged is defined as symptoms that have not improved after 10 days; many URIs have not resolved completely within 10 days, but by that time most infants and children are well on their way to full recovery. Unusually severe refers to high fever or to complications, such as periorbital cellulitis.

Unfortunately, current laboratory and imaging diagnostic methods are of little help in the diagnosis of acute sinusitis in children. The bacteria grown from a nasopharyngeal swab do not correlate well with the bacteria found in the sinuses. Transillumination of the sinuses, while helpful in adolescents and adults, is not useful in children. Because it is difficult to distinguish inflammation of the mucosal lining of the sinuses due to URI from sinusitis, even the utility of sinus radiographs and computed tomography (CT) scans has been questioned in younger children. In older children, the radiographic presence of air-fluid levels, total opacification, or more than 4 mm of mucosal thickening allows the diagnosis of sinusitis to be made more confidently.

The organisms that cause acute sinusitis are the same as those that cause acute otitis media: *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae*, and *Moraxella catarrhalis*. The drug of choice is amoxicillin, though approximately one fourth of *H. influenzae* strains and three fourths or more of *M. catarrhalis* strains produce b-lactamase, prompting consideration of alternative antibiotics such as amoxicillin with clavulanic acid. In addition, with penicillin-resistant *S. pneumoniae* on the increase, the use of high-dose amoxicillin may be considered. Duration of therapy has not been well studied but is usually 10 days, although some children may require a second course (total of 3 weeks).

Chronic sinusitis, usually defined as persistent symptoms and signs for longer than 3 months, involves different organisms and treatment. Anaerobes and staphylococci are more prominent, although the organisms causing acute sinusitis are still the most common. Antibiotic coverage must take into account the additional pathogens. However, the role of infection in chronic sinusitis may be less important than once thought. In fact, recurrent acute sinusitis and chronic sinusitis may reflect an underlying disorder, such as immune deficiency, cystic fibrosis, immotile cilia syndrome asthma, or allergy.

Complications of sinusitis include encroachment on the orbit and intracranial abscesses. The former is more common, but the latter is more serious, requiring both operative and antibiotic therapy for successful management. Encroachment of the orbit occurs because of the location of the sinuses, separated from the orbit by a single cell layer of bone and the periosteum on both sides of the bone. Initially, response to inflammation in the sinus may result in inflammatory edema in the eyelids, with minimal tenderness and no limitation of extraocular movements. Further progression may include subperiosteal abscess and edema ultimately affecting intraorbital structures, resulting in proptosis, chemosis (edema of the conjunctivae), and varying degrees of ophthalmoplegia. Severe involvement within the orbit may produce vision loss.

Edema in the periorbital tissues elicits concern because of the potential for progression to compromise of visual function, as well as the possibility of a bacteremic process. The term periorbital cellulitis is used to distinguish the location of the inflammatory process from orbital cellulitis. In the former, the tissues around the orbit are involved, but the contents of the orbit are spared. “Preseptal” and “postseptal” have been suggested as preferable terms to periorbital and orbital, referring to the orbital septum, which is an extension into the eyelids of the periosteum of the bones forming the orbit. Though anatomically more correct, this terminology generally does not help clarify the confusion regarding management of children with periorbital cellulitis because the major issue is defining the pathophysiologic process, distinguishing among sinusitis, bacteremia, allergy, trauma, and generalized edema. The bacteremic form is now quite uncommon, since it was caused primarily by *H. influenzae* type b (Hib) and has all but disappeared since the introduction of vaccination against Hib; *S. pneumoniae* and other bacteria remain causes of this form of periorbital cellulitis, however. This soft-tissue infection generally occurs in infants and is accompanied by bacteremia in the majority of cases, and thus the potential for meningitis. Affected infants are febrile and ill. Treatment consists of vancomycin and a parenteral cephalosporin capable of eradicating the bacteria from the bloodstream and the cerebrospinal fluid, such as ceftriaxone or cefotaxime. Much more common are conditions without signs of constitutional illness, such as local or systemic allergic reactions with boggy edema of the eyelids, and local trauma with or without secondary infection. In infants and young children, generalized edema such as that associated with the nephrotic syndrome may be most pronounced in the loose tissues around the orbit, thereby mimicking periorbital cellulitis; the identification of proteinuria and hypoalbuminemia direct attention to the correct diagnosis. Sinusitis, as discussed, is the most common cause of periorbital swelling; operative drainage of the infected sinuses may be required if visual function becomes compromised.

Reviews

1. Wald, E. Sinusitis. *Pediatr. Rev.* 14:345–351, 1993.
   A review by the leading investigator of sinusitis in children. (Other reviews by the same author on sinusitis include Semin. Pediatr. Infect. Dis. *6:79–84, 1995, and* N. Engl. J. Med. *326:319–323, 1992. In addition, see her helpful article on purulent nasal discharge in* Pediatr. Infect. Dis. J. *10:329–333, 1991.)*
2. Isaacson, G. Sinusitis in childhood. *Pediatr. Clin. North Am.* 43:1297–1318, 1996.
   A complete discussion on all aspects of this disease. Current surgical management is discussed in greater depth.
3. Shapiro, G., and Rachelefsky, G. Introduction and definition of sinusitis. *J. Allergy Clin. Immunol.* 90:417–565, 1992.
   The entire edition is devoted to all aspects of sinusitis, including anatomy and physiology (p. 419), physiologic changes during experimental upper respiratory infections (URIs) (p. 474), host defenses (p. 424), and complications (p. 552). Several are specific to children: history and physical examination (p. 433), imaging (p. 442), and the role of allergy (p. 515).

Acute Sinusitis

4. Bussey, M., and Moon, R. Acute sinusitis. *Pediatr. Rev.* 20:142, 1999.
   “What you need to know” in one page.
5. Williams, J., and Simel, D. Does the patient have sinusitis? Diagnosing acute sinusitis by history and physical examination. *J.A.M.A.* 270:1242–1246, 1993.
   An evidence-based examination of the literature, underscoring the difficulties in making this diagnosis in the pediatric population. Well written.
6. Wald, E., et al. Acute maxillary sinusitis in children. *N. Engl. J. Med.* 304:749–754, 1981.
   The classic study by Wald, correlating radiographic changes with bacteriologic findings from sinus aspirates. Unfortunately, correlating those findings with clinical symptoms was not as successful.

7. Wald, E., Guerra, N., and Byers, C. Upper respiratory tract infections in young children: Duration of and frequency of complications. *Pediatrics* 87:129–133, 1991.
How long is too long for an uncomplicated URI? The vast majority resolved by 10 days. However, 5–15% were prolonged; in addition, a child in daycare was almost twice as likely to have a prolonged URI than a child being cared for at home. (See also Arch. Pediatr. Adolesc. Med. *152:244–248, 1998, and* Pediatr. Infect. Dis. J. *15:576–579, 1996.)*
8. Gwaltney, J., et al. Computed tomography of the common cold. *N. Engl. J. Med.* 330:25–30, 1994.
A wonderful illustration of how an "abnormal" finding may not necessarily correlate with disease. (For more on the controversy regarding imaging studies in sinusitis, see Pediatr. Radiol. *27:837–846, 1997;* J. Pediatr. *114:45–50, 1989; and* Pediatrics *73:306–308, 1984.)*
9. O'Brien, K., et al. Acute sinusitis—Principles of judicious use of antimicrobial agents. *Pediatrics* 101:174–177, 1998.
A must read in an era of increasing antibiotic resistance! Amoxicillin remains the first-line drug of choice. This article is part of an entire supplement on the use of antibiotics for pediatric URIs. (See also B.M.J. *317:632–37, 1998, and* Contemp. Pediatr. *13:49–62, 1996.)*
10. Wald, E., Chiponis, D., and Ledesma-Medina, J. Comparative effectiveness of amoxicillin and amoxicillin-clavulanate potassium in acute paranasal sinus infections in children: A double-blind, placebo-controlled trial. *Pediatrics* 77: 795–800, 1986.
To date, the only placebo-controlled trial for the antibiotic treatment of acute sinusitis in children.

Chronic Sinusitis

11. Wald, E. Chronic sinusitis in children. *J. Pediatr.* 127:339–347, 1995.
To differentiate from subacute sinusitis, see J. Pediatr. *115:28–32, 1989. Another good review can be found in* Otolaryngol. Clin. North Am. *29:1–9, 1996. Chronic sinusitis should make one think about allergies (see below) or immunologic defects* Pediatrics *87:311–316, 1991).*
12. Gungor, A., and Corey, A. Pediatric sinusitis: A literature review with emphasis on the role of allergy. *Otolaryngol. Head Neck Surg.* 116:4–15, 1997.
Understanding the relationship between allergies and sinusitis will become increasingly important, especially now that improved treatment options for allergic rhinitis are available for children. (See also Pediatr. Ann. *27:759–766, 1998.)*
13. Lusk, R. The surgical management of chronic sinusitis in children. *Pediatr. Ann.* 27:820–827, 1998.
A look at what probably doesn't work (tonsillectomy and adenoidectomy) and what probably does work (middle meatal antrostomy and ethmoidectomy). This article also has excellent photographs. Also see Laryngoscope *108:796–99, 1998. Functional endoscopic sinus surgery is a safe and effective therapeutic modality in children with chronic sinusitis that is refractory to medical therapy.*

Periorbital and Orbital Cellulitis

14. Powell, K. Orbital and periorbital cellulitis. *Pediatr. Rev.* 16:163–167, 1995.
An excellent and readable overview.
15. Schwartz, G., and Wright, S. Changing bacteriology of periorbital cellulitis. *Ann. Emerg. Med.* 28:617–620, 1996.
*Streptococcal organisms are the most common cause of bacteremia associated with periorbital cellulitis in the post–*Haemophilus influenzae *vaccination era. In addition, lumbar punctures are no longer necessary unless clinically indicated* J. Pediatr. *122:355–359, 1993).*
16. Clary, R., Cunningham, M., and Eavey, R. Orbital complications of acute sinusitis: Comparison of computed tomography scan and surgical findings. *Ann. Otol. Rhinol. Laryngol.* 101:598–600, 1992.
Operative findings agreed in 16 of 19 cases; in 2 an abscess was predicted but not found, and in 1 an abscess was found though not predicted. For more support for clinical diagnosis and caution in interpreting computed tomography scans, see Clin. Pediatr. *31:37–43, 1992.*

Sinusitis and Intracranial Abscess

17. Johnson, D., et al. Treatment of intracranial abscesses associated with sinusitis in children and adolescents. *J. Pediatr.* 113:15–23, 1988.
No child was treated successfully with medical management alone. (Some recent adult series are also instructive. Laryngoscope *108:1635–1642, 1998, and 107: 863–867, 1997.)*

62. STREPTOCOCCAL PHARYNGITIS

Kenneth B. Roberts and Conrad J. Clemens

Sore throat is a common occurrence and the basis of numerous physician contacts. Often, other signs and symptoms of an upper respiratory tract infection (URI) are present as well, suggesting a viral etiology. In children with sore throat and fever who do not have URI symptoms, the major pathogen of concern is the group A, b-hemolytic streptococcus because it causes acute morbidity and can produce complications, both suppurative (e.g., peritonsillar abscess) and nonsuppurative (glomerulonephritis and rheumatic fever).

The streptococcus is a pyogenic gram-positive organism capable of elaborating extracellular products that are pathogenic, such as erythrogenic toxin (the cause of scarlet fever), and immunogenic, such as streptolysin O (to which antistreptolysin O [ASO] antibodies are formed). Streptococci are classified in three ways: by differences in the carbohydrate constituents in the cell wall (group), by the ability to hemolyze red cells (a, b, g), and by differences in the M protein (serotype). Group A streptococci cause tonsillopharyngitis, scarlet fever, invasive disease such as sepsis, erysipelas, pneumonia, and impetigo. Immunologic responses may lead to acute glomerulonephritis and rheumatic fever. Group B organisms are the major cause of neonatal sepsis. Group C has been associated with pharyngitis and glomerulonephritis. Group D streptococci are important causes of subacute bacterial endocarditis and urinary tract infection. The other groups are infrequently incriminated in human infection.

a-Hemolysis is characterized by the persistence of “ghost” cells microscopically and by a greenish tinge macroscopically; b-hemolysis is complete; g-hemolysis is the designation given to nonhemolytic organisms. M protein permits group A, b-hemolytic streptococci to be further classified into more than 100 serotypes; serotyping currently is performed only in research laboratories.

Group A, b-hemolytic streptococcal pharyngitis is spread by close contact with an individual shedding the organism. Bacteria multiply in the nasopharynx of the susceptible host, and after 24–48 hours the typical clinical syndrome develops in 60% of individuals of school age or older; the illness is so mild in 20% that the symptoms are overlooked, and 20% are completely asymptomatic. Hoarseness and cough are not features; their presence argues strongly for a nonstreptococcal cause of the illness. In infants, the disease is usually a nasopharyngitis with a profuse nasal discharge; since suppurative complications and acute rheumatic fever are rare in this age group and the illness is mild, throat cultures and antibiotic treatment are rarely necessary. In somewhat older children, signs and symptoms become referable to the tonsils and pharynx, but abdominal complaints are frequent as well. School-aged children manifest the classic syndrome of fever, headache, and sore throat, described more as pain on swallowing than as a feeling of pharyngeal irritation. Examination of the pharynx usually reveals an intensely red throat with moderate or marked exudate, although the exudate may not be present on the first day. Petechiae on the palate early in the course strongly suggest a streptococcal origin, and the presence of the rash of scarlet fever is virtually diagnostic. Tender anterior cervical lymph nodes at the angle of the jaw are particularly noteworthy, since they imply a more invasive infection and correlate with rises in ASO antibody.

Other organisms capable of producing an exudative pharyngotonsillitis include *Corynebacterium diphtheriae* (diphtheria), viruses such as Epstein-Barr virus (infectious mononucleosis) and adenovirus, and *Neisseria gonorrhoeae* (gonococcus). *Arcanobacterium haemolyticum* (formerly *Corynebacterium haemolyticum*) may cause a sore throat with scarlet fever–like rash in adolescents and young adults; the roles of *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and non–group A streptococci remain controversial. Because no constellation of clinical symptoms can accurately distinguish streptococcal pharyngitis from nonstreptococcal pharyngitis, the definitive diagnosis must be made by the laboratory. Rapid diagnostic testing of throat swabs for streptococcal antigen is widely used in the office setting because results are available in minutes. The rapid tests are helpful when results are positive, but some clinicians prefer to confirm negative results with a standard throat culture due to a less than acceptable rate of false negatives. The sensitivity of some of the newer rapid tests is quite good, possibly rendering the confirmatory culture unnecessary.

Antibiotics shorten the clinical course if administered early. Treatment also is effective in preventing acute rheumatic fever. The incidence of this nonsuppurative complication can be reduced ten-fold, although not eliminated, if treatment successfully eradicates the streptococci from the pharynx. The short delay inherent in processing a culture does not negate the benefit of treatment. Penicillin remains the drug of choice; for patients truly allergic to penicillin, erythromycin is the preferred alternative. The recommended treatment is oral penicillin V for 10 days or a single injection of long-acting benzathine penicillin. Penicillin by mouth is equally effective when given 2, 3, or 4 times per day. A regimen of 2 doses per day may aid compliance, particularly in school-aged children. There are fewer failures with benzathine than with oral penicillin (even when compliance with the oral regimen is ensured), but the pain associated with the injection has limited its general use. Combinations of benzathine and procaine penicillin are as effective as benzathine alone and are less painful, but children, parents, and pediatricians prefer to avoid the “shot.” Cephalosporins may be somewhat more effective in eradicating streptococci than is penicillin, and permit a shorter course of treatment (as does azithromycin), but the magnitude of the benefit has not been considered sufficient to warrant recommending these more expensive, broader-spectrum agents as first-line drugs.

It is unnecessary to obtain a throat culture following treatment, unless the child is symptomatic. After the acute infection, some children will continue to carry streptococci in their throat, regardless of the regimen of initial treatment or retreatment. The organisms differ biologically from those that caused the initial infection by virtue of the loss of M protein; this information is reassuring, since M protein appears to be a “virulence factor.” However, M-typing is not a readily available laboratory procedure, so, in practice, carriers are identified by the demonstration of repeated positive cultures. At the time of clinical illness, it is often impossible to determine whether a child is a carrier or has acquired a new, virulent streptococcal strain.

Both nonsuppurative complications of group A, b-hemolytic streptococcal infection (acute rheumatic fever and glomerulonephritis) can follow pharyngeal infection; rheumatic fever does not follow superficial skin infection with streptococci (impetigo). Glomerulonephritis results from antigen-antibody complexes. The exact mechanism by which acute rheumatic fever is produced remains unknown. Antistreptolysin O antibodies only corroborate (retrospectively) the occurrence of a streptococcal infection and do not appear to play a direct etiologic role in rheumatic fever. There is no way at present to estimate an individual child's risk for the development of acute rheumatic fever, but children who have a family history of rheumatic heart disease or who have had a previous bout of rheumatic fever deserve particular attention when they develop a sore throat.

The development of a streptococcal vaccine has been hampered by the large number of antigenically distinct strains and the concern that a vaccine might inadvertently produce rheumatic fever or glomerulonephritis.

General Reviews

1. Pichichero, M. Group A beta-hemolytic streptococcal infections. *Pediatr. Rev.* 19: 291–302, 1998.
   A great place to start for a review of epidemiology, diagnosis, and treatment. For another good review that also discusses the biology of this organism, see N. Engl. J. Med. *325:783–93, 1991.*
2. Bisno, A., et al. Diagnosis and management of group A streptococcal pharyngitis: A practice guideline. *Clin. Infect. Dis.* 25:574–583, 1997.
   An evidence-based guideline.

Diagnosis

3. Breese, B., and Disney, F. The accuracy of diagnosis of beta streptococcal infections on clinical grounds. *J. Pediatr.* 44:670–673, 1954.
   A classic: 75% accuracy in predicting positive cultures; 77% accuracy in predicting negative cultures. For a recent discussion of clinical findings in group A streptococcal (GAS) pharyngitis, see Arch. Pediatr. Adolesc. Med. *152:927–928, 1998.*
4. Berkovitch, M., et al. Group A streptococcal pharyngotonsillitis in children less than 2 years of age—More common than is thought. *Clin. Pediatr.* 38:361–363, 1999.
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11. Karpathios, T., et al. *Arcanobacterium haemolyticum* in children with presumed streptococcal pharyngotonsillitis or scarlet fever. *J. Pediatr.* 121:735–737, 1992.
    The organism was cultured from the throats of almost 10% of children with pharyngotonsillitis, some of whom had a scarlatiniform rash.
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Other

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63. BRONCHIOLITIS

Kenneth B. Roberts and Olakunle B. Akintemi

As the term suggests, bronchiolitis is an inflammatory disease of the bronchioles. It is a common disorder in infants; the incidence is estimated at 6–7 cases per 100 infants under the age of 2 years, with half of the cases occurring between 2 and 7 months of age. Males predominate 2:1; there is a seasonal clustering of cases between December and March.

Bronchiolitis is most commonly caused by respiratory syncytial virus (RSV), the most important cause of viral lower respiratory tract infections in young children worldwide. Other viruses that can cause bronchiolitis are parainfluenza viruses, influenza viruses, and adenovirus. In the United States, RSV is responsible for 90,000 hospitalizations and 4,500 deaths annually. There are two subgroups of RSV recognized, denoted as A and B. Infection is spread by droplets, but RSV is capable of persisting on environmental surfaces and being carried by adults to susceptible infants. Spread within families—and hospital inpatient units—is common. Approximately two thirds of infants become infected with RSV in their first year of life. Reinfection throughout life is also common, though the disease is milder beyond early infancy.

Disease may be a direct result of RSV infection of bronchiolar epithelium in an infant host, but it is also postulated that bronchiolitis may, at least in part, represent severe local interaction of RSV antigen and maternal, transplacentally acquired immunoglobulin G (IgG). This theory proposes that local immunoglobulin A (IgA) is the important defense against RSV and that IgG in the absence of IgA may be harmful. Supporters point out that children immunized with killed RSV vaccine in trials in the 1960s were sensitized rather than protected and had worse disease when challenged with “wild” RSV.

The small airways of infants with bronchiolitis are obstructed in two ways: The bronchiolar walls are thickened as a result of edema, lymphocytic infiltration, and, occasionally, proliferation of cells; and the lumens are plugged by mucus, cellular debris, and, in severe cases, desquamated bronchiolar epithelium. A reduction in the radius of the small airways causes a disproportionate increase in airflow resistance (since resistance is related to the radius raised to the fourth power if flow is laminar and to the fifth power if it is turbulent). The already small size of the lower airways in young infants may account for the age-related severity.

The distribution of involvement in bronchiolitis is patchy: Some areas are obstructed, and some are not. Those that are completely obstructed become atelectatic; those that are partially obstructed become overinflated. The unaffected areas remain normal and “hyperventilate” in an attempt to maintain the normalcy of the arterial Po_2 and Pco_2. The consequences of these changes are small airway obstruction, air trapping, increased inspiratory and expiratory resistance, increased work of breathing and oxygen consumption, and hypoxemia.

The first clinical sign of bronchiolitis in an infant is an upper respiratory tract infection; usually, another family member is ill with a respiratory infection. After a few days, the infant begins to cough and breathe more rapidly, often with feeding difficulty or vomiting. Wheezing and retractions may be prominent at this time, and the infant is irritable, although without much fever. Physical examination confirms the presence of agitation, retractions, wheezing, crackles, and impaired air exchange. The liver and spleen may be palpable because of air trapping with downward displacement of the diaphragm. The temperature is below 38°C (100°F) in half the patients and is rarely over 39.5°C (103°F). The respiratory rate is usually increased and provides a good guide to arterial Po_2 and Pco_2: As the respiratory rate increases, the Po_2 falls in a linear fashion (from 80 mm Hg at a respiratory rate of 20, to 60 mm Hg at a respiratory rate of 60). The relationship between respiratory rate and Pco_2 is not linear, however; Pco_2 remains normal until a respiratory rate of 50–60 is reached and then rapidly rises with increasing tachypnea (see below).

A radiograph of the chest reveals hyperinflation and small areas of collapse; it is often possible to see thickened bronchioles on end. The right upper lobe, in particular, is subject to atelectasis. Pulse oximetry provides a quantitative assessment of the degree of oxygen desaturation. Arterial blood gases indicate the patchy nature of the obstruction. The Po_2 is invariably reduced as a consequence of the obstructed and partially obstructed bronchioles, since normally ventilated areas cannot compensate for areas that are poorly ventilated but well perfused, unless oxygen is added to the inspired air. The Pco_2 is normal if the hypercapnia caused by affected areas can be balanced by the hyperventilation of normal areas; when compensation is not possible, respiratory failure supervenes.

The presence of RSV antigen can be documented by a rapid diagnostic test on nasal secretions.

Once the signs of bronchiolar obstruction appear, the peak of the illness is soon reached. In otherwise healthy infants, this phase of the illness is usually brief, on the order of a few days, but approximately 5% of affected infants require hospitalization because of apnea, hypoxemia, poor intake, or concern about the ability of caregivers to provide adequate support. Particular attention is given to children at high risk of complications, such as infants with chronic lung disease, immunodeficiency, immunosuppression, or cyanotic heart disease. After the peak of illness, improvement is gradual. Most infants have recovered by 2 weeks. Complications include pneumonia, pneumothorax, apnea, and respiratory failure; mortality is less than 1% in hospitalized infants.

The treatment of bronchiolitis is supportive, and simple measures usually suffice. Weight loss should be expected during the acute stage, and the infants should be permitted small feedings while awake, not to meet caloric needs, but to relieve the agitation caused by hunger; if respiratory distress becomes severe, oral feedings are withheld. Intravenous fluids may be required but should not be excessive, since the combination of increased negative intrathoracic pressure during inspiration (caused by airway obstruction) and excessive fluid administration may lead to pulmonary edema. A trial of inhaled bronchodilators is commonly given. Though evidence is conflicting regarding the effectiveness in clinical trials, it is clear that some infants receive benefit; the only way to distinguish responders from nonresponders is to administer the drug. Steroids do not appear to provide immediate benefit or to enhance recovery. Infants need to be monitored for evidence of tiring from the increased work of breathing; their defense against respiratory failure is the ability to maintain a two- to three-fold increase in minute ventilation. Oxygen is the “drug of choice” for hypoxic infants in respiratory distress; the desired response is a reduction in respiratory rate and the work of breathing. If respiratory failure does occur, it may be managed by a few days of controlled ventilation.

Infection with RSV can be particularly severe in some infants: those with congenital heart disease, bronchopulmonary dysplasia, prematurity, immunodeficiency, or immunosuppression. Specific antiviral therapy, ribavirin, is available for administration by inhalation to these babies, but the drug is of questionable benefit. Moreover, it is expensive, its administration is cumbersome, and questions remain about its safety to potentially pregnant caregivers. Prevention of infection in these high-risk babies with chronic lung disease or immunosuppression has been accomplished with monthly infusions of RSV-immune globulin intravenous; the infusions are expensive and cumbersome but provide protection against pathogens in addition to RSV. A monoclonal antibody preparation permits RSV-limited protection to be provided by monthly intramuscular injection, but the cost-effectiveness of this approach is questionable. Attempts continue to develop a vaccine against RSV, particularly a live attenuated vaccine that can be administered intranasally. Of concern is the experience in the past with vaccine “sensitization” and the fact that natural immunity to RSV is not durable. As noted, reinfection is common, and nearly half of 2-year-olds have been infected twice. As the biology of the virus is becoming better understood, it is hoped that a vaccine may be developed that is both immunogenic and safe.

During the acute event, it may be impossible to distinguish bronchiolitis from asthma. It seems prudent to follow all infants who have had bronchiolitis and reserve the diagnosis of asthma for those who demonstrate recurrent bouts of wheezing. Although the prognosis for short-term recovery from bronchiolitis is excellent, approximately half the infants with bronchiolitis will have reactive airway disease (asthma) later on.

Reviews

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2. Everadd, M. Bronchiolitis. Origins and optimal management. *Drugs* 49:885–896, 1995.
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Respiratory Syncytial virus

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   There are conflicting data regarding whether disease caused by subgroup A is more severe than subgroup B. A review of 15 published studies reveals that subgroup A infections are more severe in 7 studies, and of the same severity in 8 studies.
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High-Risk Groups

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   Emphasizes the role of staff in the transmission and atypical nature of the illness, with apnea a prominent feature. (Apnea is also a feature in hospitalized infants with RSV, particularly those with a history of prematurity or young postnatal age; Am. J. Dis. Child. *138:247–250, 1984.) Other groups subject to difficulty with RSV include infants with bronchopulmonary dysplasia (*Pediatrics *82: 199–203, 1988); preterm twins and triplets (*Am. J. Dis. Child. *147:303–306, 1993); infants with congenital heart disease (*N. Engl. J. Med. *307:397–400, 1982), although perhaps not to the extent previously thought (*Crit. Care Med. *20: 1406–1413, 1992); and infants with immune deficiency, such as those infected with human immunodeficiency virus (*J. Pediatr. *117:251–258, 1990).*

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11. Shaw, K., Bell, L., and Sherman, N. Outpatient assessment of infants with bronchiolitis. *Am. J. Dis. Child.* 145:151–155, 1991.
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13. Avery, M., Galina, M., and Nachman, R. Mist therapy. *Pediatrics* 39:160–165, 1967.
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Transmission and Spread

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Sequelae

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23. Kattan, M. Epidemiologic evidence of increased airway reactivity in children with a history of bronchiolitis. *J. Pediatr.* 135:S8–S13, 1999.
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Prevention

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25. The Impact-RSV Study Group. Palivizumab, a humanized respiratory syncytial antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 102:531–537, 1998.
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26. Karron, R., and Ambrosino, D. Respiratory syncytial virus vaccines. *Pediatr. Infect. Dis. J.* 1998:919–920, 1998.
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27. Prober, C., and Sullender, W. Advances in prevention of respiratory syncytial virus infections. *J. Pediatr.* 135:546–558, 1999.
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Parainfluenza Virus Bronchiolitis

28. Welliver, R., et al. Parainfluenza virus bronchiolitis: Epidemiology and pathogenesis. *Am. J. Dis. Child.* 140:34–40, 1986.
Similar to bronchiolitis caused by RSV.M

64. PNEUMONIA

Kenneth B. Roberts and Conrad J. Clemens

The respiratory tract below the vocal cords is normally sterile. This sterility is preserved by a number of host defense mechanisms, including a ciliary transport mechanism, a sheet of mucus-producing cells, and a cough reflex. Microorganisms that bypass these defenses are cleared via lymphatic channels by phagocytic cells with the help of multiple other humoral factors. Infection of the lower respiratory tract can occur through a number of ways, most commonly from aspiration of organisms that normally colonize the oropharynx, as well as by inhalation of infectious aerosols. Rarely, infection occurs from hematogenous spread.

Pneumonia can be caused by virtually every class of microorganism. Nonbacterial agents, most commonly viruses and *Mycoplasma pneumoniae*, make up 80% of childhood pneumonias. In addition, a viral agent coexists in 30–50% of the bacterial pneumonias. Unfortunately, the diagnosis of pneumonia as well as the identification of a specific etiologic agent is often difficult in pediatric patients.

In determining an etiologic agent in pediatric pneumonia, the single most useful piece of information is the age of the child. For example, in neonates pneumonia is often caused by maternal pathogens such as Group B streptococcus and *Chlamydia trachomatis*. In infants, viruses such as respiratory syncytial virus (RSV) and parainfluenza predominate. In older infants and toddlers *Streptococcus pneumoniae* becomes more common. *M. pneumoniae* and *Chlamydia pneumoniae* tend to occur more commonly in older children and adolescents. Time of year is also a valuable piece of historical data since many infectious agents (especially viruses) are seasonal in nature. For example, RSV is usually seen from late fall to springtime; parainfluenza often in the late fall. Finally, the immune status of the child is important since a number of additional etiologic agents, including fungi and parasites, can cause pneumonia in the immunocompromised child.

The physical examination of a child with possible pneumonia is critical but often frustrating since “textbook” signs are frequently absent. For example, the classic clinical picture of pneumococcal pneumonia described in adults, with shaking chills, pleuritic pain, prostration, and rusty sputum is rarely seen in children. Infants, in particular, may show only nonspecific signs such as fever and tachypnea. Therefore, when examining children with respiratory complaints for evidence of pneumonia, most clinicians depend as much on breathing patterns, particularly tachypnea and flaring of the alae nasi, as on auscultatory findings; crackles may be heard, but signs of consolidation are infrequent. It is important to remember that the absence of tachypnea quite reliably rules out pneumonia. Using a pulse oximeter to measure the degree of hypoxia, in conjunction with the child's clinical picture, can also be very useful.

Laboratory evaluation is often not helpful. While suggestive of a bacterial process, elevations in the white blood count, absolute neutrophil count, C-reactive protein, or erythrocyte sedimentation rate are of unproven utility. Children rarely are able to produce sputum for a Gram's stain and culture. Nasopharyngeal cultures may yield organisms known to cause pneumonia (e.g., *S. pneumoniae*), but do not correlate with the isolates recovered from diseased lungs. Blood cultures are rarely positive. Some laboratory tests for specific agents may be of help, such as serology for *Mycoplasma* or a tuberculin test for *Mycobacterium tuberculosis*.

A chest radiograph can identify the presence and extent of pneumonia, and the pattern may suggest the class of organism responsible. The presence of lobar consolidation or pleural effusion suggests a bacterial process, while hyperinflation or peribronchial edema suggests a viral process. However, radiographic results must be viewed in the context of the clinical picture. Many disease processes may mimic the radiologic findings of pneumonia (e.g. malignancy, collagen-vascular disease, and congestive heart failure) and radiologic findings of pneumonia may be absent or lag behind the clinical picture.

Because there is often no single diagnostic test, the diagnosis of specific childhood pneumonias is often made on the basis of recognizing a constellation of historical, physical, laboratory, and radiographic findings. A number of important constellations are described below.

Chlamydia trachomatis causes a distinctive pneumonia in 10–30% of infants who are infected at birth. These infants present between 4 and 11 weeks of age with a staccato cough and tachypnea, often with a history of rhinorrhea for the preceding 1–2 weeks. Only half the infants will have had symptomatic conjunctivitis (“inclusion blennorrhea”) as evidence of the intrapartum acquisition of *C. trachomatis*. The infants characteristically are afebrile and tachypneic, with widespread crackles readily audible. Hyperinflation and diffuse interstitial infiltrates are seen on chest x-ray. The white blood cell count is increased, often with prominent eosinophilia; this observation and the nature of the cough gave rise to the term for this pneumonia used earlier this century, “pertussoid eosinophilic pneumonia.” Erythromycin (or a newer macrolide) is the drug of choice.

In pneumococcal pneumonia, involvement is characteristically a lobar consolidation. Response to penicillin therapy is prompt, with marked improvement evident within 48 hours; radiographic resolution may take up to 6 weeks, however. The complications of concern are empyema formation and systemic dissemination with septicemia. Because of the emergence of penicillin-resistant pneumococci, vancomycin is often used when the child appears particularly ill or complications are present.

Staphylococcal pneumonia was much more frequent 40 years ago than it is today. It remains most common in the first year of life and characteristically is unilateral, with a peculiar predilection for the right hemithorax. The two typical features of staphylococcal pneumonia are pneumatocele formation and rapid progression, with worsening detectable on chest radiographs taken hours apart. Empyema, with thick, purulent fluid, is a hallmark of the disease. Treatment of staphylococcal pneumonia includes the intravenous infusion of a penicillinase-resistant penicillin in large doses and chest tube drainage of empyema. Infants who recover from staphylococcal pneumonia when tested later in childhood do not have the marked diminution in respiratory function that one might expect from the extent of the acute parenchymal disease.

Group A streptococcal pneumonia is much less common than the other bacterial pneumonias. The onset simulates pneumococcal pneumonia, but the response to penicillin is much less dramatic. Empyema occurs, as in staphylococcal pneumonia, but the fluid is serosanguineous and thin at first, becoming purulent and thick as the disease progresses. Penicillin is the drug of choice.

Mycoplasma pneumoniae is said to account for 25–35% of pneumonias in late childhood and early adulthood. The incubation period is 2–3 weeks, considerably longer than with the bacterial agents. Symptoms such as headache, malaise, fever, and cough are more dramatic than are the signs of respiratory involvement. Unlike the pattern with the bacterial pneumonias, the white blood cell count and differential count are usually normal; “cold agglutinins” may be demonstrated by the end of the first week of illness (complement-fixing antibodies appear a week later). The x-ray characteristically has more extensive involvement than the physical examination would suggest and “looks worse than the patient.” The disease is mild but prolonged, with cough in particular lasting several weeks in untreated patients. Tetracycline or a macrolide (e.g., erythromycin, azithromycin) may decrease the duration of clinical illness (with improvement evident on the chest radiograph) but does not shorten the period of shedding of the organism from the pharynx. *C. pneumoniae* appears to cause a similar clinical syndrome, and many adolescents and young adults thought to have *M. pneumoniae* infection may well have *C. pneumoniae* instead. Fortunately, the choice of antibiotics is the same.

As noted, viruses cause most bouts of pneumonia. Respiratory syncytial virus (see Chap. 63) is the most frequent agent in infancy, followed by the parainfluenza viruses. Adenovirus may cause a destructive pneumonia; influenza, while common in adults, infrequently causes severe pneumonia in children. Viral agents noted for their characteristic exanthems, such as measles and varicella (chickenpox), are also capable of causing serious or fatal pneumonias, particularly in immunosuppressed hosts. Opportunistic organisms, such as cytomegalovirus and the protozoan *Pneumocystis carinii*, have become important causes of morbidity (and mortality) in children with cancer, in premature infants, and in malnourished or immunocompromised patients. With the recent resurgence of tuberculosis, it is important to remember that a “simple” pneumonia may represent a primary infection with *M. tuberculosis.*

The decision to treat a child who has pneumonia is usually made clinically. Antibiotic therapy is directed at the most likely pathogens, as suggested by the child's age,

clinical presentation (including severity of illness), and, if obtained, the pattern on chest x-ray. Expectorants have not been shown to be of benefit at recommended dosages. In some children, pneumonias are recurrent, and further investigation is then required; considerations include cystic fibrosis, reactive airway disease, aspiration, immunodeficiency, and anatomic disorders.

Pneumonia: Reviews

1. Jadavji, T., et al. A practical guide for the diagnosis and treatment of pediatric pneumonia. *Can. Med. Assoc. J.* 156:S703–S711, 1997.
   Excellent! A concise review of the past 30 years of literature by a consensus group of pediatric specialists from Canada.
2. Schidlow, D., and Callahan, C. Pneumonia. *Pediatr. Rev.* 17:300–309, 1996.
   A basic review with an excellent section on clinical signs of pneumonia. In addition, cases are discussed illustrating how age affects the presentation and epidemiology of childhood pneumonia. For another excellent review, see Pediatr. Infect. Dis. J. *19:373–377, 2000.*
3. Denny, F., and Clyde, W. Acute lower respiratory tract infections in nonhospitalized children. *J. Pediatr.* 108:635–646, 1986.
   Still very pertinent 15 years later. Puts pneumonia in perspective with other lower respiratory infections, addressing age, season, and clinical syndromes.
4. McCarthy, P., et al. Lower respiratory tract infections in children. *Curr. Opin. Pediatr.* 11:96–105, 1999.
   These yearly updates assume a basic knowledge of pediatric lower respiratory disease, but include a comprehensive discussion of recent advances as well as annotated references.

Evaluation and Diagnosis

5. Margolis, P., and Gadomski, A. Does this infant have pneumonia? *J.A.M.A.* 279:308–313, 1998.
   A systematic review of assessing various historical and physical findings. Important findings: (1) the absence of tachypnea is the most reliable to rule out pneumonia; and (2) in the absence of clinical signs of pneumonia, chest radiographs are of little utility. For more on when to get a chest x-ray, see Pediatrics *92:524–526, 1993.*
6. Correa, A. Diagnostic approach to pneumonia in children. *Semin. Respir. Infect.* 11:131–138, 1996.
   Based on a review of the literature, the authors conclude that unless a child (1) is less than 3 months old, (2) has recurrent or nonresolving pneumonia, or (3) is immunocompromised, the diagnosis of pneumonia should rely on history and physical examination.
7. Taylor, J., et al. Establishing clinically relevant standards for tachypnea in febrile children younger than 2 years. *Arch. Pediatr. Adolesc. Med.* 149:283–287, 1995.
   Again, emphasizing the importance of tachypnea in the diagnosis of pneumonia. For more on this, see Arch. Dis. Child. *66:81–84, 1991.*
8. Weber, M., et al. Predictors of hypoxemia in hospital admissions with acute lower respiratory tract infection in a developing country. *Arch. Dis. Child.* 76:310–314, 1997.
   Oximetry can be useful in assessing severity of lower respiratory infection (LRI) in children—at least in developing countries. However, agreement between observers about the presence and severity of various clinical signs, as well as the correlation between these clinical signs and degree of hypoxemia, can be a problem—see Am. Rev. Respir. Dis. *145:106–110, 1992.*
9. Spencer, P. Pneumonia, diagnosed on the abdominal radiograph, as a cause for acute abdomen in children. *Br. J. Radiol.* 63:306–308, 1990.
   A reminder that children with pneumonia may present with abdominal pain mimicking appendicitis. (Conversely, infants presenting with an acute abdomen may present with grunting respirations: Pediatr. Emerg. Care *8:354–358, 1992.)*
10. Markowitz, R., and Ruchelli, E. Pneumonia in infants and children: Radiological-pathological correlation. *Semin. Roentgenol.* 33:151–162, 1998.
    Concise but extremely valuable reading with excellent radiographic ilustrations. See also Am. J. Dis. Child. *142:43–46, 1988, for some good radiographs of viral respiratory tract infection.*
11. Wahlgren, H., et al. Radiographic patterns and viral studies in childhood pneumonia at various ages. *Pediatr. Radiol.* 25:627–630, 1995.
    A sobering, prospective study illustrating the inability of a chest radiograph to distinguish between viral and bacterial pneumonia. The study dispels the myth that "focal infiltrates" are pathognomonic for a bacterial process. For more on the limitations of chest x-rays, see Acta Pediatr. Scand. *79:219–225, 1990.*
12. Davies, H., et. al. Reliability of the chest radiograph in the diagnosis of lower respiratory infections in young children. *Pediatr. Infect. Dis. J.* 15:600–604, 1996.
    Even radiologists disagree on chest x-ray interpretations! For more on chest x-ray bias and disagreement in the diagnosis of pneumonia, see Pediatrics *90:11–13, 1992, and* Clin. Pediatr. *20:686–691, 1981.*
13. Turner, R., et al. Pneumonia in pediatric outpatients: Cause and clinical manifestations. *J. Pediatr.* 111:194–200, 1987.
    Of 98 patients studied, 38 had a viral infection and 19 had bacterial (of whom 10 also had a virus). The clinical, laboratory, and radiographic findings could not reliably distinguish viral from bacterial causes.
14. Ramsey, B., et al. Use of bacterial antigen detection in the diagnosis of pediatric lower respiratory tract infections. *Pediatrics* 78:1–9, 1986.
    Antigenuria is more common than bacteremia.
15. Nohynek, H., et. al. Erythrocyte sedimentation rate, white blood cell count and serum C-reactive protein in assessing etiologic diagnosis of acute lower respiratory infections in children. *Pediatr. Infect. Dis. J.* 14:484–490, 1995.
    These laboratory studies appear to be of little help.
16. Hickey, R., Bowman, M., and Smith, G. Utility of blood cultures in pediatric patients found to have pneumonia in the emergency department. *Ann. Emerg. Med.* 27:721–725, 1996.
    Blood cultures are not much help either. Less than 3% were positive and, more importantly, no changes in medical management were made on the basis of results of the blood culture.
17. Adcock, P., et al. Effect of rapid viral diagnosis on the management of children hospitalized with lower respiratory tract infection. *Pediatr. Infect. Dis. J.* 16:842–846, 1997.
    A positive RSV-enzyme immunoassay often prevents the use of antibiotics in a child presenting with LRI.

Specific Agents

18. Hammerschlag, M. Atypical pneumonias in children. *Adv. Pediatr. Infect. Dis.* 10:1–39, 1995.
    An excellent review of Mycoplasma, Chlamydia, Rickettsia, *and* Legionella *among other atypical causes of pneumonia. An excellent article on* Chlamydia pneumoniae *by the same author can also be found in* Contemp. Pediatr. *16:57–75, 1999.*
19. Cimolai, N. *Mycoplasma pneumoniae* respiratory infection. *Pediatr. Rev.* 19: 327–331, 1998.
    Important in pointing out some of the extrarespiratory manifestions of Mycoplasma pneumoniae *infections, such as Stevens-Johnson syndrome. For more on* M. pneumoniae, *as well as* C. pneumoniae, *see* Semin. Respir. Infect. *4:19–31, 1989.*
20. Darville, T. *Chlamydia. Pediatr. Rev.* 19:85–91, 1998.
    Focus is on Chlamydia trachomatis *with a good section on its presentation in neonates. See also* Can. Med. Assoc. J. *140:615–622, 1989.*
21. Townsend, E., and Decancq, H. Pneumococcic segmental (lobar) pneumonia. *Clin. Pediatr.* 4:117–122, 1965.
    The clinical response to penicillin is dramatic, even to a small dose—as long as the pneumococci are not penicillin resistant. (Radiographic resolution takes weeks, however: N. Engl. J. Med. *293:798–801, 1975.)*
22. Chartrand, S., and McCracken, G. *Staphylococcal pneumonia* in childhood. *Pediatr. Infect. Dis.* 1:19–23, 1982.
    A somewhat dated series (1965–1978), but still quite relevant.

Treatment

23. Harris, J. Antimicrobial therapy of pneumonia in infants and children. *Semin. Respir. Infect.* 11:139–147, 1996.
    Current treatment recommendations, although in the age of increasing resistence the author seems somewhat liberal with the use of ceftriaxone. See below.
24. Congeni, B. The use of ceftriaxone for bacterial pneumonia in pediatric patients. *Clin. Pediatr.* 29:640–641, 1990.
    The companion editorial to an article touting ceftriaxone (p. 634), providing some perspective about the use and limitations of ceftriaxone to treat pneumonia.

Complication of Pneumonia

25. Wald, E. Recurrent pneumonia in children. *Adv. Pediatr. Infect. Dis.* 5:183–203, 1990.
    Distinguishes recurrent pneumonia in a single lobe from recurrent pneumonia involving multiple lobes and discusses each (20 pages, 77 references).
26. Lewis, K., and Bukstein, D. Parapneumonic empyema in children: Diagnosis and management. *Am. Fam. Phys.* 46:1443–1455, 1992.
    A clear description of the anatomy and pathophysiology involved. For a more updated discussion about management issues, see Curr. Opin. Pediatr. *7:278–282, 1995.*

Other

27. Johnston, I., Strachan, D., and Anderson, H. Effect of pneumonia and whooping cough in childhood on adult lung function. *N. Engl J. Med.* 338:581–587, 1998.
    Even controlling for possible confounders, a history of childhood pneumonia significantly decreased adult lung function.
28. Cushing, A. Breastfeeding reduces risk of respiratory illness in infants. *Am. J. Epidemiol.* 147:863–870, 1998.
    Given the results of the previous reference, perhaps breast-feeding will also, indirectly, improve adult lung function!

65. ASTHMA

Brian P. O'Sullivan

Asthma is a disease characterized by (1) reversible airway obstruction; (2) airway inflammation; and (3) increased airway responsiveness to a variety of stimuli (hyperreactive airways). It is estimated that 10 million persons in the United States have asthma and that 5–10% of children suffer from this disease. The prevalence of asthma may be even greater if children with mild symptoms such as chronic cough, recurrent croup, and exercise-induced asthma (EIA) are included.

The onset of childhood asthma is before the age of 5 years in more than half of the patients. Some children have multiple bouts of status asthmaticus (see Chap. 5), while others experience only occasional mild symptoms. Many infants will have occasional wheezing with viral respiratory illnesses. The majority of these children will not develop chronic asthma symptoms. Overall, approximately half of children “outgrow” their asthma by adolescence. Unfortunately, it is not possible to predict the course in the individual child with certainty.

In the last decade, the importance of airway inflammation in the genesis of asthma has been recognized. Mast cells, eosinophils, and neutrophils can all be found in the airways of people with asthma, even when they are asymptomatic. These cells elaborate a number of mediators that lead to airway edema, bronchospasm, excess mucus production, and recruitment of more inflammatory cells into the airway. New therapeutic strategies are based on a better understanding of the importance of these inflammatory mediators in causing and potentiating exacerbations of asthma.

There is no single diagnostic test for asthma in young children, although a number of challenge tests (histamine, methacholine, cold air) may be helpful in older children and adults. The diagnosis is generally made based on the chronic and recurrent nature of symptoms, the ability to identify specific triggers, family history, and response to appropriate therapy.

Wheezing is the physical sign most associated with asthma; however, it is now recognized that many children with reactive airways have chronic cough rather than wheezing as their major symptom. In fact, a history of coughing with deep inspiration or laughing is a common presenting complaint. Other physical findings in the child with asthma may include prolonged expiratory phase of respiration, hyperresonance to chest percussion, and pulsus paradoxus. Generally, the total eosinophil count is elevated in children with asthma and is correlated with severity of disease; it is not sufficiently sensitive or specific to be helpful for making the diagnosis in an individual child, however. Chest roentgenograms demonstrate nonspecific changes related to peribronchial edema and air trapping. Pulmonary function tests (PFTs) can be helpful in children old enough to perform them (usually 6 years or older); in the asthmatic child with narrowed airways, there is evidence of air trapping and a characteristic decrease in flows at low lung volumes. Many children with mild asthma will have normal PFTs when well, reflecting the reversible nature of the disease.

Allergies, respiratory tract infections, exercise, cold air, and exposure to cigarette smoke are common triggers for the asthmatic child. Avoidance of known allergens is helpful for those children who have allergies. Desensitization (“allergy shots”) may be beneficial for some children with specific allergies, but it is more efficacious for control of nasal symptoms than lower airway problems, it requires injections (which are unpleasant for children), and it requires months of therapy before benefits are seen. Exposure to cigarette smoke is known to cause increased respiratory symptoms in children; in fact, the incidence of asthma and of asthma exacerbations is twice as high in children whose mothers smoke cigarettes compared to children from smoke-free households. Thus, parents of children with asthma should be encouraged strongly to refrain from smoking cigarettes.

Exercise-induced asthma (EIA) occurs in 70–90% of individuals with asthma, 35–40% of atopic patients, and 3–14% of high performance athletes. It may be the only symptom of reactive airway disease in many children. Typically, EIA occurs only after several minutes of exercise and does not accompany short bursts of activity. There is often an increase in airflow at the onset of exercise (perhaps due to catecholamine release) followed by a decrease in flow that is most marked after cessation of exercise. Although the precise pathophysiology of EIA is not known, it is clear that airway cooling and evaporative water loss are important factors. For these reasons, ice-skating and cross-country skiing are potentially difficult sports for children with asthma, whereas swimming (where the inhaled air is warmed and highly saturated with water) is generally well tolerated. Therapy for EIA consists of pretreatment with an inhaled b-agonist, cromolyn sodium, or both. Leukotriene receptor antagonists may also be helpful for treatment of EIA.

Nocturnal asthma is not a separate entity but rather represents the changes seen within the airways as a result of circadian rhythms. Endogenous corticosteroid and epinephrine levels are at their nadirs between midnight and 6:00 A.M. During these hours, children who have marginally controlled asthma may experience increased airway inflammation, cough, and wheezing. Wide swings between morning peak flow readings and those obtained later in the day indicate that airways inflammation is not well controlled at night. Gastroesophageal reflux (GER) with esophagitis has also been implicated as a trigger for nocturnal asthma. Although there is some controversy about the importance of GER in childhood asthma, it should be considered in children who do not respond to standard therapy.

Asthma may masquerade as recurrent pneumonia, chronic cough, recurrent croup, or intolerance to physical activity. However, it should be kept in mind that other conditions may be mistaken for asthma. These include foreign body aspiration, sinusitis, cystic fibrosis, bronchopulmonary dysplasia, psychogenic stridor/wheezing (also known as vocal cord dysfunction), immunodeficiency, GER with or without aspiration, swallowing dysfunction with aspiration, congestive heart failure, vascular rings, and ciliary dyskinesia. Certain parasite infections (e.g., *Toxocara*, *Strongyloides*, *Ascaris*), drug reactions, and collagen vascular diseases present with pulmonary infiltrates and eosinophilia, and can be mistaken for asthma initially.

A decade ago, asthma was underdiagnosed. Now, if anything, this disease is being overdiagnosed. The primary care physician must be careful to avoid the trap of labeling all respiratory problems in children as asthma. Lack of physical fitness leads to shortness of breath with exercise. This dyspnea is often attributed to asthma when it is really secondary to poor conditioning. Pulmonary function testing before and after exercise can help clarify this situation. Habit pattern cough, a behavioral problem, is also frequently diagnosed as cough variant asthma. Habit pattern cough is nonproductive and disappears when the child is asleep. At its extreme, psychogenic cough is extremely disruptive to the family and has a characteristic honking quality that is unmistakable. Children receive secondary gain from this remarkable cough in the form of parental attention and absence from school. Therapy of habit pattern cough consists of ignoring the symptom and removing secondary gain. In addition, some children may require behavioral modification therapy.

Long-term management of asthma is based on treating the underlying inflammation, with the goal of returning the child to normal function. The success of therapy should be judged in large part by how well the child is able to participate in age-appropriate activities and attend school. At the time of initial diagnosis and during any acute exacerbation, therapy should include oral corticosteroids. Early use of oral corticosteroids during upper respiratory tract infections in children with asthma has been shown to decrease emergency room visits and hospitalizations. First-line, inhaled, chronic anti-inflammatory therapy in pediatric patients usually consists of cromolyn sodium. This drug is known to stabilize mast cells, thereby inhibiting release of inflammatory mediators. Cromolyn undoubtedly has other, as yet unknown, mechanisms of action that further inhibit inflammation. Cromolyn is a mild but extremely safe anti-inflammatory agent. It can be used daily for years without adverse effects.

Inhaled corticosteroids should be considered for children who have frequent exacerbations of their asthma or need daily albuterol despite receiving cromolyn. It has been shown that early use of inhaled steroids has a positive effect on long-term asthma symptomatology. There is a lot of controversy surrounding the safety of inhaled steroids in children. Although some studies have shown decreases in short-term growth and collagen turnover in children treated with these medications, long-term studies show no adverse effect on eventual height. There have been reports of adrenal suppression in children using inhaled corticosteroids, and cataracts have been reported in adults taking high-dose inhaled steroids over a long period of time. Recognizing that serious long-term complications are rare, it is still wise to use the lowest dose of inhaled steroids that controls the symptoms. Usually, the dose needed to get symptoms under control is greater than will be needed to maintain

control. Examples of high doses of inhaled steroids to avoid would include fluticasone propionate >440 µg/day or beclamethasone >880 µg/day.

Acute episodes of bronchospasm should be treated with inhaled b-agonists (e.g., albuterol, terbutaline). Since these drugs work rapidly, they can be used on an as-needed basis. Longer acting preparations that allow twice a day dosing are available. Long-acting salmeterol given at bedtime is especially useful for control of nocturnal symptoms. Salmeterol has also been recommended for prevention of EIA, but one study has demonstrated tachyphylaxis and loss of efficacy of this drug when used for EIA over a 30-day period. Oral albuterol preparations are not especially useful because they cause more systemic side effects without providing as much bronchodilatation as inhaled b-agonists. A spacing device should be used when administering any inhaled medication to a child. These devices enhance pulmonary deposition and minimize systemic absorption and side effects.

Theophylline, once the mainstay of asthma therapy in the United States, is no longer considered a first-line medication for bronchospasm. Several studies have demonstrated that intravenous theophylline (aminophylline) does not improve hospital care for moderate-to-severe asthma attacks if the patient is already receiving adequate amounts of steroids and albuterol.

The recent introduction of leukotriene D3 (LTD3) receptor antagonists has provided another class of drugs for control of asthma symptoms. These drugs block only one of the many mediators that contribute to airway edema, accumulation of cells in airways, and bronchospasm. Therefore, in those patients in whom LTD3 is an important contributor to the symptoms, these receptor antagonists will be very useful. In other patients, these drugs will be less helpful. The major advantage of these antagonists is that they can be given orally. This improves adherence to therapy since pill-taking requires no special equipment such as a nebulizer or spacing device, and it is easily supervised by a parent. Montelukast, an LTD3 receptor antagonist that can be given once a day, has no significant interactions with other medications, has minimal side effects, and comes in a chewable formulation, is especially well suited for pediatric patients.

Despite a better understanding of the pathophysiology of asthma and an increased use of anti-inflammatory agents, the morbidity and mortality from this disease have been rising. A large portion of this increase has been in inner-city populations and is thought to be due to decreased access to health care resources. However, mortality has been noted to be increased in all populations. Overreliance of patients on the use of inhaled b-agonists, which provide immediate relief from symptoms without treating the underlying inflammatory process, may be at the root of this problem. With frequent, high-dose b-agonist administration tachyphylaxis develops, airway edema progresses, and acute airway obstruction occurs. Furthermore, repeated self-administration of b-agonists by hypoxic patients can lead to cardiac arrhythmias and sudden death. It is important, therefore, that patients understand the importance of using antiinflammatory agents early in the course of asthma exacerbations, and know to contact their physicians if their need for b-agonists increases markedly.

Reviews and Natural History

1. National Heart, Lung and Blood Institute National Asthma Education and Prevention Program Expert Panel. Guidelines for the Diagnosis and Management of Asthma. (Available at: http://nhlbi.nih.gov/nhlbi/lung/lung.htm)
   The authoritative text of asthma incidence, natural history, pathophysiology, and therapy. This consensus report incorporates the thoughts of the leading asthma experts in the United States and has set a new standard of care. The first report was issued in 1991. This update is available on the World Wide Web, along with links to several other sites suitable for either patients or physicians.
2. Kwong, K., and Jones, C. Chronic asthma therapy. *Pediatr. Rev.* 20:327–334, 1999.
   A very nice and up-to-date review of the subject, including tables on the classification of asthma (intermittent, mild, moderate, severe) and on dose equivalency of various inhaled steroids. A very useful resource.
3. Larsen, G. Asthma in children. *N. Engl. J. Med.* 326:1540–1545, 1992.
   Specific review of asthma as a function of age, with emphasis on pediatric pharmacotherapy. For a more general overview, see N. Engl. J. Med. *327:1928–1937, 1992 (148 references).*
4. Martinez, F., et al. Asthma and wheezing in the first six years of life. *N. Engl. J. Med.* 332:133–138, 1995.
   A longitudinal study of children born between 1980–84. Although roughly one third of all children had wheezing in conjunction with respiratory tract illnesses at some time in their first 3 years of life, nearly 60% of these children had stopped wheezing by 6 years of age. Therefore, "wheezy bronchitis" has a benign prognosis in the majority of patients. See also Am. J. Respir. Crit. Care Med. *149:106–112, 1994, for confirmation of these results.*

Allergy and Air Pollution

5. Martinez, F., Cline, M., and Burrows, B. Increased incidence of asthma in children of smoking mothers. *Pediatrics* 89:21–26, 1992.
   *The title says it all. In lower socioeconomic households, children were 2.5 times more likely to develop asthma than controls if their mothers smoked cigarettes. Chiilmonczyk et al. (*N. Engl. J. Med. *328:1665–1659, 1993) demonstrated a similar increased risk for asthma exacerbations in children exposed to cigarette smoke.*
6. Middleton, E., Jr. Asthma, inhaled allergens, and washing the cat. *Am. Rev. Respir. Dis.* 143:1209–1210, 1991.
   If you can't talk the family out of having a cat, at least have them wash it regularly!
7. Bousquet, J., Hejjaoui, A., and Michel, F. Specific immunotherapy in asthma. *J. Allergy Clin. Immunol.* 86:292–305, 1990.
   Allergen avoidance is the treatment of choice, but allergy shots can be useful for children with specific allergies.

Differential Diagnosis and Asthma Variants

8. Eigen, H., Laughlin, J., and Homrighausen, J. Recurrent pneumonia in children and its relationship to bronchial hyperreactivity. *Pediatrics* 70:698–704, 1982.
   Persistent or recurrent pneumonia can be caused by asthma and is the initial symptom of asthma in some children.
9. Fireman, P. The wheezing infant. *Pediatr. Rev.* 7:247–254, 1986.
   Pathophysiology and differential diagnosis of wheezing. This paper and another from 1989 (Parks, D., et al. Chronic cough in childhood: Approach to diagnosis and treatment. J. Pediatr. *115:856–862, 1989) nicely describe variations on the presentation of asthma. Asthma may present as chronic cough without wheeze, but not all that wheezes is asthma!*
10. Wiens, L., et al. Chest pain in otherwise healthy children and adolescents is frequently caused by exercise induced asthma. *Pediatrics* 90:350–353, 1992.
    Many children referred to a pediatric cardiology clinic for chest pain had abnormal pulmonary function tests following exercise; chest pain resolved with bronchodilator therapy.
11. Wood, R., and Milgrom, H. Vocal cord dysfunction. *J. Allergy Clin. Immunol.* 98: 481–485, 1996.
    A review of this interesting entity that can present with severe inspiratory stridor or expiratory noise (psychogenic wheeze). The key is that the pulse oximetry is normal and the child is usually less distressed than the caretakers. For a lovely picture of the inappropriate apposition of the vocal cords during expiration, see Chest *106:615–616, 1994.*

Nocturnal and Exercise-Induced Asthma

12. Busse, W. Pathogenesis and pathophysiology of nocturnal asthma. *Am. J. Med.* 85(S1B):24–29, 1988.
    *Circadian rhythms, allergen exposure, sleep, airway cooling, and decreased clearance of airway secretions all contribute to worsening of symptoms at night. Use of a long-acting b-agonist at bedtime will help relieve symptoms (*Chest *111:1249–1254, 1997).*
13. McFadden, E., Jr. Exercise-induced asthma: Assessment of current etiologic concepts. *Chest* 91:151S–157S, 1987.
    Although written over a decade ago, this remains a very good overview of the topic. Rapid airway cooling and rewarming are crucial to the genesis of exercise-induced asthma (EIA).
14. Schwartzstein RM. Asthma: To run or not to run? *Am. Rev. Respir. Dis.* 145: 739–740, 1992.
    Patients with asthma can and should be encouraged to participate in physical activity.
15. Kemp, J., et al. Montelukast once daily inhibits exercise induced bronchoconstriction in 6–14 year old children with asthma. *J. Pediatr.* 133:424–428, 1998.
    *As few as 2 days of therapy with this leukotriene D4 receptor antagonist attenuates the bronchospastic response to exercise, compared to placebo. In a group of 15- to 45-year-olds with EIA, 12 weeks of therapy with montelukast provided protection against bronchospasm without tachyphylaxis (*N. Engl. J. Med. *339:147–152, 1998). On the other hand, the b-agonist salmeterol is less efficacious for EIA when used over a long period of time (*N. Engl. J. Med. *339:141–46, 1998).*

Fatal Asthma

16. Molfino, N., et al. Respiratory arrest in near-fatal asthma. *N. Engl. J. Med.* 324:285–288, 1991.
    Severe asphyxia and undertreatment are more likely to cause severe life-threatening episodes than is overtreatment. (For a review of epidemiology and pathophysiology of fatal asthma, see: N. Engl. J. Med. *314:423–429, 1986.)*
17. Sheffer, A. (ed.). *Fatal Asthma. Lung Biology in Health and Disease.* Vol. 115. New York, NY: Marcel Dekker, 1998.
    A complete textbook from a well-respected series, this volume goes through the epidemiology, risk factors, causes, and preventive measures one can take in the approach to fatal asthma.

Pharmacotherapy

18. Barnes, P. A new approach to the treatment of asthma. *N. Engl. J. Med.* 321: 1517–1527, 1989.
    Therapy of asthma based on the concept of asthma as an inflammatory disease; the emphasis is on b-agonists and anti-inflammatory agents.
19. Newhouse, M. Asthma therapy with aerosols: Are nebulizers obsolete? A continuing controversy. *J. Pediatr.* 135:5–7, 1999.
    *This editorial reviews the pros and cons of use of meter dose inhalers (MDIs) in children and comes down squarely in favor of use of MDIs with spacing devices even for acute status asthmaticus. The accompanying article by Schuh et al. (*J. Pediatr. *135:22–27, 1999) concludes that 2 puffs of albuterol delivered via MDI and spacing device is equivalent to routine nebulized albuterol administration in children with mild acute asthma.*
20. Murphy, S., and Kelly, H. Advances in the management of acute asthma in children. *Pediatr. Rev.* 17:227–234, 1996.
    A wonderful overview of current management, with an emphasis on emergency room treatment. The final recommendation: For status asthmaticus, give high dose b-agonists and lots of steroids.
21. Burrows, B., and Lebowitz, M. The beta-agonist dilemma. *N. Engl. J. Med.* 326: 560–561, 1992.

An editorial spurred by an article in the same issue (pp. 501–506) that raised the concern of death from regular, heavy use of b-agonists. Physicians are left sliding down the razor blade of life: b-agonists are potent, rapid bronchodilators, but their effectiveness may lead some patients to overuse them and ignore the need for anti-inflammatory therapy.

22. Anonymous. Drugs for asthma. *Med. Lett. Drugs Ther.* 41:5–10, 1999.
    This update of available drugs for asthma includes costs, some of which are shocking and all of which should be known by prescribing practitioners.
23. Straus, R., et al. Aminophylline therapy does not improve outcome and increases adverse effects in children hospitalized with acute asthmatic exacerbations. *Pediatrics* 93:205, 1994.
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28. Hogshead, N., and Couzens, G. *Asthma and Exercise.* New York, NY: Henry Holt & Co., 1989.
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29. Asthma Information Center. (Available at: http://www.pharminfo.com/disease/immun/asthma/asthma_info.html .)
    This web page has links to many resources for both the patient and the physician. Included are asthma knowledge quizzes and answers to frequently asked questions for patients, as well as medical literature references for physicians.

66. CYSTIC FIBROSIS

Dennis C. Stokes

Cystic fibrosis (CF) is an autosomal recessive inherited, generalized disorder of exocrine gland function caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) protein, a cyclic adenosine monophosphate–activated chloride transport protein localized in epithelial cells. Chronic obstructive pulmonary disease, pancreatic insufficiency, and an abnormally high electrolyte concentration in sweat are the hallmarks of the disease, but there is a remarkable variability in severity and expression among affected persons. It is a disease primarily of whites of northern European ancestry and, with an estimated incidence of approximately 1 in 2,500 to 2,750 live births, is the most common serious genetic disorder in this population. There are only very rare reported cases in native African blacks (although 3% of patients in the US CF Registry are African-American), and an incidence of only 1 in 90,000 in Mongolians and other Asian populations.

The CF gene is located on the long arm of chromosome 7. In 1989, the CF gene was isolated, its product identified, and its structure determined as a chloride channel. More than 700 different gene mutations in CFTR have been identified, most of which give rise to CF. Some mutations produce partial function of CFTR and can be associated with milder disease. The most common CF mutation is a three-base pair deletion at position 508, called delta F508; approximately 75% of abnormal CF genes are delta F508. Delta F508 produces a protein that is not normally processed in the Golgi apparatus for transport to the epithelial cell surface, although it is abundant in the cell interior. Other mutations produce incomplete or absent proteins, or proteins that make it to the cell surface but are not functional. Individuals homozygous for delta F508 almost all have pancreatic insufficiency, but there is still a remarkable variability in respiratory involvement in homozygous F508 patients.

Chronic progressive pulmonary disease is the most serious manifestation of CF, responsible for most of the morbidity and the early death of these patients. Chronic cough, wheezing, hyperinflation, or lower respiratory tract infections are the usual initial pulmonary manifestations and may begin at any age, from weeks to months or years after birth. Studies using bronchoscopy cultures and pulmonary function in infants identified by newborn screening programs demonstrate that airway inflammation, infection, and airway obstruction begin very early in the disease, before infants become symptomatic.

The pathogenic mechanism responsible for the pulmonary disease was initially revealed by studies demonstrating that the respiratory epithelial cell (and sweat duct epithelium) is impermeable to chloride, resulting in abnormal chloride and water content of respiratory secretions. Patients with CF have an increase in measured voltage across respiratory epithelium (usually measured across the nasal epithelium) that can be explained by increased sodium absorption across epithelial cells impermeable to chloride. The exact mechanism by which altered chloride transport produces lung disease in CF is still uncertain, and may relate to an altered lung environment that alters local innate immune function or to other functions of CFTR.

Obstruction of small airways and resulting inflammatory bronchiolitis results from mucus plugging and persistent inflammation (with or without infection), leading to a cycle that favors persistent bacterial infection. Initial pulmonary infections are frequently with *Staphylococcus aureus* or *Haemophilus influenzae*, but *Pseudomonas* species are isolated after repeated antibiotic therapy eliminates more susceptible organisms. “Mucoid” *Pseudomonas aeruginosa* strains, which are heavy “slime” producers and are unique to CF patients, are frequently isolated from the sputum. *Pseudomonas* strains generally cannot be eliminated from the sputum, although some European studies indicate that early intensive treatment of initial *Pseudomonas* isolation can delay respiratory colonization. More resistant organisms such as *Burkholderia cepacia*, methicillin-resistant *Staphylococcus aureus*, and *Stenotrophomonas maltophilia* have also become more prevalent. Cystic fibrosis patients can also develop infection with atypical mycobacterial infections. *B. cepacia* emerged as a particularly troublesome pathogen for many CF centers because of its multiple antibiotic resistance and potential for person-to-person transmission. Although the exact role of *Pseudomonas* infection in contributing to the progressive pulmonary disease is uncertain, it has been suggested that circulating *Pseudomonas* antibodies contribute to a hypersenstitivity reaction in bronchial walls, and proteases from either host inflammatory cells or bacterial origin contribute to active proteolytic destruction of lung tissue.

The early physiologic consequences of small-airway obstruction are abnormalities in ventilation-perfusion distribution, focal hyperinflation, and focal atelectasis (best seen by high resolution computed tomography of the chest). Infant pulmonary function tests can demonstrate early obstructive changes, and with continued inflammation and obstruction, there is increased obstruction, loss of lung elastic recoil, bronchiectasis, and multiple microabscesses. The results of this progressive pulmonary disease are progressive large-airway obstruction, increased airway resistance, and profound hypoxemia and hypercapnia. The course of pulmonary function decline is highly variable. Females appear to have accelerated decline in lung function, particularly after adolescence. Other factors associated with accelerated decline include *Pseudomonas* and *B. cepacia* infection and poor nutrition, as well as socioeconomic factors such as parental smoking and insurance status.

Right heart enlargement and strain (cor pulmonale) follow the development of hypoxic pulmonary vascular constriction and formally occurred in up to 70% of patients dying with CF. The early clinical evidence of cor pulmonale is complicated by the difficulty in appreciating the physical signs of right heart failure, and overt heart failure is less common now that oxygen therapy and lung transplantation are more common, although it remains a grave prognostic sign.

Other serious pulmonary complications of CF include lung abscesses, cysts, persistent atelectasis, recurrent pneumothoraces, and massive—occasionally fatal—hemoptysis. All are associated with advanced disease, although submassive hemoptypsis can occur in patients with milder disease and localized bronchiectasis. Recurrent or persistent pneumothorax is best managed by closed thoracotomy drainage and instillation of a sclerosing agent, or by surgery and pleural abrasion or resection of obvious blebs. Massive hemoptysis can be managed successfully by embolization of the bronchial arteries that have hypertrophied due to chronic bronchial inflammation.

Clubbing as the result of hypoxemia is an early and occasionally useful diagnostic finding as the disease progresses. Hypertrophic osteoarthropathy, with joint swelling, pain, and tenderness, is present occasionally, and episodic arthropathies (often with rash) can be seen as an immune-mediated phenomenon.

Although chronic pulmonary infections are the rule in CF, systemic infections (sepsis, bacteremia, meningitis) are rare, even in severely debilitated patients, but longer survival and more resistant organisms have led to increased reports of these complications. Cell-mediated immunity is normal, and immunoglobulin levels tend to be normal or increased.

Many patients with CF show considerable reversibility in airway obstruction when bronchodilators are used. Respiratory allergy, asthma, and CF clearly occur together, although the role of atopy in accelerating lung decline is uncertain. Allergic bronchopulmonary aspergillosis (ABPA), a type II (Arthus) reaction to noninvasive *Aspergillus* colonization of airways and mucus plugs, also occurs commonly and is diagnosed by delayed skin tests, serum antibodies, and elevated immunoglobulin E.

Approximately 20% of CF patients have nasal polyps. Symptomatic sinus disease is not uncommon and almost all patients have radiologic evidence of chronic sinusitis.

Gastrointestinal (GI) obstruction due to meconium ileus occurs in 10–15% of patients with CF at birth and is the earliest presenting manifestation. Meconium ileus is produced by the abnormal character of the meconium, which has a higher protein content and is “stickier” and drier than normal meconium. Obstruction of the distal ileum may lead to perforation and meconium peritonitis (occasionally occurring in utero), atresia, or volvulus. Delayed passage of meconium—also called meconium

plug syndrome—occurs in both normal and CF infants but is increased in frequency in CF infants. Although loss of significant bowel by complications of meconium ileus can complicate subsequent nutrition, patients who survive the complications of meconium ileus do not have a worse prognosis than patients without this complication.

Distal intestinal obstruction syndrome (meconium ileus equivalent) occurs in older children, adolescents, and adults with CF, due to collection of abnormal fecal material in the cecum, ileum, and colon. The clinical manifestations may be recurrent abdominal pain, abdominal masses, intestinal obstruction, or intussusception.

Pancreatic insufficiency with absent trypsin, chymotrypsin, lipases, and amylase leads to the characteristic fat- and protein-maldigestive stools: bulky, foul-smelling, greasy, and often accompanied by gas and abdominal pain. Treatment is accomplished by pancreatic enzyme supplements (up to 10,000 U lipase per kg body weight per day). Colon strictures have been associated with use of high-dose pancreatic enzyme formulations and excessive doses of enzyme therapy.

Malabsorption secondary to pancreatic insufficiency occurs in most patients, but 10–15% of patients may have residual or normal pancreatic function; this group has milder clinical symptoms and includes patients with CF genes that produce partial CFTR function. Patients with residual pancreatic function are at higher risk for recurrent bouts of pancreatitis. Abnormal pancreatic function may also be found in older patients with CF as a result of the disturbance in pancreatic organization. Chemical diabetes (as manifested by glucose tolerance test abnormalities or elevated glycosylated hemoglobin levels) due to impaired insulin release occurs in 40% of patients and precedes the onset of clinical diabetes mellitus. With increased survival into adulthood, diabetes is common in this population. Impaired insulin release is partly compensated for by increased peripheral tissue sensitivity to insulin in these patients, and ketoacidosis is rare. Diabetes can adversely affect weight gain but its effect on pulmonary function decline is debated.

In infants with CF fed soy-based formulas (perhaps as treatment for their diarrhea), a clinical picture characterized by hypoproteinemia, edema, and anemia may develop. This may occur in breast-fed infants because of the relatively low protein content of these diets compared to cow milk formulas. Affected infants with edema may appear more well nourished than they actually are, and can have a falsely low sweat chloride determination that becomes diagnostic with proper nutritional management, such as the use of an elemental formula or enzyme replacement.

Although clinical expression is uncommon, fat-soluble vitamins A, D, E, and K are usually deficient in new patients due to fat malabsorption, and thus require supplementation. Vitamin A supplementation may result in a bulging fontanelle due to pseudotumor cerebri (which is also described as a rare presenting manifestation of vitamin A deficiency in CF infants). Other common types of GI involvement in CF include rectal prolapse (20% of patients; related to chronic cough, passage of large, bulky stools, or malnutrition). Focal biliary cirrhosis, with the development of portal hypertension, esophageal varices, and hyperplenism, occurs in 2–5% of patients, although abnormal liver enzyme elevations are more common. Cirrhosis may occur in patients with very mild lung disease and may be the only presenting manifestation of CF. The mechanism leading to the cirrhosis involves abnormalities in bile character and plugging of the intrahepatic bile ducts. Liver transplantation has been successful in CF patients with cirrhosis and mild lung disease, and therapy with an artificial bile acid, ursodeoxycholic acid, is generally prescribed for patients with persistent liver enzyme abnormalities.

The sweat glands are morphologically normal in CF but produce sweat with excessive amounts of sodium and chloride. This provides the basis for the diagnostic “sweat test,” which measures chloride (and sometimes sodium) in sweat collected by stimulating the glands by pilocarpine iontophoresis. A sweat chloride concentration of 50–60 mEq/L is borderline (and must be repeated), but one above 60 mEq/L is abnormal and, taken together with the clinical features of cystic fibrosis, establishes the diagnosis. There are a few causes of falsely elevated sweat chloride, including adrenal insufficiency, hypothyroidism, and malnutrition, that can usually be excluded. It is important to know that an adequate amount of sweat (>75 mg) has been collected, and the patient's age considered, since sweat chloride normally increases with age. Some screening systems for measurement of sweat osmolality can give both false-positives and false-negatives. Genetic testing generally supplements sweat testing for diagnosis because of the large number of CF mutations, but current commercial genetic testing for CF mutations is such that less than 10% of individuals with clinical CF will have mutations that go undetected.

The abnormal sweat electrolyte losses are of clinical significance in heat-stressed patients, particularly infants, and may lead to hyponatremic dehydration. Occasionally, it provides an early diagnostic clue when a parent notes that the infant's skin tastes “salty.”

Males with CF are generally sterile, and obstructive pathologic changes are found in the vas deferens and epididymis; testes are normal and adults are now able to conceive using extracted sperm and in vitro fertilization. In females, the character of the cervical mucus is abnormal, but many affected females have borne children successfully. There is often a delay in menarche and development of secondary sexual characteristics due to the chronic lung disease and/or malnutrition. Recently, patients have been identified with abnormalities in CFTR and sterility due to obstructive changes in the vas deferens, but without pulmonary or GI disease. This disorder is called congenital absence of the vas deferens.

Early recognition and diagnosis; institution of chest physical therapy and nutrition counseling; mucus-clearing drugs; intensive oral, inhaled, and intravenous antibiotic therapy; and careful follow-up are important aspects of the comprehensive regional CF treatment programs. These programs have undoubtedly improved the outlook for patients with CF. The median survival for CF patients is now 30 years (although median age of patients who die is only 22 years). Cystic fibrosis is no longer solely a pediatric disease; the problems of young adult patients such as marriage, fertility, contraception, and employment are increasingly important. Attempts to develop effective gene therapy for CF lung disease using modified viral vectors or liposomes (artificial lipid membranes) to carry the normal CFTR to respiratory epithelial cells have proven difficult due to host inflammatory responses to viral vectors and low levels of gene expression. Pharmacologic manipulation of electrolyte transport using agents that enhance CFTR expression is another promising area of investigation. Recombinant human deoxyribonuclease alters the character of CF sputum by cleaving the DNA released from inflammatory cells, improving mucus clearance; it has been shown to be effective in a large clinical trial in CF patients. Anti-inflammatory therapy with glucocorticoids and ibuprofen has also been shown to slow the progression of CF lung disease, and inhaled antibiotics such as tobramycin are useful in patients chronically infected with *Pseudomonas.*

History

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67. HEPATITIS

Olakunle B. Akintemi

Hepatitis may be acute or chronic, and is characterized by “inflammation and necrosis of the liver.” The underlying inflammatory liver injury may be infective, toxic, metabolic, or autoimmune. Acute infective hepatitis is caused by viruses (hepatotropic, nonhepatotropic) and nonviruses (bacteria, protozoa, helminths). Hepatotropic viruses are responsible for most cases of hepatitis. Currently, there are seven hepatotropic viruses, and with advances in molecular biology, the “hepatitis alphabet” list may continue to expand. These viruses are hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), hepatitis F virus (HFV), and hepatitis G virus (HGV). Nonhepatotropic viral causes of hepatitis include adenovirus, herpes simplex virus type 1 and 2, varicella-zoster virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpesvirus 6,7 (HHV-6 and -7). Others include enteroviruses, paramyxovirus (e.g., measles), togavirus (e.g., rubella), human immunodeficiency virus (HIV), flaviviruses (e.g., yellow fever, dengue), Filovirus (i.e., Marburg virus, Ebola virus), and arenavirus (e.g., Lassa fever). Nonviral causes of hepatitis are bacteria *(Bartonella henselae* and *Bartonella quintana*, *Brucella melitensis*, *Legionella pneumophilia*, *Leptospira ictohaemorrhagica*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Salmonella typhi*); protozoa (*Toxoplasma gondii*, *Entamoeba histolytica*), helminths (cestodes, nematodes [*Ascaris lumbricoides*, *Toxocara canis*], and trematodes). Metabolic causes of hepatitis include a $_1$-antitrypsin deficiency, glycogen storage diseases, tyrosinemia, Wilson's disease, and Reyes syndrome. Acetaminophen, valproic acid, isoniazid, halothane, carbon tetrachloride, methyldopa, and toxic mushrooms are some of the agents that cause toxic hepatitis.

Hepatitis A virus, HBV, and HCV are responsible for over 90% of causes of viral hepatitis. Despite differences in virology, pathogenic mechanisms, and route of transmission, they all produce similar symptoms. Although most infections in children are asymptomatic, some are fulminant with hepatic failure (HBV, HDV), and others progress to a chronic stage (HBV, HCV, HDV). In 1997, according to the Centers for Disease Control and Prevention (CDC), there were approximately 45,000 cases of acute viral hepatitis.

Acute viral hepatitis is classically divided into four clinical stages: incubation period, preicteric stage, icteric stage, and convalescence (recovery) stage. Depending on the particular virus involved, incubation period may range from a few weeks to several months. The incubation period of HAV averages 28 days (range 14–49), HBV about 80 days (range 28–180), HCV about 50 days (range 14–160), and HEV about 40 days (range 15–60). The incubation period of HDV is probably similar to HBV, and that of HGV is unknown. The preicteric stage, which usually lasts 3–10 days, is characterized by malaise, weakness, anorexia, nausea, vomiting, and right upper quadrant abdominal pain. In some patients with viral hepatitis (especially HAV), the onset of disease is described as an “influenzalike illness,” with cough, sore throat, fever, chills, headaches, and myalgias. Some patients with HBV may have a “serum sickness—like syndrome” or arthritis-dermatitis syndrome at the beginning of their illness. The symptoms include fever, rash (urticaria, angioedema, palpable purpura, rash), and arthritis (elbows, wrists, knee, and small joints of the hand). Other immune-complex diseases associated with HBV include polyarteritis nodosa, erythema nodosum, and glomerulonephritis (membranous nephropathy and membranoproliferative glomerulonephritis). Jaundice, dark urine, clay-colored or pale stools, and pruritus appear during the icteric stage, although children younger than 3 years of age may be anicteric. In addition, an icteric stage is absent in about 50% of cases of HBV and in most cases of HCV.

After the icteric phase, most patients recover with clearing of jaundice and the disappearance of the systemic symptoms, usually over several months. However, fulminant hepatitis may develop with hepatic failure, encephalopathy, and even death. This is more likely to occur with HBV and HDV but has been reported (although rarely) in HAV infection. Chronic hepatitis (symptomatic biochemical or serologic evidence of hepatic disease for more than 6 months) may complicate HBV, HCV, and HDV. Long-term complications of chronic hepatitis include chronic liver disease, cirrhosis, and hepatocellular carcinoma.

Laboratory tests are helpful to confirm the clinical suspicion of hepatitis. Certain hematologic and biochemical abnormalities occur during the incubation period, preicteric, and icteric stages of the disease. Bilirubinuria is the first detectable laboratory abnormality at the onset of the icteric phase. Both conjugated and unconjugated bilirubin levels are increased, with total bilirubin levels rarely exceeding 20 mg/dL (although higher levels may occur in individuals with sickle cell disease and glucose-6-phosphate dehydrogenese deficiency). The most characteristic sensitive tests of hepatocellular damage are elevations of aminotransferases: aspartate aminotransferase (AST), and the more liver-specific alanine aminotransferase (ALT). Aminotransferase may reach levels 20–100 times normal when jaundice appears. Alanine aminotransferase levels are usually more abnormal than AST; the AST-to-ALT ratio is less than 1. Although aminotransferase levels are higher in symptomatic/icteric patients than in asymptomatic/anicteric patients, there is little correlation between the levels and prognosis of viral hepatitis. Other laboratory abnormalities (although not specific) include leukopenia, aplastic anemia, atypical lymphocytosis, elevated immunoglobulin M (IgM[HAV]), decreased complement levels (HBV), increased serum anti-DNA antibody titers, and increased serum triglycerides. Because of the similarities in symptoms of acute hepatitis caused by HAV, HBV, HCV, HDV, and HEV, clinical history and specific serologic assays are helpful in identifying the specific viral agent responsible. Hepatitis A virus and HEV are transmitted by the fecal-oral route and are described first. This is followed by a discussion of HBV, HDV, HCV, HGV, and finally HFV.

Hepatitis A virus is widespread, occurs throughout the world, and is endemic in countries with overcrowding, poor sanitation, and substandard personal hygiene practice. In 1997, a total of 30,021 cases were reported to the CDC's National Notifiable Diseases Surveillance System. However, this figure may be an underestimate because most HAV infections are asymptomatic. American Indians and Alaskan natives have the highest incidence rate, and Asians the lowest. The highest rates are in children 5–14 years of age, and infection is acquired by the fecal-oral route from an infected individual. Risk factors for infection include household contact or sexual contact with an individual with HAV, and contact with children in daycare centers. Additional risk factors are foreign travel, illicit drug use, and homosexuality (men who have sex with men). However, in about 50% of cases, no risk factor or source of infection is identified. Outbreaks of HAV infection have occurred in prisons, military camps, residential centers for the disabled, and daycare centers. When outbreaks occur in daycare centers, only the adult caregivers develop symptoms. Over 90% of children younger than 5 years of age have asymptomatic infections and are anicteric. The outcome of HAV infection is excellent, fulminant hepatitis is rare, and chronic infection has not been reported. The presence of IgM antibody to the capsid proteins of HAV (IgM anti-HAV) is diagnostic of acute infection. The IgM anti-HAV is detectable 5–10 days after infection and can persist for 3–12 months (average 6 months). Immunoglobulin G (IgG) anti-HAV appears early in the disease, persists for life, indicates past infections, and confers immunity.

Hepatitis E virus is also transmitted by the fecal-oral route, frequently through contaminated water. It is endemic to and epidemics have been reported from sub-Saharan Africa, the Indian subcontinent, China, Southeast and Central Asia, and Mexico. Hepatitis E virus affects mainly adults, with a high mortality (20%) in pregnant women. Sporadic cases in the United States have occurred among travelers from endemic areas. In most cases, HEV is self-limited, no chronic infection is reported, and the mortality rate is less than 1%. Immunoglobulin M anti-HEV appears at the onset of the illness, persists 2–4 weeks, and is replaced by IgG anti-HEV, which persists for life.

Hepatitis B virus is a major public health problem globally. It is estimated that 300 million persons worldwide have chronic HBV infection, with 1 million in the United States. Chronic HBV infection is the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Hepatitis B virus is transmitted sexually, through blood transfusions, by percutaneous or permucosal exposure to infectious body fluids (needle-stick accidents), and perinatally from an infected mother to a neonate (vertical transmission). Infected newborns are usually asymptomatic, but about 90% develop chronic HBV infection. The rate of chronic HBV infection is lower in children infected between ages 1 and 5 years (15–50%), and lower still in infected older children, adolescents, and adults (10%).

Serologic tests are used to diagnose and determine the stage of HBV infection. In acute infection, the following are present: hepatitis B surface antigen (HBsAg), IgM antibody against the core (IgM anti-HBc), “little e” antigen (HBeAg, an indicator of high viral load and infectivity), and HBV-DNA (the most sensitive marker of viral replication). Recovery is indicated by the disappearance of HBV-DNA and of HBsAg, about 20 weeks after its appearance; anti-HBs, anti-HBc, and anti-HBe then appear. The “window period” between the disappearance of HBsAg and the appearance of anti-HBs is distinguished from no infection by the presence of IgM anti-HBc. Anti-HBs is a protective antibody and indicates immunity (including post-vaccination). The presence of HBsAg beyond 6 months indicates chronic infection; HBsAg remains detectable for life along with HBV-DNA.

Hepatitis D virus, also called delta agent and hepatitis delta virus, is a small defective RNA virus that requires the presence of HBV to replicate. Its epidemiology is therefore similar to that of HBV. It is endemic in Southern Italy, the Middle East, Northern Africa, the northern part of South America, and Romania. It can occur as a coinfection with HBV or as a superinfection in a chronic HBV carrier. Sexual and perinatal transmission is less common than with HBV infection. Coinfection with HBV results in mild to fulminant hepatitis, with chronic infection very rare. However, when HDV is superimposed on chronic HBV infection, fulminant, acute severe hepatitis and chronic HBV/HDV hepatitis with cirrhosis may develop. Serologic tests are used to detect HDV infection. Acute coinfection with HBV is characterized by detection of IgM against hepatitis D antigen (HDAg) and HBcAg.

According to the CDC, HCV infection is the most common bloodborne infection in the United States. Based on data from the Third National Health and Nutrition Examination Survey, 3.9 million Americans are infected with HCV. Although HCV infection affects all age groups, the highest seroprevalence rate is in adults aged 30–49 years. The overall prevalence in the general population is 2%; but among children, the seroprevalence is 0.2% in those younger than 12 years and 0.4% in those aged 12–19 years. The seroprevalence of HCV infection is highly variable among population subgroups. The rates are 60–90% among IV drug abusers and hemophiliacs; 20% among hemodialysis patients; 10% in persons with high-risk sexual behavior; and 1–10% among household contacts of infected persons. Most pediatric infections with HCV are asymptomatic, but symptomatic infections are mild and fulminant hepatitis very uncommon. It is estimated that 70–85% of patients with acute HCV develop chronic HCV infection, and 20–30% of those will develop cirrhosis. Hepatitis C virus is transmitted mainly through large exposure to infected blood (blood transfusion, blood products, organ transplantation) or repeated percutaneous exposures (sharing of infected needles among intravenous [IV] drug abusers). Since the availability of anti-HCV screening in 1990 and the more sensitive multiantigen testing in 1992, transfusion-associated HCV infections have been substantially reduced, although not completely eliminated. Sexual, perinatal, and nonsexual household contact with an infected person are other means of transmission of HCV infection. For most infected children and adolescents, the source of infection is unknown. Serologic tests (enzyme-linked immunosorbent assay [ELISA] and recombinant immunoblot assay [RIBA]), and reverse transcriptase polymerase chain reaction are used for laboratory diagnosis of HCV.

Hepatitis G virus, also called hepatitis GBV-C (HGBV-C), is a newly discovered virus. It is a flavivirus and a distant relative of HCV. Most persons infected with HGV are either asymptomatic or have mild disease. The mode of transmission is parenteral; the epidemiology is not well known. It is unclear whether significant hepatic diseases are associated with HGV infection, and reliable serologic tests are not yet available.

Hepatitis F virus, also called hepatitis non–A-E virus, was recovered from the stool of some patients with hepatitis with subsequent transmission to primates. This virus has yet to be characterized.

Treatment of acute hepatitis is mainly supportive, consisting of rest and a balanced diet. Chronic HCV and HBV infections may respond to interferon-a2b. Liver transplantation may be indicated for patients with chronic liver disease from HBV, HCV, HDV, autoimmune hepatitis, or fulminant acute hepatitis.

Immunization is the most effective means of hepatitis prevention. In 1991, the Advisory Committee on Immunization Practices (ACIP) of the U.S. Public Health Service developed a comprehensive strategy to eliminate transmission of HBV in the United States. The strategy includes prevention of perinatal HBV infection by routine prenatal screening of all pregnant women for HBsAg; routine vaccination of infants born to HBsAg-negative mothers; vaccination of adolescents; and vaccination of selected high-risk groups. These high-risk groups are sexually active adolescents and adults with a recently diagnosed STD, homosexual and bisexual adolescent and adult men, household contacts and sexual partners of HBsAg-positive individuals, workers and clients at institutions for the developmentally disabled, and hemodialysis patients. Other high-risk groups include foreign-born adoptees from countries where HBV infection is endemic, inmates of long-term correctional facilities, international travelers (especially children) in areas of high or intermediate rates for HBV infection, and healthcare workers. In this country, two recombinant DNA vaccines (Recombivax HB, Engerix-B) are licensed for all age groups as a 3-dose series. The first 2 doses are given at least 1 month apart, and the third dose is administered at least 4 months after the first dose and at least 2 months after the second dose (but not before age 6 months in newborns). Hepatitis B vaccine is also available as a combination vaccine with *Haemophilus influenzae* type b (Comvax).

Two inactivated HAV vaccines are currently licensed in the United States (Havrix, Vaqta). Indications for administration of these vaccines include children >2 years in communities with high rates of hepatitis A, travel to countries highly endemic for HAV, daycare employees, homosexual males, users of illegal drugs, sewage workers, patients with chronic liver disease, food handlers, and persons with clotting-factor disorders.

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68. GASTROESOPHAGEAL REFLUX

Kenneth B. Roberts

Gastroesophageal reflux (GER) was not even mentioned in textbooks 50 years ago, nor were comparable terms such as chalasia. Within the past 25 years, so much has been made of GER that the distinction between a physiological process and a disease state (GERD) is commonly blurred, and other phenomena of infancy, such as sudden infant death syndrome (SIDS), have been attributed to GER ("guilt by association"). The pathologic process underlying GER is often considered to be transient relaxation of the lower esophageal sphincter. In fact, this process is physiologic, permitting the stomach a "vent"; transient relaxation of the lower esophageal sphincter is triggered by gastric distention (such as occurs with overfeeding). Compromised control of this transient relaxation frequently results in GERD in children with neurologic handicaps.

Though reflux and vomiting appear to be synonymous terms, the formal definition of reflux includes the qualification "effortless," while vomiting involves some effort. During infancy, reflux is common, with half of 0- to 3-month-olds having at least one visible episode of milk dribbling from the mouth daily. The incidence peaks at 4 months, when two thirds of babies have daily episodes, then drops at 6–7 months to 20%. By age 10–12 months, approximately 5% of infants are having daily episodes. The relative frequency of infants with more than one episode daily has a similar age distribution. One quarter of parents report the regurgitation to be troubling or a problem by the time their infant is 6 months old, but nearly half of those infants are felt to "outgrow" the problem by age 1 year, and virtually all do so by 1½ to 2 years.

The decision to perform tests or prescribe pharmacologic treatment should take into account that most neurologically normal infants have GER that is self-limited. There is no clear point at which "regurgitation" or "spitting up" becomes a disease to be evaluated and treated. To parents, the problem is defined by the volume and frequency of regurgitation, crying or apparent discomfort, or arching and posturing. To physicians, the disease is defined by complications, such as acid esophagitis, failure to thrive, or compromise of the respiratory tract (apnea or aspiration). Acid esophagitis may manifest as pain, with discomfort and posturing (Sandifer syndrome), or by ongoing inflammation with failure to thrive, or both.

Various tests can be employed to evaluate GER, each of which measures something different, and none of which can be considered a "gold standard." A barium swallow can identify if anatomic obstruction is present, but it is not very sensitive for identifying GER, since only a short period of peristalsis is observed. A pH probe can identify the number of episodes of acid entering the esophagus and the total time of acid exposure. A multichannel study can correlate acid reflux with apnea, breathholding, or, if the patient is being observed, with posturing. Having an observer present is particularly helpful if the purpose of the test is to distinguish GER-induced posturing from seizures. A milk scintiscan permits quantitation of gastric emptying over time and has the added value of permitting the detection of aspiration, if the lung fields are scanned after the stomach has emptied. Esophagoscopy with biopsy is clearly more invasive and costly than the other modalities, but is essentially the only way to confirm the presence and extent of esophagitis. Most clinicians institute conservative treatment measures to treat "spitty" babies without using any of these tests. If more treatment is needed, the decision to perform tests depends on the availability of the various tests and the comfort of the clinician both with the diagnosis and with the use of the pharmacologic agents.

Commonly, the initial treatment is to switch formulas, based on the hope that the baby may tolerate one product better than another, or as a ploy by the physician to "buy time." No commercial formula, milk based or soy based, appears to match breast milk or to be superior to any other commercial formula, however. Breast-feeding is thought to minimize GER in two ways. First, breast milk has faster gastric emptying compared to formulas. Second, breast-feeding is less likely to result in overfeeding or gastric distention, compared to formula feeding. In both formula-fed and breast-fed babies, frequent burping may be helpful, and thickening feedings with infant cereals is often recommended. (Commercial formulas have become available that are intended to provide the benefit of thickened feedings but still flow through a regular nipple; the formula thickens when acted upon by stomach acid.)

Positioning during and after feedings has had an interesting history in the last 20 years. Initially, the upright position was promoted, since it was logically presumed that gravity would help keep stomach contents below the diaphragm. The method of keeping children upright was to feed them in infant seats and keep them there after feedings. Once this conventional wisdom was tested, it proved not to be the case, and a retrospective look questioned whether the use of infant seats might even contribute to making GER worse, since the sitting position with hips flexed increases intra-abdominal pressure! The prone position with the head flat or raised approximately 30° was identified as optimal to reduce GER. This position is contrary to the recommendation that infants sleep on their back, however, so most pediatricians try to keep infants on their back (or on their side) during the period of greatest risk of SIDS; if GER persists thereafter, sleeping position is generally moot, because of the infant's ability to roll over, except in neurologically handicapped children. Current studies of prematures and newborns suggest that the left lateral decubitus position is superior to right decubitus or supine position for controlling reflux and is nearly as good as prone.

If conservative measures do not produce the desired result, pharmacologic agents are the next step. Pharmacologic agents are often welcomed by parents and lauded as beneficial, but controlled studies generally do not confirm the benefit, using tests such as pH probe. Before prescribing any of the available drugs, it should be remembered that all of them have side effects and that the condition is self-limited in most neurologically normal children. Antacids may be able to help prevent or relieve symptoms of acid esophagitis, but the doses required are large and need to be given frequently, interfering with nutrition. Histamine $_2$ (H_2) blockers (cimetidine, ranitidine) reduce gastric acidity effectively in most babies, but a second drug may been needed to control GERD. Drugs that "tighten" the lower esophageal sphincter and "relax" the pylorus were recommended during the 1980s but have generally been abandoned because of their worrisome toxicity. Cisapride offered prokinetic activity but concern grew about its ability to produce potentially fatal electrocardiographic changes, including torsades de pointes and prolongation of the QT interval. Moreover, cisapride was metabolized by the cytochrome P450 system in the liver and, therefore, had to be used with caution in patients receiving such agents as macrolide antibiotics, azole antifungals, protease inhibitors, cimetidine, and cyclosporine. The drug was withdrawn in July, 2000.

Omeprazole could be listed with antacids and H_2 blockers, since it reduces (or ablates) gastric acidity, but it deserves separate mention, since it may succeed as monotherapy. It is a "proton pump inhibitor," inhibiting H+/K+–adenosine triphosphatase, the enzyme that mediates the final critical step in gastric acid formation. It is so effective at reducing or ablating gastric acidity that some experts proclaim it the drug of choice—but others are more cautious because omeprazole stimulates gastrin secretion, and chronic elevations of gastrin have been shown to lead to gastric carcinoid tumors in rats. Omeprazole is tolerated well acutely, only needs to be given once a day, and has a wide therapeutic index. It can raise the concentration of concurrently used phenytoin or digoxin, however. The cost of omeprazole is high, but in many children with severe GERD, the use of omeprazole can obviate the need for surgery, with a net savings: The cost of a laparascopic fundoplication is estimated to equal the cost of 10 years of omeprazole therapy.

Despite the availability of all these agents, some children, particularly those with neurologic disability, ultimately require surgery anyway. Fundoplication is now one of the most commonly performed procedures by pediatric surgeons (excluding herniorraphy and venous line placements). Outcome studies have generally been disappointing, but as the placement of a gastrostomy tube is generally performed with the fundoplication, many families report that their quality of life has improved following surgery, even if the fundoplication has not been as successful as hoped. Laparascopic fundoplication reduces the acute morbidity and cost of the procedure.

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Complications

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   Abnormal reflux into the proximal esophagus occurs in the majority of asthmatic children with difficult-to-control disease. The barium swallow and scintiscan compare poorly with pH probe in diagnosing reflux. Treatment of reflux with recommended does of H_2 blockers and prokinetic agents has a high failure rate, and follow-up studies are essential.
8. Halstead, L. Role of gastroesophageal reflux in pediatric upper airway disorders. *Otolaryngol. Head Neck Surg.* 120:208–214, 1999.
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Treatment: Review

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    This article and the one that followed it (pp. 187–189) identified improved sleeping, reduced crying, and increased nutrition—but no actual improvement of GER, prompting the accompanying editorial (pp. 254–255) to ask: "Is nothing sacred?"
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Treatment: Medical

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Treatment: Surgical

16. Fonkalsrud, E., and Ament, M. Gastroesophageal reflux in childhood. *Curr. Prob. Surg.* 33:1–70, 1996.
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Treatment Alternativestosurgery

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    In this retrospective review of 28 patients, ongoing or new gastrointestinal symptoms and minor complications were common. Larger children had fewer complications.

69. ACUTE INFECTIOUS DIARRHEA

Kenneth B. Roberts and Conrad J. Clemens

Acute diarrhea is a common problem in infants and children, and its complications, dehydration and malnutrition, are major causes of morbidity and mortality, especially in developing countries. Diarrhea is frequently associated with infection, either intestinal or extraintestinal (so-called parenteral diarrhea). Other etiologies include overfeeding, medications, flare-ups of inflammatory bowel disease, and the various causes of chronic diarrhea and malabsorption (see Chap. 70).

Organisms may cause diarrhea by one or more of three mechanisms. Some remain in the lumen and produce an enterotoxin that acts on the mucosa of the small intestine to cause a profuse secretory watery diarrhea (e.g., cholera, enterotoxigenic *Escherichia coli*); some are cytotoxic for small-bowel cells, resulting, again, in a watery diarrhea (e.g., rotavirus); and some invade the epithelial cells of the colon and cause inflammation, shedding blood, mucus, and inflammatory cells into the stool (e.g., *Shigella, Campylobacter*). Once the process has been initiated, secondary factors may perpetuate the diarrhea. For example, the cytotoxic effect of rotavirus causes the loss of superficial mucosal cells from villi in the small intestine, where lactase activity is highest; as a result, lactose intolerance may develop and produce an osmotic diarrhea. Other osmotically active substances, including the high sugar content of many “clear liquids,” may further contribute to water loss.

Clinically, it is useful to distinguish two syndromes produced by gastrointestinal infection: *watery diarrhea* and *inflammatory diarrhea. Watery diarrhea* results from involvement of the small bowel. Diarrhea is of high volume and is not bloody. The patient generally has mild systemic symptoms, except for dehydration, which may be profound. The usual pathogen in the United States is rotavirus. *Inflammatory diarrhea* results from infection of the colon. The clinical picture is of dysentery. Stools are small and frequent, with blood, mucus, and white blood cells. Fever is high, and the patient may appear “toxic.” This syndrome is more likely to be produced by bacterial pathogens, such as *Shigella* or *Campylobacter.*

The leading cause of diarrhea in infants in both developing and developed nations is the rotavirus; by age 3, approximately 90% of children have been infected worldwide. Rotavirus is responsible for 30–50% of severe diarrheal episodes. It is most common in the winter, affecting infants younger than 2 years. Vomiting may be a significant feature, and dehydration is common due to the combination of stool losses and difficulty taking in fluids.

The second most common viruses are the enteric adenoviruses, although some recent studies suggest astroviruses to be as frequent. Norwalk virus and Norwalk-like viruses generally appear in outbreaks, affect older children and adults, and cause mild, self-limited disease. No specific therapy is available for any of the viral agents.

Shigella is most frequently a pathogen in children between 1 and 5 years of age; it rarely causes disease in the first days of life. The organism proliferates in the small bowel 8–40 hours after ingestion, and causes fever and watery diarrhea. Shortly thereafter, the colon is invaded, stool cultures become positive, the temperature begins to return toward normal, and the characteristic bloody, mucoid stools appear. Tenesmus may be prominent, reflecting mucosal destruction. One fourth of the patients will have only watery diarrhea; another fourth will have high fever but few gastrointestinal complaints. Between 10% and 45% of children will have a seizure. Bacteremia is rare, and mortality is less than 1%. The diagnosis of shigellosis is suggested by the presence of polymorphonuclear leukocytes in a stained stool specimen and an increased number of band forms in the peripheral blood, irrespective of the total white blood cell count; a positive stool culture confirms the diagnosis. Antibiotic therapy reduces the duration of fever, diarrhea, positive cultures, and days in the hospital. Antibiotic resistance is a problem in many areas, so that recommendations for ampicillin, trimethoprim-sulfamethoxazole, or a newer cephalosporin are made on the basis of susceptibility testing and local experience.

Campylobacter causes a dysentery syndrome similar to that caused by *Shigella;* the differential white blood cell count may show a shift to the left as in *Shigella* infection, although usually to a less marked degree. Treatment with erythromycin decreases the duration of shedding the organism and, if administered early, may shorten the clinical course.

Salmonella is said to infect more living creatures than any other organism because of its ubiquitous distribution and ability to infect animals as well as humans. Roughly one third of the contacts of a known *Salmonella* excreter (half the contacts under age 5 years) become culture positive. Of human clinical infections, 70% or more are acute uncomplicated gastroenteritis; the remainder are “enteric fever,” bacteremia, or a prolonged carrier state.

The incubation period prior to enteritis is 6–48 hours. The diagnosis of *Salmonella* as the responsible organism is suggested by the passage of green stools that are particularly malodorous; polymorphonuclear leukocytes may be observed in the stool, but blood or mucus is less common. Vomiting is more prominent than in other forms of bacterial gastroenteritis. Although the symptoms are self-limited and generally brief (2–5 days), shedding of the organism in the stool occurs for weeks and often much longer, particularly in infants. Antibiotics are not indicated for the treatment of uncomplicated gastroenteritis, and may serve to prolong the period of shedding and increase the relapse rate. Unlike *Shigella, Salmonella* causes disease in the neonatal period, and is a particular problem in nurseries and institutions. Newborns, older compromised hosts, and infants whose infection is associated with failure to thrive may warrant antibiotic therapy.

The classic enteric fever is typhoid fever, caused by *Salmonella typhi*, a disease only of humans. The organism multiplies rapidly in the gastrointestinal tract and penetrates the epithelium, assuming an intracellular location within 24 hours. Mesenteric lymph nodes halt the progress of the organism but permit continued multiplication. The organisms reach the bloodstream by the end of the first week and infect the biliary tract. Two days after the bacteremia, fever occurs, accompanied shortly thereafter by headache and abdominal pain; chills and sweats are uncommon, but myalgias, malaise, and anorexia are pronounced. The course is usually more abrupt in infants than in adults, “rose spots” are less common, and there is greater prominence of both gastrointestinal and central nervous system signs. The child may appear “septic,” and an antibiotic is likely to be administered before the organism is isolated and identified. Ceftriaxone or cefotaxime should be administered if *Salmonella* is suspected. Despite in vitro sensitivity to gentamicin, this agent is ineffective in treating disease or even sterilizing the bloodstream.

Bacteremia occurs with salmonellae other than *Salmonella typhosa.* The association between sickle cell disease and *Salmonella*-related osteomyelitis should be remembered when *Salmonella* is isolated from the blood of a child.

Escherichia coli can cause diarrhea by elaborating an enterotoxin, by invading the mucosa, or by at least three additional mechanisms, identified as enteroinvasive, enteropathogenic, and enterohemorrhagic. Of these mechanisms, the most frequent is the production of toxin; enterotoxigenic *E. coli* is the major cause of traveler's diarrhea. Both heat-labile and heat-stable enterotoxins have been identified. The organism attaches to the epithelial surface of the small-intestine mucosa but does not damage it; after only approximately 30 minutes, toxin has stimulated adenyl cyclase to decrease the absorption of sodium, increase the secretion of chloride, and induce a profuse loss of water. The capacity to produce toxin is conferred by an episome (R factor), which is transferred from organism to organism. The identification of diarrhea-causing *E. coli* requires tests not commonly performed in clinical laboratories. The primary defense against traveler's diarrhea is vigilance in the selection of food and drink. Chemoprophylaxis consists of bismuth subsalicylate (Pepto-Bismol) or an antibiotic (trimethoprim-sulfamethoxazole or a fluoroquinolone). Though bismuth subsalicylate is less effective than an antibiotic, it has fewer side effects; if diarrhea develops during bismuth subsalicylate prophylaxis, an antibiotic can be started promptly. In general, however, traveler's diarrhea is a brief, self-limited disorder, and prophylaxis is discouraged for infants, children, and healthy adults.

Enterohemorrhagic E. coli, particularly the strain O157:H7, is of particular concern because of the propensity for causing hemolytic-uremic syndrome (see Chap. 75). Outbreaks due to contaminated beef have resulted in deaths and have prompted many jurisdictions to prohibit restaurants from preparing ground beef any rarer than “medium.”

Yersinia is notable because it may produce a clinical picture indistinguishable from appendicitis, with severe abdominal pain. Young infants may develop bacteremia.

Disease confined to the gastrointestinal tract is usually self-limited and does not require treatment.

Evaluation of a patient with infectious diarrhea includes assessment of the state of hydration and an estimate of the likelihood of a pathogen that requires specific consideration in management. Specific stool tests are not required in patients with watery diarrhea unless cholera or *Clostridium difficile* toxin is suspected. Microscopic examination of dysenteric stools for polymorphonuclear leukocytes has a higher yield for bacterial pathogens than does stool culture, is considerably faster, and is far less expensive. A stool culture is of greatest value when *Shigella* is suspected and the likely antibiotic sensitivity pattern is unclear. Stool cultures are also of value for public health purposes.

Since the major morbidity relates to dehydration and malnutrition, emphasis in management should focus on (re)hydration and nutrition. Appreciation of the physiology of the transport of glucose, sodium, and water in the small bowel has given rise to oral rehydration solutions that permit infants and children to receive fluid and electrolyte therapy without intravenous infusions, and to avoid the problems associated with “clear liquids” that are hyperosmolar or hypotonic. Though oral rehydration solutions are capable of restoring fluid balance, they do not reduce ongoing stool losses. Multiple studies have shown that nutrition should be addressed early in the episode; a period of “bowel rest,” formerly encouraged, is now recognized as unnecessary starvation. Bismuth subsalicylate may help control water loss during acute diarrhea. Other potent pharmacologic agents designed to slow or halt intestinal motility are dangerous in infants because they permit fluid to pool in the intestine unnoticed; the diarrhea ceases, but dehydration may progress. In addition, animal studies suggest that diarrhea is a physiologic “purging” mechanism, protective against invasive bacterial infection.

As is the case with most pediatric infectious diseases, prevention, rather than treatment, is the ultimate goal. Personal hygiene such as hand-washing is simple and effective; however, the increasing use of daycare centers and other forms of group child care makes transmission of many of these infectious agents of greater concern. Therefore, vaccine development for many etiologic agents continues. Recently, a live-attenuated vaccine against rotavirus was shown to be effective in preventing hospitalizations for severe dehydration. Unfortunately, this particular vaccine, Rotashield, was withdrawn from the market due to an apparent increased incidence of intussusception in vaccinated children. Hopefully, safe, effective vaccines will soon be developed.

Reviews

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   An entire journal edition devoted to the topic, with articles on specific pathogens, laboratory diagnosis, and treatment. Articles are quite readable, although somewhat superficial.
3. Aranda-Michel, J., and Giannella, R. Acute diarrhea: A practical review. *Am. J. Med.* 106:670–676, 1999.
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Epidemiology

4. Ho, M., et al. Diarrheal deaths in American children: Are they preventable? *J.A.M.A.* 260:3281–3285, 1988.
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Diagnosis

6. Hoshiko, M. Laboratory diagnosis of infectious diarrhea. *Pediatr. Ann.* 23:570–574, 1994.
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7. DeWitt, T., Humphrey, K., and McCarthy, P. Clinical predictors of acute bacterial diarrhea in young children. *Pediatrics* 76:551–556, 1985.
   Fecal leukocytes predicted bacterial infection with a sensitivity of 0.85 and specificity of 0.88. A cluster of three historical items also was associated with bacterial infection: abrupt onset of diarrhea, more than four stools per day, and no vomiting before the onset of diarrhea. More recently, the use of fecal lactoferrin levels may be even more helpful. See Pediatr. Infect. Dis. J. *15:486–494, 1996.*
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Specific Pathogens

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    Concise but complete. Also Pediatr. Ann. *23:529–35, 1994, and* Emerg. Infect. Dis. *4:561–70, 1998.*
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    Wonderful discussion of all aspects regarding Clostridium difficile. *Great pictures. For a pediatric-specific discussion see* Pediatr. Infect. Dis. J. *14:598–603, 1995.*
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    Looks at causes of parasitic diarrhea in both developed and developing world. Good section on helminths.
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Compared clinical signs in children with acute gastroenteritis to acute weight recovery in hospital; dehydration was not indicated by signs thought to reflect dehydration (such as history of oliguria, sunken eyes, dry mouth, absence of tears, or sunken fontanelle). Moreover, dehydration appeared at 3–4% rather than 5%, as usually taught, leading to an overestimate in the degree of dehydration. For more on the clinical evaluation of dehydration, see Curr. Opin. Pediatr. *10:461–469, 1998, and* Pediatrics *99(5):e6, 1997. (Available at: www.pediatrics.org/cgi/content/full/99/5/e6.) See also Chap. 72.*

Treatment

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28. Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis: Practice Parameter: The management of acute gastroenteritis in young children. *Pediatrics* 97:424–433, 1996.
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Hygiene and Prevention

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70. CHRONIC DIARRHEA AND MALABSORPTION

Margaret E. Mohrmann and Kenneth B. Roberts

The evaluation of a child with “chronic diarrhea” begins with determining whether an abnormality indeed exists. Because there is a wide range of normal stool patterns in childhood, defining diarrhea solely as frequent, loose stools may be misleading. For example, that definition aptly describes the normal stool pattern of a breast-fed infant; conversely, a child with significant fat malabsorption (steatorrhea) may pass only one or two firm stools daily. A diagnosis of diarrhea must take into account both the patient's usual stool pattern and the nature (consistency, color) of the stools passed. Chronic diarrhea may be defined as diarrhea that persists beyond a period of time, perhaps 2 weeks, that could reasonably be ascribed to an acute episode of gastroenteritis. Most important is the effect on the child's nutrition and growth.

Important aspects to consider in the initial interview include the presence or absence of associated symptoms; a recent history of gastroenteritis, or a past history of constipation, diarrhea, or both; and the relationship of the onset of diarrhea to diet or dietary changes. A detailed family history should also be obtained. The physical examination should help define the chronicity and nutritional significance of the disorder, with measurements of height, weight, and head circumference being most revealing in this regard.

Decisions as to the extent of further evaluation of chronic diarrhea are difficult and cannot be approached dogmatically. In general, poor weight gain (“failure to thrive”) is the single most compelling reason to perform an elaborate work-up. The child whose growth continues to follow a normal percentile curve is unlikely to have significant disease. In contrast, an infant who is failing to gain weight at an appropriate rate or an older child with evidence of growth retardation requires a careful study of bowel function, even if the stool is of normal frequency and consistency, recalling that significant malabsorption can occur without diarrhea.

In toddlers, persistent diarrhea with normal growth is likely to be due to “chronic nonspecific diarrhea” or, as it is commonly termed, “toddler's diarrhea.” This entity is characterized by intermittent episodes of increased stool frequency and amount, without signs of growth retardation, malnutrition, or dehydration. Most affected children present at about 1 year of age. Many believe this syndrome represents the pediatric equivalent of the “irritable colon” in adults. Others associate it with the increased mobility of the child and the resultant stimulation of intestinal motility. Whatever the initial cause, by the time medical attention is sought, dietary manipulations have generally been instituted that actually serve to perpetuate the symptoms. Parents are alarmed to see foods such as corn appear undigested in the stool, confirming for them the belief that the child has a disorder that requires treatment. (The appearance of undigested corn and similar items in the stool is normal.) In an effort to make the diet “more easily digestible,” parents may remove fat-containing foods. Since fat slows gastric emptying, adding fat back to the diet by recommending return to a normal diet may slow the transit of food and provide some relief from symptoms. In addition, children on restricted diets may drink large quantities of fruit juices and create an osmotic diarrhea; symptoms respond promptly to a more appropriate diet. More than 90% of children with chronic nonspecific diarrhea are free of diarrhea by the age of 3 years. Other causes of chronic diarrhea in children who are growing normally are recurrent bouts of gastroenteritis (particularly common among those in group child care), infestation with *Giardia lamblia*, and specific food allergies.

Children with chronic diarrhea who have normal growth need few diagnostic tests when first seen. These may include measurement of hemoglobin or hematocrit, stool culture, examination of the stool for blood and parasites, urinalysis, and urine culture, as persistent diarrhea may be the only manifestation of urinary tract infection in the very young. If the results of these studies are normal, the patient is probably best managed with a combination of nutritional advice, reassurance, and monitoring of growth.

Among infants with persistent diarrhea who are failing to thrive, some will be malnourished because of nutritional mismanagement of acute gastroenteritis. The frequent passage of loose, green “starvation stools” by an infant whose acute diarrhea has been treated with a sugar-water diet for a few days may be misinterpreted as evidence of ongoing enteritis, leading the physician or parent to continue the regimen. The lack of protein and the inadequacy of calories in such a diet impair the bowel mucosa's ability to recover from the initial infectious insult and to replace the normal daily loss of superficial cells, thereby prolonging the diarrhea; moreover, significant malnutrition can develop quickly because of the high metabolic rate of the young infant. The prolonged use of sugar water as the sole source of nutrition—whether given as a prescribed oral hydrating solution or other clear liquid, such as Jello water, or as an intravenous infusion of a glucose-electrolyte solution—can lead to protein-calorie malnutrition if the child's nutritional status is already marginal or if the duration of such treatment is extreme. A detailed history of treatment of the diarrhea to date is essential for diagnosis.

The presence or absence of edema and skin breakdown (a manifestation of fatty acid as well as protein deficiency) should be noted on physical examination. It is important to remember that infants with protein-calorie malnutrition may not show weight loss commensurate with their loss of lean body mass, because of hypoproteinemic edema. Management of this potentially life-threatening illness includes provision of adequate dietary protein and fat. The cycle of diarrhea–malnutrition–further diarrhea–further malnutrition was initially termed “intractable diarrhea of infancy”; therapy with elemental formulas and parenteral nutrition have been sufficiently successful for the name to have been changed to “protracted diarrhea of infancy.” Current recommendations to prevent acute diarrhea from becoming protracted include continuing breast-feeding during episodes of acute diarrhea, or in infants who are not breast-fed, resuming feeding within 24 hours, whether or not the diarrhea persists.

In children with chronic diarrhea and growth failure, whose history does not stem from a bout of protracted enteritis and who have not been subjected to undue dietary restrictions, the evaluation proceeds to determine the presence of maldigestion, malabsorption, or both. Strictly speaking, *digestion* refers to the process of breaking down complex foodstuffs into simple molecules, involves enzymes, and takes place in the lumen or at the mucosal surface; *absorption* involves the transport of the molecules across the enterocyte into the circulation. Clinically, the two processes are interrelated, however. If digestion is inadequate, then absorption cannot proceed normally (e.g., pancreatic enzyme insufficiency leading to steatorrhea; lactase deficiency leading to lactose intolerance). Moreover, disorders that disrupt mucosal integrity and impair absorption are likely to injure the superficial cells and affect lactase activity, leading to maldigestion of lactose. Thus, though it may be useful to consider digestion and absorption separately to determine the primary abnormality, the term *malabsorption* is often used (and will be used here) to refer to a problem with either process, maldigestion or malabsorption.

Findings from history and physical examination, plus the gross appearance of the stool, are often helpful in determining the initial direction of a staged search for evidence of a problem with dietary sugar, fat, or protein. Sugar malabsorption causes watery, acid diarrhea that excoriates the buttocks; steatorrhea is usually associated with frothy, bulky stools that may not be increased in frequency; protein malabsorption—or protein-losing enteropathy—is almost always accompanied by some degree of steatorrhea and may present as hypoproteinemic edema.

The most common cause of sugar malabsorption is transient lactase deficiency in the postgastroenteritis period. Lactase is the least abundant and the most superficially located of the mucosal enzymes; it is “the first to go and the last to return,” occasionally requiring 3–6 months to return to normal levels after an acute episode of diarrhea. There are two functional lactases. Congenital alactasia is rare, explained teleologically by the need for the newborn and young infant to be able to digest lactose in human milk. After the age of weaning, lactase is not as necessary; the primary lactase wanes, and approximately 70% of individuals of color (though only 5–10% of Caucasians) develop “hypolactasia.” Other disorders of disaccharide digestion—specifically, sucrase-isomaltase deficiency—are rare. Transient defects of monosaccharide absorption due to mucosal injury occur infrequently after severe diarrhea.

Screening tests for sugar malabsorption detect either the unabsorbed sugars or the products of their fermentation by intestinal bacteria. Clinitest tablets may be used to detect reducing substances (all dietary sugars except sucrose) in the stool. Bacterial fermentation of intraluminal sugar results in the production of hydrogen, which is freely absorbed into the blood, is excreted via the lungs, and can be measured in expired air (hydrogen breath test). The production of hydrogen ions also lowers the pH of the stool, but because of the wide range of stool pH values in healthy infants, this test is probably more reliable in following an individual patient than as a

screen. Tolerance tests for specific sugars may be performed by giving a standard oral dosage of the sugar in question, followed by serial blood glucose determinations and measurements of breath hydrogen content to assess digestion and absorption. Such tests should be conducted under close supervision because even a test dose may cause significant diarrhea and dehydration in an affected child. In a child with probable postgastroenteritis transient lactase deficiency, tolerance tests are unnecessary; a trial of lactose-free formula is a more reasonable—and therapeutic—approach.

A broad range of disease states may cause steatorrhea, including disorders of bile metabolism, pancreatic enzyme production, and mucosal integrity. Cystic fibrosis is the most common cause of significant steatorrhea in children in the United States and should receive prime consideration in the differential diagnosis of fat malabsorption, even in the absence of respiratory symptoms and growth retardation. In a patient with apparent pancreatic enzyme deficiency but with a normal sweat chloride determination, a diagnosis of Shwachman syndrome (pancreatic insufficiency and neutropenia) should be entertained. The child with steatorrhea caused by gluten sensitivity (celiac disease) presents after gluten has been introduced into the diet, generally in the middle to end of the first year of life. Signs and symptoms include growth retardation, abdominal distention, muscle wasting and hypotonia, anorexia, and marked irritability, with an appearance of total misery. The stools are pale, bulky, frothy, and malodorous. Only half of the patients with celiac disease have the classic syndrome, however; others, particularly older children, may present with vomiting or with manifestations of nutritional deficiencies. Celiac disease can be identified by the presence of antigliadin or antiendomysial antibodies in serum, but because the disorder requires the lifelong dietary exclusion of gluten, the diagnosis is confirmed with a small bowel biopsy.

Cow milk protein intolerance, found in fewer than 1% of the total population when specific milk protein challenge tests are used to confirm the diagnosis, has its onset in the first 6 months of life. Vomiting and diarrhea (steatorrhea), often with blood, are the most common symptoms, but there is a significant incidence of eczema, asthma, and anaphylaxis. The child's tolerance of milk protein is usually normal by 24–30 months of age. Abetalipoproteinemia is a rare disease that presents in infancy with steatorrhea and acanthocytosis, followed later in childhood by retinal and neurologic changes.

The examination of a single stool specimen for fat is not as valid a quantitative test for steatorrhea as a 3-day fecal fat determination. Indirect evidence of fat malabsorption may be obtained from determinations of serum carotene and the prothrombin time, which are indicators of absorption of the fat-soluble vitamins A and K. A sweat chloride concentration should be determined in every child with malabsorption of fat. Radiologic examination of the gastrointestinal tract with barium may show mucosal edema or other abnormalities. Criteria for the use of a peroral biopsy of the duodenal or jejunal mucosa vary considerably, with the only definite indications being a strong suspicion of celiac disease (with plans for instituting or maintaining a gluten-free diet) or a severely growth-retarding or life-threatening diarrhea in a child for whom a diagnosis has not been made by other means.

Protein malabsorption is most commonly seen in syndromes of pancreatic insufficiency and is accompanied by steatorrhea. (Only rarely, as in the case of enterokinase deficiency, is protein malabsorption an isolated finding.) Intestinal lymphangiectasia is a protein-losing enteropathy characterized by hypoproteinemia, hypogammaglobulinemia, steatorrhea, and lymphopenia; it may be a primary disorder, with generalized dilatation of lymphatics, or occur as a result of constrictive pericarditis. Many patients who have mucosal damage and malabsorption as a result of sensitivity to cow milk protein will exhibit protein loss, hypoproteinemia, and edema. Similarly, any disease causing severe mucosal injury may result in a clinically significant loss of protein, reflected by decreased serum levels of protein, albumin, and g-globulin. Protein-losing enteropathies can be diagnosed by demonstrating high levels of a $_1$-antitrypsin in the stool.

In addition to specific syndromes of sugar, fat, and protein malabsorption, there are numerous disorders that cause generalized mucosal damage and consequent diarrhea, including drug effects, acrodermatitis enteropathica (zinc deficiency), familial chloride diarrhea, inflammatory bowel disease, and severe iron deficiency. Inadequate mucosal surface area is the problem in short-gut syndrome, such as occurs after surgical resection for midgut volvulus or extensive necrotizing enterocolitis in the newborn. Persistent diarrhea is a major manifestation of many immunodeficiency states, especially the acquired immunodeficiency syndrome, selective immunoglobulin A deficiency, severe combined immunodeficiency, and the “variable immune deficiency” of adults. Although the cause of the diarrhea remains obscure, many of the immunodeficiency-related malabsorptive disorders are associated with infestation by *Giardia lamblia* or other pathogens.

Reviews

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   Focus is on the mechanisms of digestion and absorption and what can go wrong, complete with some brief case studies.
3. Branski, D., Lerner, A., and Lebenthal, E. Chronic diarrhea and malabsorption. *Pediatr. Clin. North Am.* 43:307–331, 1996.
   Briefly considers mechanisms and moves on to causes (107 references).

Chronic Nonspecific Diarrhea

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8. Brown, K., Peerson, J., and Fontaine, O. Use of non-human milks in the dietary management of young children with acute diarrhea: A meta-analysis of clinical trials. *Pediatrics* 93:17–27, 1994.
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    The first section of the report reviews the multiple factors causing malnutrition and a negative energy balance in cystic fibrosis, among which is maldigestion. The second section provides guidelines for nutritional assessment and recommendations for dietary supplements, vitamin supplements, and pancreatic enzyme replacement.
13. Shwachman, H., et al. The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J. Pediatr.* 65:645–663, 1964.
    Original description (five cases) of Shwachman syndrome, with a comprehensive listing of diagnostic features.
14. Troncone, R., Greco, L., and Auricchio, S. Gluten-sensitive enteropathy. *Pediatr. Clin. North Am.* 43:355–373, 1996.
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71. INFLAMMATORY BOWEL DISEASE: ULCERATIVE COLITIS AND CROHN DISEASE

Kenneth B. Roberts

Until about 20 years ago, all children with inflammatory disease of the colon were considered to have ulcerative colitis (UC). With the identification of Crohn disease of the colon as an entity and the recognition of other causes of inflammation, it is clear that some of the older reviews on UC in children included patients with other diagnoses. Although no single measure successfully distinguishes between UC and Crohn colitis, the results of clinical evaluation (including radiographic, endoscopic, and histologic studies) strongly suggest one or the other diagnosis in about 80% of patients with inflammatory bowel disease (IBD). In UC, involvement characteristically begins in the rectum and extends proximally without “skip areas.” The perianal area is unaffected, and inflammation is limited to the mucosa. In Crohn disease, involvement is patchy (discontinuous) and may include any part of the gastrointestinal tract; perianal ulcers and fistulas are characteristic, and inflammation is transmural, involving all layers of the intestinal wall. Entities other than UC and Crohn disease in the differential diagnosis include the so-called irritable bowel of childhood, bacterial and amebic dysenteries, malignancy, the hemolytic-uremic syndrome, collagen vascular diseases, and pseudomembranous colitis.

Children constitute about 15% of the patients with *ulcerative colitis*. The disease is rare in infants younger than 1 year of age, and its frequency increases progressively throughout childhood. The female preponderance in adult-onset UC is not seen in the pediatric age group, and in some series, boys outnumber girls 2:1. Ulcerative colitis is more common in those of Jewish ancestry than in non-Jews, and tends to cluster in families.

The most common presenting complaint is diarrhea, often mucoid and bloody. Tenesmus and abdominal pain are common, and palpation of the abdomen often produces tenderness. Impaired growth and maturation may be apparent but are usually less striking than in Crohn disease. Extraintestinal manifestations are common and may antedate gastrointestinal symptoms. Rectal fistulas do not occur, and perianal disease is rare.

A barium enema demonstrates an abnormal rectum with disease extending proximally, including a “backwash ileitis” in 20–30% of patients. The notable x-ray features are decreased distensibility of the rectum, and contraction and shortening of the colon, with diffuse, symmetric serration of margins. On postevaluation films, the mucosa appears coarsened and irregular. Widening of the presacral space and loss of the normal haustral pattern are commonly seen but do not differentiate UC from other forms of colitis.

Endoscopy reveals diffuse involvement of the rectum, with vascular congestion, multiple small ulcerations, diffuse fine granularity and friability, purulent exudate, and occasionally inflammatory polyps. Once the disease is well established, rectal narrowing may be noted, with mucosal dullness reflecting loss of the normal vascular pattern. Biopsy specimens reveal acute and chronic inflammation limited to the mucosa. Loss of mucus from the epithelial cells is characteristic of active disease and is followed by atrophy of the glands in severe cases. Specimens obtained at proctocolectomy show not only the superficial inflammatory changes, but crypt abscesses, hemorrhage, and ulcerations as well.

Mild disease is defined by fewer than four bowel movements per day and no constitutional signs. Moderately severe disease consists of diarrhea with abdominal cramps and fever. Severe disease is characterized by diarrhea with more than six bowel movements per day, anemia, fever, tachycardia, weight loss, and an incidence of toxic megacolon of 2–5%. Toxic megacolon is a massive dilatation of the colon involving all layers, including the muscularis. Although it is usually a complication of well-established severe disease, it may be the presenting feature of UC. The mortality associated with toxic megacolon remains high, despite vigorous medical management that includes administration of intravenous fluids, corticosteroids, and antibiotics; constant nasogastric suction; and prohibition of oral intake. Emergency colectomy is purported to reduce mortality to 5% but is not the universally accepted approach to management. Other indications for surgery in toxic megacolon include perforation, massive hemorrhage, worsening in the first several hours despite “resuscitative” medical management, lack of clinical improvement by 48–72 hours, or failure of the megacolon to recede by 12–14 days.

The other colonic complication of UC is cancer, which occurs at a rate of 20% per decade after the first 10 years of the disease; thus, colonic cancer develops in 50% of patients with UC after 35 years of disease. Extracolonic manifestations include growth retardation, mucocutaneous lesions, and liver disease. Growth occurs if disease can be controlled and calorie intake is adequate; a growth spurt frequently occurs after colectomy. Arthritis of either a rheumatoid type or an ankylosing spondylitis type develops in 20% of patients. The rheumatoid type of arthritis is peripheral, associated with mucocutaneous lesions, and benign; it may precede the gastrointestinal symptoms. Its course is unrelated to the severity of the diarrheal disease, but it remits following colectomy. The ankylosing spondylitis type of arthritis is unassociated with mucocutaneous lesions and is progressive. It also proceeds unrelated to the severity of the diarrheal disease but does not respond to colectomy and may prove to be a severe, disabling feature of the illness. A high percentage of children with ankylosing spondylitis have histocompatibility antigen HLA-B27. Mucocutaneous lesions include erythema nodosum, pyoderma gangrenosum, and oral ulcers. Hepatic involvement is characterized by periportal lymphocytic inflammation, which may progress to ductal proliferation, portal and periportal fibrosis, liver necrosis, and cirrhosis. The hepatitis may improve following colectomy—although this is not yet clear—but once cirrhosis is present, the damage is irreversible.

Systemic corticosteroids are of benefit for acute severe disease and as part of an in-hospital regimen. Steroid enemas may have a salutary effect on localized proctocolitis. Once “remission” is achieved, corticosteroids are tapered as oral maintenance therapy is begun. Until the past decade, the agent for maintenance therapy was sulfasalazine (Azulfidine), an early “designer drug,” formulated with two components, sulfapyridine and 5-aminosalicylate (5-ASA), because of the belief that the disease might have infectious and inflammatory components. Studies have identified that the 5-ASA is the active agent, and sulfapyridine is merely a carrier to deliver the 5-ASA to the mucosa of the colon. This knowledge permitted the development of sulfa-free forms of 5-ASA, with effectiveness comparable to sulfasalazine but with less toxicity.

Emergency colectomy is indicated for massive bleeding, perforation, and perhaps, as previously noted, toxic megacolon. Elective proctocolectomy is performed to prevent cancer and to provide relief from debilitation. Colectomy has beneficial effects on the peripheral arthritis, skin disease, growth impairment, and clubbing of the fingers, and may halt progressive liver dysfunction; it prevents cancer and cures the gastrointestinal disease (“no colon, no colitis”). Colectomy does not halt the progression of ankylosing spondylitis and, although it does help certain features, creates the problems of coping with an ileostomy. It is hoped that the procedures currently used, ileoanal anastomosis or ileal pouch—anal anastomosis, will lessen such adjustment problems.

Crohn disease is distinguished from UC by transmural involvement, which leads to fistulas and abscesses, and the tendency to form granulomas. Perianal disease and a patchy distribution of affected areas are characteristic. Although it was once believed that Crohn disease was confined to the small intestine (regional ileitis), it is now clear that all portions of the gastrointestinal tract may be involved; the colon is involved in 50% of children with Crohn disease.

The demographic characteristics of Crohn disease are similar to those of UC. The disease runs in families, and the incidence in those of Jewish ancestry is approximately 6 times that in non-Jews. The disorder is particularly uncommon in blacks, American Indians, and Hispanics. The sexes are affected equally. Crohn disease is uncommon in infants, but when it occurs, it is usually severe, with intestinal obstruction a prominent feature. The disease is most common among adolescents and young adults, although careful histories often reveal signs (e.g., growth failure) or symptoms (e.g., early satiety despite a good appetite) that predate the diagnosis by many months or years.

The clinical presentation of Crohn disease is usually much less dramatic than that of UC. Crampy abdominal pain and mucoid, bloody diarrhea are unusual. When abdominal pain and diarrhea are present, they are usually overshadowed by fever and growth retardation or by joint complaints. (The exception to this generalization is acute Crohn disease of the ileum, which may mimic appendicitis sufficiently to require laparotomy to establish the correct diagnosis.) Approximately 5% of children with Crohn disease present with predominant perianal manifestations: perianal fistula, abscess, or hypertrophy, and edema of rectal tags. Rectal strictures are not

uncommon in this situation.

Joint disease is of two types, as in UC, but is less common than in UC. Eye manifestations include episcleritis, uveitis, and iridocyclitis. Skin lesions, aphthous ulcers, and clubbing also occur. Renal stones and gallstones are common in adult patients with Crohn disease, but the incidence in children is unknown. Local complications of intestinal disease include fistulas, abscesses, fibrosis, and obstruction. The ureters may be irritated by direct extension of the inflammation from the gastrointestinal tract, resulting in a functional or anatomic obstruction, and hydronephrosis.

There is no laboratory test diagnostic of Crohn disease. Anemia and elevation of the erythrocyte sedimentation rate are usually present. A barium enema is suggestive of Crohn colitis when “skip areas” are identified, when ulcers are greater than 2 mm in depth, or when fistulas or abscesses are visualized. In the small bowel, findings include wide separation of adjacent loops, suggesting thickening of the bowel wall; replacement of normal mucosal pattern by a “cobblestone” appearance; narrowing and rigidity of segments of bowel with pseudodiverticula; and trapping of barium in fissures. At endoscopic examination, particular attention should be paid to the perianal area. Biopsies of colonic mucosa should be performed in patients with suspected Crohn disease, even when the gross appearance of the colon is normal, as they frequently reveal the diagnosis. Histologically, inflammation is transmural, and noncaseating granulomas are present in 30–50% of patients.

Medical management includes the administration of anti-inflammatory agents, nutritional support, psychological support, and, in some situations, metronidazole. At the onset of treatment, corticosteroid therapy is used to gain control over the disease and reverse growth failure. Although corticosteroids have direct adverse effects on linear growth, such effects are quantitatively less severe for many patients than those caused by uncontrolled Crohn disease. Patients with disease involving the colon are also given maintenance therapy similar to that for patients with UC, with a 5-ASA preparation. Malnutrition is a significant problem in patients with Crohn disease and requires particular attention. Although malabsorption and chronic inflammation undoubtedly contribute to the malnutrition, the main cause is inadequate caloric intake, often a learned response to the discomfort associated with eating. Nighttime tube feedings, parenteral nutrition, or both are used to establish adequate nutrition and restore growth. Enteral feeding appears to have a salutary effect on the mucosa beyond that which can be attributed to improved nutrition per se; it is therefore preferable to parenteral nutrition whenever possible. Psychological support is particularly important for children with Crohn disease, as their disease is not only chronic but unpredictable, potentially embarrassing, and at times debilitating. Metronidazole is used in the management of perianal disease, abscesses, and fistulas. Immunosuppressives (6-mercaptopurine, azothioprine, and cyclosporine) may have a role in the treatment of disease refractory to other medications. A monoclonal antibody against tumor necrosis factor-a (infliximab) is being studied in children.

Approximately 80% of patients with Crohn disease have an operation at some point. The correct timing of procedures is usually a difficult decision for the physician, surgeon, and patient. Intestinal perforation or obstruction, massive hemorrhage, and toxic megacolon are certain indications for operative intervention, but these complications are infrequent. Other indications that have been proposed include fistulas, strictures, rectal bleeding, perianal disease, growth failure, and small-bowel carcinoma. (Small-bowel carcinoma is more common in patients with Crohn disease than in the general population, but it is still uncommon.) Surgery is not curative in Crohn disease, as in UC, and recurrent flairs must be expected.

Disease confined to the small bowel is said to be associated with a better prognosis, but colonic disease offers the hope of cure by colectomy. At present, Crohn disease is a chronic, often debilitating, and sometimes mutilating inflammatory disorder of unknown cause, for which adequate treatment is lacking. Management is geared to controlling disease activity while maximizing growth. Requirements for medication are often high, and associated morbidity is significant.

Reviews and Collections

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Evaluation

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Complications

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   Provides the useful categorization that colitis-related complications include diseases of the joints, skin, mouth, and eyes, and complications related to small-bowel disease include malabsorption, gallstones, kidney stones, hydronephrosis, and hydroureter. (See also Hyams, ref. 3, for more on the extraintestinal manifestations of Crohn disease in children.)
9. Das, K. Relationship of extraintestinal involvements in inflammatory bowel disease. New insights into autoimmune pathogenesis. *Dig. Dis. Sci.* 44:1–13, 1999.
   A table on p. 2 lists the common and uncommon extraintestinal manifestations, followed by an extensive discussion of possible pathogenetic mechanisms (pp. 4–10) and 118 references.
10. Lindsley, C., and Schaller, J. Arthritis associated with inflammatory bowel disease in children. *J. Pediatr.* 84:16–20, 1974.
    Arthritis of two types occurred in 21% of patients with ulcerative colitis (UC): peripheral (a few large joints, benign) and central (ankylosing spondylitis, progressive). Mucocutaneous lesions were present with the former but not with the latter. There was no obvious relationship between these extracolonic manifestations and the severity of UC.
11. Hutchinson, R., et al. Pathogenesis of gall stones in Crohn';s disease: An alternative explanation. *Gut* 35:94–97, 1994.
    Age, duration, and previous surgery were positive risk factors, but site of disease and previous intestinal resection were not.

Therapy

12. Mascarenhas, M., and Altschuler, S. Consultation with the specialist: Treatment of inflammatory bowel disease. *Pediatr. Rev.* 18:95–98, 1997.
    An overview of available therapies, with the important reminder that none have been demonstrated to alter the long-term course of Crohn disease.
13. del Rosario, F., et al. Retrospective analysis of alternate-day prednisone maintenance therapy for Crohn's disease. *Clin. Pediatr.* 37:413–419, 421–426, 1998.
    Alternate day steroids may reduce symptomatic flares without inhibiting growth. (The companion editorial reviews available drugs: pp. 421–426).
14. Camma, C., et al. Mesalamine in the maintenance treatment of Crohn's disease: A meta-analysis adjusted for confounding variables. *Gastroenterology* 113:1465–1473, 1997.
    The salicylate preparations appear effective in reducing symptomatic flares but most of the effectiveness is seen in patients who have had surgery. For an update on maintenance therapies, biologic agents, and the biology of disease, see Curr. Opin. Pediatr. *10:499–506, 1998.*
15. D'Haens, G., et al. Endoscopic and histologic healing with infliximab anti-tumor necrosis factor antibodies in Crohn's disease: A European multicenter trial. *Gastroenterology* 116:1029–1034, 1999.
    This study provides an optimistic note in adults; studies in children are underway. (For more on novel immunosuppressive therapies, see Curr. Opin. Pediatr. *11:390–395, 1999.)*
16. Janowitz, H. The natural history of inflammatory bowel disease and therapeutic decisions. *Am. J. Gastroenterol.* 82:498–503, 1987.
    A useful perspective when reading about new treatments: What benefit should be attributed to them and what to natural history (placebo)?
17. Ruemmele, F., et al. Nutrition as primary therapy in pediatric Crohn's disease: Fact or fantasy? *J. Pediatr.* 136:285–291, 2000.
    Addresses efficacy, mechanism(s), and practical issues. Concludes that the “ideal candidate” is a “newly diagnosed adolescent with terminal ileitis complicated by growth failure and delayed malnutrition.’
18. Rao, S., et al. Studies on the mechanism of bowel disturbance in ulcerative colitis. *Gastroenterology* 93:934–940, 1987.
    The diarrhea is due to rectosigmoid irritability rather than rapid transit, suggesting that antimotility agents may be inappropriate.

Prognosis

19. Harper, P., et al. The long-term outcome in Crohn's disease. *Dis. Colon Rectum* 30:174–179, 1987.
    Follow-up of 139 patients for a minimum of 15 years; the news is not good. (The news is better in UC: Med. Clin. North Am. *74:210–218, 1990.)*
20. Gryboski, J. Crohn's disease in children 10 years old and younger: Comparison with ulcerative colitis. *J. Pediatr. Gastroenterol. Nutr.* 18:174–182, 1994.
    The 40 children with Crohn disease (mean age at onset 7.5 years) did not fare as well as the 38 children with UC (previously reported in J. Pediatr. Gastroenterol. Nutr. *17:24–31, 1993).*

Operation was required in 42.5% (compared with 5% of those with UC), and 35% of those required a later reoperation.

History

21. Crohn, B., Ginzburg, L., and Oppenheimer, G. Regional ileitis: A pathological and clinical entity. *J.A.M.A.* 251:73–79, 1984.
The 1932 classic description is reprinted, with an editorial commentary (p. 80).

72. BASIC FLUID THERAPY

Kenneth B. Roberts

Dehydration in infants and children, generally caused by diarrhea, remains a major source of morbidity worldwide and of mortality in "third world" countries. Infants are at particular risk because of their relatively large ratio of surface area to volume (resulting in large evaporative losses), their susceptibility to enteric pathogens, and their inability to make their needs known or to replace their losses independently. The capability to provide fluid and electrolytes intravenously with safety and effectiveness has developed over the past several decades; more recently, the safety and effectiveness of oral rehydration solutions have been recognized and promoted.

Almost all clinical fluid and electrolyte problems can be managed with the combination of organization, basic knowledge of fluid and electrolyte physiology, a commitment to monitor the child's progress in detail with serial observations, and practice (experience). The approach is simplified by considering separately the fluid and electrolytes needed to replace any deficit incurred, provide for maintenance requirements, and keep up with ongoing losses. (These three categories are generally assessed in different ways and measured in different units, adding to the confusion unless they are considered separately.) It is useful to dissect the problem further by determining the amount of water (fluid) and its composition (electrolytes) separately, even though they will be administered together.

Maintenance fluid needs are generally the part of fluid and electrolyte therapy that causes confusion. The amount of fluid needed to satisfy *maintenance* requirements cannot be converted directly (linearly) from body weight as deficit replacement can, nor can it be measured easily as ongoing losses can. Fluid is required primarily to maintain homeostasis by replacing the water used to eliminate the two by-products of metabolism: heat and solute. Heat is dissipated by the evaporation of water at the skin surface; solute is excreted in urine. (Smaller amounts of fluid are also required to replace the water added by the nasal mucosa to humidify inspired air before it enters the lungs; this water is lost when exhaled as water vapor and is thought of as respiratory loss. A small, generally insignificant volume of fluid is also lost daily from gastrointestinal secretions in the stool.) Maintenance fluid needs, therefore, are mainly related to metabolic rate, which is not related linearly to weight. Three "systems" are used commonly to calculate maintenance requirements: surface area, basal calorie, and the formula devised by Holliday and Segar. Each has its proponents. The surface area system involves determining the child's surface area, using tables based on height and weight or tables based on weight alone, and calculating needs at 1,500–2,000 mL/m^2/d. The basal calorie method is the most flexible and also the most conservative. It requires a table of basal calories by body weight, an estimate of activity, and provision of extra water for conditions such as fever. The Holliday-Segar formula is currently the most frequently used because of its ease of application. The formula is used to calculate the total number of calories needed per day (or per hour): 100 cal/kg/d (4 cal/kg/h) for the first 10 kg of body weight, plus 50 cal/kg/d (2 cal/kg/h) for the next 10 kg of body weight, plus 20 cal/kg/d (1 cal/kg/h) for each kilogram thereafter. Calories are equated to milliliters. This formula provides an acceptable approximation, though it consistently overestimates the needs of children if their activity level is markedly reduced. The closer the child is to "basal" state (i.e., coma), the greater the overestimate; in a 10-kg infant, this overestimate may be nearly 100% of basal needs. The overestimate is acceptable for most children with normal central nervous system, cardiac and renal function, but may be too much if these systems are compromised.

Maintenance requirements provide water for insensible losses and urinary losses in roughly equal proportions. Of the 50% of maintenance fluid required to replace "insensible losses," roughly two thirds is for the evaporative losses from the skin and one third for replacing the water lost as water vapor during exhalation. The 50% provided for urine flow is calculated to provide urine that is neither concentrated nor dilute (i.e., containing approximately 300 mOsm/L, specific gravity of 1.010). The general rule, that urine and insensible losses each constitute approximately half of maintenance fluid needs, has useful clinical implications; for example, an anuric patient should receive only 50% of usual maintenance fluid requirement.

The composition of maintenance fluids is based on the need to replace the solute produced as a result of basal metabolism. This electrolyte loss is proportional to caloric expenditure, not body weight, in a fixed relationship to the amount of water. Virtually all electrolyte loss is in the urine, with none in the water vapor exhaled from the respiratory tract and very little on the skin after evaporation. The "universal" maintenance solution approximates 0.2 (or 0.25) normal saline with 20 mEq/L potassium salt and added glucose (5% in solutions for intravenous infusion, 2% in solutions for oral hydration).

Maintenance fluid and electrolytes are generally infused evenly over 24 hours when given intravenously, but it is not necessary to do it this way, particularly when maintenance is being provided enterally!

The amount of a *deficit* incurred prior to treatment is often referred to in terms of "percent dehydration," meaning the percentage of body weight lost. Weight loss in excess of 1% of body weight per day virtually has to be fluid, so if the change in weight is known, the amount of fluid lost can be calculated directly: 1 kg = 1 L. Usually, however, the weight prior to the episode of dehydration is not known, so the deficit is estimated clinically. Thirst is the first symptom of dehydration. Clinical signs such as decreased urination (with increased concentration), dry mouth, and reduced ability to make tears reflect mild dehydration, a weight loss of approximately 5% in infants and 3% in adolescents. Poor skin turgor (i.e., decreased recoil of the skin when stretched), a sunken fontanelle in infants, and tachycardia imply moderate dehydration, a weight loss of approximately 10% in infants and 5% in adolescents. Tachycardia, hypotension, and poor peripheral perfusion (slow capillary refill) indicate severe dehydration, a weight loss of approximately 15% in infants and 7% in adolescents. The difference between infants and adolescents is due to the relatively larger percentage of body weight contributed by water in infants compared to adolescents, and the greater amount of extracellular fluid (ECF). It is useful to recognize that 5% of body weight can also be expressed as 50 mL/kg, 10% as 100 mL/kg, and so on.

The composition of fluid to be used to replace a deficit depends on the time period of loss, the source of the loss, and the current serum sodium concentration. "Hyperacute" loss over hours approximates the composition of ECF, so fluids similar to ECF, such as Ringer's lactate or normal saline, are used. If, as occurs in the majority of cases, the loss is incurred over a few days, there is more time for equilibration between ECF and the intracellular fluid (ICF), resulting in less sodium and more potassium being lost. In unusual circumstances, the loss may be chronic, occurring over weeks, providing even more time to equilibrate, resulting in less sodium lost and total body potassium depletion.

The serum sodium defines whether the dehydration is isotonic (135–150 mEq/L), hypertonic (>150 mEq/L), or hypotonic (<135 mEq/L). Hypertonic dehydration causes the amount of deficit to be *underestimated* by physical examination, since the intravascular volume and circulation are bolstered (at the expense of the ICF). Hypotonic dehydration, by contrast, causes the amount of deficit to be *overestimated* by physical examination. It is important to note that hyponatremia more often represents excess of water than insufficiency of sodium.

The rate at which fluid and electrolyte deficits should be replaced was described qualitatively by Hippocrates, whose recommendations have not yet been improved upon: "Those bodies which have been slowly emaciated should be slowly recruited; and those which have been quickly emaciated should be quickly recruited." If fluid is needed to support the intravascular volume, as evidenced by tachycardia, hypotension, or poor peripheral circulation, a bolus of ECF-like fluid (Ringer's lactate or normal saline) is infused rapidly. The amount chosen should be sufficient to support the circulation but not so much as to produce congestive failure. For infants and young children with moderate-to-severe dehydration, 20 mL/kg (2% body weight) is generally given; if assessment after the first infusion reveals continued signs of reduced intravascular volume, additional fluid is provided until a normal circulating volume is restored. The remainder of the deficit can be given over several hours. Prompt rehydration has the additional benefit of "recruiting" the child, increasing the likelihood of oral intake being successful. If there is reason to be concerned about impaired function of the brain, heart, or kidneys, however, it is prudent to rehydrate more slowly. It is particularly important to rehydrate slowly in hypertonic states, such as diabetic ketoacidosis or hypernatremic dehydration. The usual approach is to replace the sum of the deficit and 2 days of maintenance needs at an even rate over 48 hours. This empirically-derived approach minimizes the cerebral disturbances (e.g., seizures, cerebral edema) caused by fluid shifts that can occur if fluid is infused too rapidly.

The amount of abnormal, nonmaintenance *ongoing losses* (e.g., diarrhea, drainage through a nasogastric tube) is measured directly. Exceptions include "third space"

losses (e.g., in the lumen of an obstructed intestine) and radiant losses (e.g., during phototherapy or intraoperatively, with pleura or peritoneum exposed); these must be estimated according to various guidelines. The electrolyte composition is estimated from tables or, if profuse or prolonged, analyzed in the chemistry laboratory. The rate of replacement should be calculated and considered as frequently as needed (e.g., every hour, every 4 hours). For convenience, fluid and electrolytes to replace ongoing losses are often infused “piggy-back,” separate from maintenance, to simplify calculations and provide flexibility in adjusting the rate of replacement as ongoing losses change.

It needs to be clear that all guidelines regarding fluids and electrolytes are approximations that in no way can replace careful monitoring of the patient. Furthermore, no single, simple sign or test infallibly reflects fluid and electrolyte balance. The following measures are listed in roughly decreasing order of practical value, considering degree of ease, availability, invasiveness, time to perform, and cost: physical signs of dehydration; body weight; urine volume and specific gravity; input and output measurements, with direct measurements of all losses; serum urea nitrogen concentration; hematocrit; concurrent serum and urine osmolalities; and serum electrolyte concentrations (which, by themselves, say little about the state of hydration). The frequency of monitoring must be individualized, depending on the present severity of the disorder and the potential rate of change. Once daily is not sufficient in a child whose dehydration is severe enough to warrant hospitalization.

Reviews

1. Arnold, W., and Kallen, R. (eds.). Fluid and electrolyte therapy. *Pediatr. Clin. North Am.* 37(2), 1990.
   A collection of 16 articles, specifically addressing body composition and the “normal anatomy” of body fluids (p. 241), maintenance fluid requirements (p. 257), parenteral management of diarrheal dehydration (p. 265), oral rehydration therapy (p. 295), and more.
2. Hellerstein, S. Fluids and electrolytes: Physiology. *Pediatr. Rev.* 14:70–79, 1993.
   A review of relevant physiology: body composition; regulatory mechanisms of osmolality, water, sodium, and acid-base balance; and renal function.
3. Hellerstein, S. Fluids and electrolytes: Clinical aspects. *Pediatr. Rev.* 14:103–115, 1993.
   Considers maintenance requirements plus rehydration, with specific consideration to several clinical situations. (Stick with this review in preference to the newer article with the same title in the same journal: Pediatr. Rev. *17:395–403, 1996.)*

Maintenance Fluids and Electrolytes

4. Holliday, M., and Segar, W. *Pediatrics* 19:823–832, 1957.
   The source of the formula most widely used to calculate maintenance fluids. Note that the authors considered the concentration of electrolytes as well. See Pediatr. Rev. *20:429–430, 1999.*

Estimating Dehydration

5. Mackenzie, A., Barnes, G., and Shann, F. Clinical signs of dehydration in children. *Lancet* 2:605–607, 1989.
   The authors compared clinical signs in children with acute gastroenteritis to acute weight recovery in hospital; dehydration was not indicated by signs thought to reflect dehydration (e.g., history of oliguria, sunken eyes, dry mouth, absence of tears, or sunken fontanelle). Moreover, dehydration appeared at 3–4% rather than 5%, as usually taught, leading to an overestimate in the degree of dehydration.
6. Gorelick, M., Shaw, K., and Murphy, K. Validity and reliability of clinical signs in the diagnosis of dehydration in children. *Pediatrics* 99:e6, 1997. (Available at: www.pediatrics.org/cgi/content/full/99/5/e6.)
   The presence of two or more of the following indicated a deficit of at least 5% of body weight: capillary refill >2 seconds, absent tears, dry mucous membranes, ill general appearance.
7. Bonadio, W., et al. Efficacy of measuring BUN in assessing children with dehydration due to gastroenteritis. *Ann. Emerg. Med.* 18:755–757, 1989.
   Of 50 children with gastroenteritis, dehydration, and metabolic acidosis, 44 (88%) had a normal blood urea nitrogen (BUN) concentration.
8. Baraff, L. Capillary refill: Is it a useful clinical sign? *Pediatrics* 92:723–724, 1993.
   No, and the author of this editorial (accompanying a study of the effect of ambient temperature on capillary refill, p. 699) describes why it isn't and how we came to be deceived.

Dehydration

9. Duggan, C., Santosham, M., and Glass, R. The management of acute diarrhea in children: Oral rehydration, maintenance, and nutritional therapy. *M.M.W.R.* 41(RR-16):1–20, 1992.
   A 20-page review, including oral rehydration, dietary therapy, pharmacologic therapy, and recommendations based on the degree of dehydration.
10. Grisanti, K., and Jaffe, D. Dehydration syndromes. Oral rehydration and fluid replacement. *Emerg. Clin. North Am.* 9:565–588, 1991.
    Discusses diarrhea and outlines the management of three illustrative cases step by step.

Fluid “Resuscitation”

11. DeBruin, W., Greenwald, B., and Notterman, D. Fluid resuscitation in pediatrics. *Crit. Care Clin.* 8:423–438, 1992.
    Considers multiple forms of shock.(Volume is on fluid resuscitation of the critically ill and includes reviews of colloids and crystalloids, p. 235; use of blood products in shock, p. 255; albumin, p. 311; traumatic hemorrhagic shock, p. 323; patient with increased vascular permeability, p. 341; burns, p. 355; neurologic injury, p. 367; and systemic complications of fluid resuscitation, p. 439.)

Hypernatremic Dehydration

12. Paneth, N. Hypernatremic dehydration of infancy. *Am. J. Dis. Child.* 134:785–792, 1980.
    A scholarly review of the epidemiology.
13. Finberg, L. Treatment of dehydration in infancy. *Pediatr. Rev.* 3:113–120, 1981.
    Use this for his discussion of hypernatremic dehydration.
14. Lohr, J., Springate, J., and Feld, L. Seizures during correction of hypernatremic dehydration. *Am. J. Kidney Dis.* 14:232–235, 1989.
    A case discussion, focusing on three questions: the cause of hypernatremia in a breast-fed infant, the etiology of neurologic deterioration, and relationship of idiogenic osmols to optimal rate of fluid administration.
15. Bruck, E., et al. Therapy of infants with hypertonic dehydration due to diarrhea. *Am. J. Dis. Child.* 115:281–301, 1968.
    A controlled study demonstrating a greater frequency of seizures with 10% dextrose in water than with electrolyte solutions.
16. Fomon, S., and Ziegler, E. Renal solute load and potential renal solute load in infancy. *J. Pediatr.* 134:10–14, 1999.
    Formula contains solute that is excreted by the kidney, taking water with it; this explains why high-solute formula (e.g., skim milk) produced hypernatremic dehydration more commonly than breast milk.
17. Rowland, T., et al. Malnutrition and hypernatremic dehydration in breast-fed infants. *J.A.M.A.* 247:1016–1017, 1982.
    Hypernatremic dehydration can occur in breast-fed babies—so gradually that parents are not aware of it.
18. Listernick, R., and Sidransky, E. Hypernatremic dehydration in children with severe psychomotor retardation. *Clin. Pediatr.* 24:440–442, 1985.
    A result of the unfortunate combination of processed foods and inadequate free water.

Salt Poisoning

19. Miller, N., and Finberg, L. Peritoneal dialysis for salt poisoning. *N. Engl. J. Med.* 263:1347–1350, 1960.
    Salt poisoning is more likely to have sequelae than is hypernatremic dehydration and requires more aggressive intervention.

73. HEMATURIA AND PROTEINURIA

Richard A. Cohn

Reviews
Hematuria
Proteinuria

Hematuria in the context of acute nephritis (see Chap. 74) and proteinuria associated with the nephrotic syndrome (see Chap. 76) usually present few diagnostic problems for the pediatrician. Asymptomatic, isolated hematuria or proteinuria, on the other hand, is often perplexing. The problem is not uncommon; approximately 6% of school-aged children have hematuria or proteinuria at some time.

Hematuria is defined as three or more red blood cells (RBCs) per high-power field (hpf), found in two centrifuged specimens of freshly voided urine. It is important to show that the hematuria is persistent, since transient hematuria may occur after vigorous exercise, after minor trauma, or with fever. The orthotoluidine test strip (Hemastix) is very sensitive (trace = 1–3 RBC/hpf) but is also positive in the presence of free hemoglobin, myoglobin, or certain peroxidase-producing bacteria. False-negative results are rare.

Gross hematuria in a child is usually frightening to the patient and parents. The most common causes are glomerulonephritis, urinary infection, and hypercalciuria (with or without nephrolithiasis). Upper urinary tract causes of bleeding may result in urine that is red or brown (smoky, rusty, tea- or cola-colored), while bleeding from lower sites is usually bright red and may include clots. Certain medications (e.g., rifampin, phenolphthalein) and other substances (e.g., pigment in beets) may cause urine to appear bloody; the dipstick test easily differentiates this discoloration from true hematuria.

Recent studies have shown that hypercalciuria is one of the most common identifiable causes of isolated hematuria (either gross or microscopic) in children. The child with hematuria resulting from hypercalciuria may complain of abdominal pain or dysuria, often has a family history of renal stones, and is at risk of future stone formation and osteopenia, if untreated.

Other causes of nonglomerular hematuria include major trauma; hydronephrosis, in which bleeding frequently follows minor trauma and is often visible; and hemoglobinopathies, especially sickle cell trait (SA) and hemoglobin SC disease. Polycystic kidney disease may present with hematuria; hypertension may also be present. As many as 25% of children with Wilms tumor have hematuria, but it is seldom the sole manifestation of disease. Hemangioma of the kidney, angiomyolipomata of the kidney as seen in tuberous sclerosis, and renal tuberculosis are rare causes of hematuria in children.

Glomerular hematuria, suggested by the presence of RBC casts in the urinary sediment, may be caused by acute glomerulonephritis, immunoglobulin A (IgA) nephropathy, Alport syndrome, or various basement membrane nephropathies. The nephritis of Henoch-Schönlein purpura can occur weeks after resolution of the more characteristic nonrenal symptoms. Systemic lupus erythematosus rarely presents as nephritis alone.

Immunoglobulin A nephropathy (Berger disease) is one of the most common nephropathies worldwide, and though the short-term prognosis may be excellent for most children, 10- to 20-year follow-up indicates that slow progression into renal failure is not uncommon. The disease is characterized by persistent or intermittent microscopic hematuria with episodes of gross hematuria during infections of any type; immunofluorescence microscopy of renal biopsy material reveals mesangial deposition of IgA, immunoglobulin G, and C3. Most children with IgA nephropathy with hypertension, significant proteinuria, or renal insufficiency at the time of diagnosis progress to renal failure.

Evaluation of a child with hematuria begins with a thorough history, including family history of renal disease, hematuria, hearing loss, hemoglobinopathies, or bleeding disorders; drug use (e.g., anticoagulants, aspirin, sulfonamides); trauma; abdominal or suprapubic pain; and recent illnesses. If the hematuria has been visible, description of an episode (color, when the blood appeared in the urinary stream, associated symptoms) is helpful. Physical examination is directed toward detecting evidence of acute nephritis (hypertension, edema) or chronic renal disease (pallor, growth failure), abdominal mass or tenderness, rash, joint abnormalities, or congenital anomalies.

Laboratory evaluation of all children with persistent hematuria must include examination of freshly voided urine for RBC casts and protein. Any amount of protein (more than an occasional “trace”) in the presence of microscopic hematuria is abnormal; in the case of gross hematuria, protein excretion of more than 500 mg/m ^{2}/d (or a spot urine protein-to-creatinine ratio >1.0) is significant. Other studies to be obtained on all patients are urine culture and measurement of urinary calcium excretion; complete blood count; determinations of serum electrolytes, urea nitrogen and creatinine, and complement; and serologic tests for evidence of streptococcal infection. Hemoglobin electrophoresis should be performed in children with hematuria likely to carry sickle genes.

Renal ultrasonography is a noninvasive, though expensive, screening test for anatomic abnormalities. Cystoscopy is rarely helpful in evaluating microscopic hematuria and only infrequently reveals the cause of asymptomatic gross hematuria in children; bladder tumors are rare in children and usually present with symptoms of voiding dysfunction rather than with hematuria.

Most children with asymptomatic, isolated hematuria with fewer than 20 RBC/hpf have a benign condition; if the family screening, renal anatomy, blood pressure, and renal function tests are normal, extensive evaluation is not warranted. The child should be followed at 6- to 12-month intervals for any clinical changes. Renal biopsy should be considered in the presence of persistent (longer than 8 weeks) hypocomplementemia, hypertension, significant proteinuria, or abnormal renal function in a patient without an acute nephritis syndrome whose renal ultrasound examination is nondiagnostic. Examination of biopsy specimens may reveal a treatable disease, and may provide a diagnosis and a more accurate long-term prognosis.

Hematuria is usually more frightening to both patients and physicians, but *proteinuria* is more likely to indicate potentially serious renal disease. The initial diagnosis of proteinuria is made on the basis of a positive result on the dipstick test: A strip impregnated with tribromophenol blue (Albustix) changes color in the presence of a protein concentration of 30 mg/dL or greater. Results may be false-negative if the urine is very dilute or false-positive if it is alkaline. The true definition of proteinuria requires a quantitative measurement of urinary protein excretion. “Spot” or random urine samples are as good for quantitation as more cumbersome 24-hour collections (if not the preferred method), if the ratio of protein to creatinine is calculated. A protein-to-creatinine ratio below 0.2 is normal; values between 0.2 and 1.0 reflect low-grade proteinuria; values between 1.0 and 5.0 reflect moderate proteinuria; values in excess of 5.0 are typical of nephrotic-range proteinuria.

The list of causes of isolated proteinuria include membranous and membranoproliferative glomerulonephritis, reflux nephropathy, and all etiologies of childhood nephrotic syndrome (see Chap. 76).

Older children and adolescents with proteinuria should be tested for orthostatic proteinuria, a normal variant in which the first morning urine is protein-free (urine protein-to-creatinine ratio <0.2), but urine samples when the child is upright and active have a ratio generally between 0.2 and 1.3.

Initial evaluation of a child with proteinuria includes many of the historical points noted in the discussion of hematuria, plus questions about episodes of edema, urinary tract infection, and exposure to potential toxins. During the physical examination, one should note the presence or absence of hypertension, edema, and growth failure.

Once the presence of persistent proteinuria has been established by an abnormal protein-to-creatinine ratio, evaluation should include careful analysis of freshly voided urine for blood and casts, urine culture, tests of renal function and anatomy, serum albumin, cholesterol, and C3.

Children who exhibit orthostatic excretion of protein and have normal renal function and anatomy require no further evaluation but should be followed for any change. Those with nephrotic syndrome should be managed accordingly. In all other asymptomatic patients, the urine protein-to-creatinine should be determined at 6- to 12-month intervals for indications of resolution or exacerbation of the problem. Electrophoresis of urinary protein may be helpful; selective excretion (i.e.,

predominantly albumin) usually indicates mild glomerular disease such as minimal change nephrotic syndrome, while nonselective proteinuria implies either severe glomerular disease (“leakage” of large-molecular-weight globulins) or tubular disease (failure to resorb small-molecular-weight globulins). Relative indications for renal biopsy include nephrotic syndrome in children younger than 1 year or older than 8 years, hematuria, abnormal renal function, hypocomplementemia, and tubular proteinuria.

A child with persistent hematuria *plus* proteinuria, who does not fit the symptom complex or laboratory characteristics of acute nephritis or minimal-change nephrotic syndrome, may have potentially serious renal disease, and renal biopsy should be considered.

Reviews

1. Dodge, W., et al. Proteinuria and hematuria in school children: Epidemiology and early natural history. *J. Pediatr.* 88:327–347, 1976.
   Largest series (12,000 children) for prevalence figures; conclusions include fruitlessness both of screening programs and of complex evaluations of isolated hematuria and proteinuria in absence of other abnormalities.
2. Norman, M. An office approach to hematuria and proteinuria. *Pediatr. Clin. North Am.* 34:545–560, 1987.
   Presents cases as the basis for discussing an approach to diagnosis.

Hematuria

3. Kaplan, M. Hematuria in childhood. *Pediatr. Rev.* 5:99–105, 1983.
   A general review, including a flow diagram approach to diagnosis.
4. Boineau, F., and Lewy, J. Evaluation of hematuria in children and adolescents. *Pediatr. Rev.* 11:101–108, 1989.
   Reviews the differential diagnosis (including the finding of red urine not due to blood) and evaluation.
5. Garcia, C., Miller, L., and Stapleton, F. Natural history of hematuria associated with hypercalciuria in children. *Am. J. Dis. Child.* 145:1204–1207, 1991.
   Hypercalciuria is a common cause of hematuria in children and may lead to nephrolithiasis. (See also Kidney Int. *37:807–811, 1990, for a multicenter survey of causes of isolated hematuria in children.) For a bone mineral density study in children, see* Pediatr. Nephrol. *11:578–583, 1997.*
6. Gubler, M., Knebelmann, B., and Antignac, C. Inherited glomerular disease. In: Barratt, T. (ed.). *Pediatric Nephrology*. 4th ed. Baltimore: Lippincott Williams & Wilkins 1999:475–495.
   A comprehensive review.
7. Yoshikawa, N., et al. The thin glomerular basement membrane in children with hematuria. *J. Pathol.* 142:253–257, 1984.
   For electron photomicrographs of renal biopsies in children with hematuria, see J. Pediatr. *101:358–365, 1982.*
8. D'Amico, G., et al. Idiopathic IgA mesangial nephropathy: Clinical and histological study of 374 patients. *Medicine* 64:49–60, 1985.
   Large review of this entity.
9. Waldo, B., et al. Treatment of IgA nephropathy in children: Efficacy of alternate-day oral prednisone. *Pediatr. Nephrol.* 7:529–532, 1993.
   Treatment may improve the short-term prognosis; long-term prognosis remains unknown. (For results of a study using fish oil in immunoglobulin A [IgA] nephropathy, see N. Engl. J. Med. *331:1194–1199, 1994.)*
10. Berg, U., and Widstam-Attorps, U. Follow-up of renal function and urinary protein excretion in childhood IgA nephropathy. *Pediatr. Nephrol.* 7:123–129, 1993.
    An excellent review of 36 patients, correlating glomerular filtration rate, proteinuria, and biopsy findings.
11. Williams, D. Pathogenesis of IgA nephropathy. *Pediatr. Nephrol.* 7:303–311, 1993.
    A detailed review of the biology of IgA, human leukocyte antigen, and possible mechanisms involved in IgA nephropathy (71 references).

Proteinuria

12. Bergstein, J. A practical approach to proteinuria. *Pediatr. Nephrol.* 13:697–700, 1999.
    Short but thorough review of concepts and approach to proteinuria in children.
13. Houser, M. Assessment of proteinuria using random urine samples. *J. Pediatr.* 104:845–848, 1984.
    Random urine samples for protein-to-creatinine ratio were as reliable as and less burdensome than 12- or 24-hour timed urine collections.
14. Schwab, S., et al. Quantitation of proteinuria by the use of protein-to-creatinine ratios in single urine samples. *Arch. Intern. Med.* 147:943–944, 1987.
    Another study that emphasizes the utility of “spot” samples; a graph on page 944, relating protein-to-creatinine ratios to 24-hour urine collections, says it all! (In a retrospective study of 53 children, however, 47% had significant glomerular changes: J. Pediatr. *119:375–379, 1991.) For more on proteinuria occurring after exercise, see* J.A.M.A. *253:236–240, 1985.*
15. Rytand, D., and Spreiter, S. Prognosis in postural (orthostatic) proteinuria. *N. Engl. J. Med.* 305:618–621, 1981.
    The long-term prognosis in this condition is favorable. (See also the companion editorial, p. 639.)
16. Brenner, B., Hostetter, T., and Humes, H. Molecular basis of proteinuria of glomerular origin. *N. Engl. J. Med.* 298:826–832, 1978.
    Though not a new article, this should be required reading for anyone interested in glomerular structure, function, or disease.
17. Trachtman, H., and Gauthier, B. Effect of angiotensin-converting enzyme inhibitor therapy on proteinuria in children with renal disease. *J. Pediatr.* 112:295–298, 1988.
    Angiotensin-converting enzyme inhibition reduced urinary protein excretion by 60–70% in children with a variety of renal disorders.

74. ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Kenneth B. Roberts and Conrad J. Clemens

Acute poststreptococcal glomerulonephritis (APSGN) is a nonsuppurative sequela of group A, b-hemolytic streptococcal infection. Unlike rheumatic fever, glomerulonephritis may follow streptococcal infection either of the pharynx or of the skin, but only certain strains of streptococci are nephritogenic. The pathogenesis is considered to be the deposition of circulating immune complexes in the kidney.

The “nephritis triad” consists of edema, hypertension, and urinary abnormalities (e.g., hematuria). The most common clinical feature is edema, frequently of the eyelids and face; often, the edema is recognized by the family but not by the physician except in retrospect after diuresis. Hypertension is the next most common sign and is due primarily to the increase in vascular volume. It may be symptomatic, with headache and vomiting, but more often, as with the edema, it is not apparent until recovery, when a lower blood pressure is recorded. Hypertensive encephalopathy occurs in less than 5% of the patients; papilledema is rare, and residua are uncommon. Circulatory congestion, the result of fluid and electrolyte retention, is manifested clinically as “congestive heart failure,” and radiographically by cardiomegaly and increased pulmonary vascular markings; myocardial function and cardiac output are normal (or above normal). The affected child appears pale because of the edema and hemodilution. Mild anemia, with unchanged red cell mass, is due to the increased intravascular fluid. Any of these clinical findings may be absent in biopsy-proven glomerulonephritis.

During the acute phase of glomerulonephritis, the patient excretes a reduced amount of urine with high specific gravity. A variable degree of proteinuria is noted in individual voidings, but the 24-hour quantity is usually not massive, and the nephrotic syndrome is rare. Gross hematuria occurs in over one third of the patients (up to 70% of hospitalized patients) and gives the urine its smoky, rusty, or tea- or cola-colored appearance. The gross hematuria usually disappears after a few days but may continue for up to 2 weeks; microscopic hematuria persists long after the gross hematuria has cleared. Red cell casts are seen more frequently in acid than in alkaline urine, and are most easily found at the edge of the coverslip during microscopic examination of freshly voided urine. Hyaline and granular casts are usually present but do not have the same significance.

Serum complement concentration is decreased, apparently because of decreased synthesis and increased breakdown as a result of reaction with immune complexes; levels are usually normal by 6 weeks. The sedimentation rate is almost always increased, but neither the magnitude of the increase nor the return to normal correlates well with the severity of the disease. Cholesterol is initially modestly elevated in 40% of patients and returns to normal within 3–4 weeks. Serum albumin concentration may also be abnormal, but the slight decrease is usually due to hemodilution rather than to proteinuria. During the acute stage, the concentrations of creatinine and urea nitrogen in the serum are increased, and creatinine clearance is reduced.

Renal biopsy is rarely necessary; when performed, the characteristic findings are hypercellular glomeruli, compressed capillary lumens, and infiltration by leukocytes and macrophages. Immunofluorescence techniques demonstrate the foci of complement and immunoglobulin on the epithelial side of the basement membrane.

Poststreptococcal glomerulonephritis may be subclinical, as demonstrated both by complement levels and by biopsy findings in the siblings of children with clinical acute glomerulonephritis. In addition, many children have mild proteinuria and microscopic hematuria during acute streptococcal infections. Although this is usually ascribed to the “toxic phase” of febrile illness, it may also occur with impetigo, in the absence of constitutional symptoms. Hematuria that is not associated with proteinuria or persists after the toxic period is cause for concern and periodic follow-up. Subclinical poststreptococcal glomerulonephritis is a possibility in such situations, but it is also possible that the streptococcal infection is coincidental, superimposed on previously unrecognized renal disease.

Treatment of poststreptococcal glomerulonephritis is supportive, and consists of fluid and salt restriction during the oliguric or anuric phase, and control of circulatory congestion and hypertension. Many pediatricians also prescribe penicillin to eradicate any persistent streptococci.

Recurrences have been noted, but they are rare. The number of nephritogenic strains of streptococci in the community is usually limited, and type-specific immunity protects against reinfection. Penicillin prophylaxis, as would be prescribed after acute rheumatic fever, is therefore not warranted.

The prognosis for children with APSGN is considered to be uniformly good. However, other glomerulonephritides that are not so benign may mimic acute poststreptococcal disease; these include other postinfection nephritides, immunoglobulin A nephropathy, familial nephritis (Alport syndrome), membranoproliferative glomerulonephritis, and the nephritides of Henoch-Schönlein syndrome, systemic lupus erythematosus, polyarteritis nodosa, bacterial endocarditis, and toxins.

Reviews

1. Couser, W. Glomerulonephritis. *Lancet* 353:1509–1515, 1999.
   A well-written review that includes a section of suggested readings.
2. Hricik, D., Chung-Park, M., and Sedor, J. Glomerulonephritis. *N. Engl. J. Med.* 339:888–99, 1998.
   Complete discussion of all types of glomerulonephritis, including acute poststreptococcal glomerulonephritis (APSGN).
3. Simckes, A., and Spitzer, A. Poststreptococcal acute glomoerulonephritis. *Pediatr. Rev.* 16:278–279, 1995.
   A 2-page bullet on the topic. For more depth, see Nephron *55:1–5, 1990.*
4. Ayoub, E., and Chun, C. Nonsuppurative complications of group A streptococcal infection. *Adv. Pediatr. Infect. Dis.* 5:69–92, 1990.
   The concise overview of APSGN begins on p. 82. See also Pediatr. Clin. North Am. *29:857–874, 1982.*

Diagnosis

5. Madaio, M., and Harrington, J. The diagnosis of acute glomerulonephritis. *N. Engl. J. Med.* 309:1299–1302, 1983.
   A step-by-step approach, starting with determination of serum complement. For more on serum complement levels in glomerulonephritis, see B.M.J. *3:668–672, 1973.*
6. Nordby, J. Neurological presentation of poststreptococcal glomerulonephritis. *Clin. Pediatr.* 36:105–108, 1997.
   Hypertensive encephalopathy can be the presentation of APSGN.
7. Kirkpatrick, J., and Fleisher, D. The roentgen diagnosis of the chest in acute glomerulonephritis in children. *J. Pediatr.* 64:492–498, 1964.
   In 86% of patients, the chest x-ray is abnormal: cardiomegaly, evidence of circulatory congestion.
8. Vardi, P., et al. The heart in acute glomerulonephritis: An echocardiographic study. *Pediatrics* 63:782–787, 1979.
   Confirms data obtained prior to echocardiography: The signs of heart failure are not due to myocardial damage but to fluid overload (so digoxin is of no value: J. Pediatr. *69:1054–1062, 1966).*

Subclinical Infection

9. Derrick, C., Reeves, M., and Dillon, H. Complement in overt and symptomatic nephritis after skin infection. *J. Clin. Invest.* 49:1178–1187, 1970.
   In siblings of index cases, complement also decreased. Some also developed hematuria.
10. Rodriguez-Iturbe, D., Rubin, L., and Garcia, R. Attack rate of poststreptococcal nephritis in families. *Lancet* 1:401–403, 1981.
    Secondary attack rate in siblings approached 40%; the ratio of subclinical-to-clinical cases was 4:1. See also Pediatrics *40:1028–1030, 1967.*
11. Sagel, I., et al. Occurrence and nature of glomerular lesion after group A streptococcal infections in children. *Ann. Intern. Med.* 79:492–429, 1973.
    Among 24 children with streptococcal infection, there were 15 with abnormal urine, 19 with decreased complement, and 20 with both; all were asymptomatic. The biopsy findings were suggestive of acute glomerulonephritis in all 24.

Epidemiology and Prevention

12. Roy, S., and Stapleton, F. Changing perspectives in children hospitalized with poststreptococcal acute glomerulonephritis. *Pediatr. Nephrol.* 4:585–588, 1990.
    Between 1961 and 1970, more than 300 children were diagnosed with APSGN, 70% of whom had antecedent impetigo; between 1979 and 1988, there was a total of 95, only 38% of whom had

impetigo.
13. Weinstein, L., and LeFrock, J. Does antimicrobial therapy of streptococcal pharyngitis or pyoderma alter the risk of glomerulonephritis? *J. Infect. Dis.* 124:229–233, 1971.
A review of the evidence leaves the questions unanswered; no answer has been forthcoming in the subsequent 3 decades.

Treatment

14. Repetto, H., et al. The renal function response to furosemide in children with acute glomerulonephritis. *J. Pediatr.* 80:660–666, 1972.
It works.
15. Powell, H., et al. Plasma renin activity in acute poststreptococcal glomerulonephritis and the haemolytic-uraemic syndrome. *Arch. Dis. Child.* 49:802–807, 1974.
Acute glomerulonephritis is a low-renin state.

Natural History and Prognosis

16. Potter, E., et al. Twelve- to seventeen-year follow-up patients with poststreptococcal acute glomerulonephritis in Trinidad. *N. Engl. J. Med.* 307:725–729, 1982.
The prognosis is good after endemic or epidemic APSGN. See also Nephron *58: 393–399, 1991.*
17. Roy, S., Wall, H., and Etteldorf, J. Second attacks of acute glomerulonephritis. *J. Pediatr.* 75:758–67, 1969.
Uncommon, but they occur. The biopsy specimens appeared no worse the second time around.

75. HEMOLYTIC-UREMIC SYNDROME

Kenneth B. Roberts

Hemolytic-uremic syndrome (HUS) is the most common cause of acute renal failure in infants and children who do not have underlying structural renal disease. The syndrome consists of the triad of thrombocytopenia, hemolytic anemia, and acute renal failure. Approximately 90% of cases are diarrhea associated (D+HUS). The remaining 10% of cases are associated with various malignancies, transplantation, drugs, and nonenteric pathogens; non–diarrhea-associated HUS (D–HUS, atypical HUS) also occurs as an inherited disorder.

Hemolytic-uremic syndrome stems from damage to glomerular endothelium, resulting in thrombin deposition, microangiopathic hemolytic anemia, and platelet trapping. The classic model for D+HUS has been *Shigella*, with its enterotoxin. However, *Escherichia coli*, especially serotype O157:H7, has emerged as the predominent pathogen in North America, accounting for virtually all cases of D+HUS, triggering HUS with a verotoxin. In outbreaks of *E. coli* O157:H7, 8–10% of affected children develop HUS. The diarrhea is generally bloody, accounting for the designation enterohemorrhagic *E. coli*. The acute phase of HUS begins 3–7 days later. Anemia and pallor rapidly become prominent; the hematocrit can fall by 50% in 48 hours. Fever, abdominal pain, and vomiting are frequent accompanying complaints. Patients at this stage may be oliguric or frankly anuric. On examination, small ecchymoses and purpura may be noted, along with petechiae; central nervous system (CNS) signs (drowsiness, convulsions, or coma) may also be present. One half of patients have organomegaly, one half have hypertension, and one third are edematous.

The three cardinal features of HUS are also present in thrombotic thrombocytopenic purpura (TTP), which includes fever and variable neurologic manifestations as additional components that define the syndrome. Thrombotic thrombocytopenic purpura generally occurs in adults and has a worse prognosis than HUS. The two disorders were thought to be age-related manifestations of the same disease until the recent discovery that patients with TTP lack von Willebrand factor–cleaving protease activity, while children with HUS do not. Although the pathogenesis (and, therefore, the treatment) of the two syndromes is distinct, the clinical similarities remain useful: Children with HUS who have a TTP-like course with CNS signs such as convulsions or coma have a less favorable prognosis than other children with HUS.

The striking laboratory features give HUS its name. The hemolytic anemia may be marked, with fragmented forms, burr cells, and other evidence of microangiopathic hemolysis readily apparent on peripheral blood smear; the Coombs test is negative. Platelets are acutely decreased (<50,000/mm ^{3}) in half of the patients; megakaryocytes are present in the marrow, and the thrombocytopenia usually resolves within a few weeks. The blood urea nitrogen and creatinine concentrations rise over a period of days. Once the values are abnormally elevated, the rate of rise is generally constant in a given patient (though it varies from patient to patient), and can be plotted as a straight line. Serum complement concentration is normal. Renal biopsy, if performed, reveals fibrin thrombi and cortical necrosis.

Vigorous supportive care is the essence of therapy. Particular attention must be given to fluid balance, control of hypertension, and appropriate institution of dialysis; transfusions are provided as needed. Plasma therapy appears to be of benefit to patients with TTP and some patients with D–HUS.

Acute mortality in HUS has been reported to be as high as 25%, but recent estimates are closer to 5%. It is not clear whether the change is due to an alteration in the disease, the diagnosis of milder cases, the emergence of *E. coli* O157:H7 as the major trigger, or the earlier use of dialysis. As noted above, CNS involvement is associated with increased mortality.

Hypertension and chronic renal failure are the major sequelae of HUS. In long-term follow-up studies, renal impairment is demonstrated in 30–40% of patients. Prolonged anuria or oliguria is a poor prognostic sign, but even patients with quick recovery are at risk and should continue to be followed for several years.

Currently, efforts are underway to identify methods of preventing HUS. These include veterinary initiatives, vaccine, and administration of SYNSORB Pk, a synthetic molecule that binds the verotoxin. A preliminary trial suggested that the rate of HUS could be cut in half if SYNSORB Pk is given during the first 3 days of illness. A multicenter trial is in progress.

Reviews

1. Stewart, C., and Tina, L. Hemolytic uremic syndrome. *Pediatr. Rev.* 14:218–224, 1993.
   This review holds up well as a good place to start, though you will want to supplement your reading with some of the newer information that has been generated.
2. Kaplan, B., Meyers, K., and Schulman, S. The pathogenesis and treatment of hemolytic uremic syndrome. *J. Am. Soc. Nephrol.* 9:1126–1133, 1998.
   The authors correctly note that diarrhea-associated (D+) hemolytic-uremic syndrome (HUS) is an inappropriate designation, since Escherichia coli *O157:H7 from other sites (e.g., urinary tract infection:* Clin. Infect. Dis. *27:310–315, 1998) can cause HUS; they prefer Shiga-toxin–HUS (Stx+HUS). This review provides more about non–diarrhea-associated (D–) HUS (or Stx-HUS) than most.*

Diarrhea-Associated Hemolytic-Uremic Syndrome and *Escherichia coli* O157:H7

3. Cohen, M. *Escherichia coli* O157:H7 infections: A frequent cause of bloody diarrhea and the hemolytic-uremic syndrome. *Adv. Pediatr.* 43:171–207, 1996.
   An extensive review, with 187 references.
4. Slutsker, L., et al. A nationwide case-control study of *Escherichia coli* O157:H7 infection in the United States. *J. Infect. Dis.* 177:962–966, 1998.
   Although multiple foodstuffs can be contaminated with E. coli *O157:H7 and cause disease (e.g., leaf lettuce:* J. Infect. Dis. *177:1588–1593, 1998; unpasteurized commercial apple juice:* Ann. Intern. Med. *130:202–209, 1999), this national perspective from the Centers for Disease Control and Prevention reminds us that undercooked hamburger remains the main culprit.*
5. Rowe, P., et al. Risk of hemolytic uremic syndrome after sporadic *Escherichia coli* O157:H7 infection: Results of a Canadian collaborative study. Investigators of the Canadian Pediatric Kidney Disease Research Center. *J. Pediatr.* 132:777–782, 1998.
   The risk was 8.1% overall, 12.9% in children younger than 5 years.
6. Bell, B., et al. Predictors of hemolytic uremic syndrome in children during a large outbreak of *Escherichia coli* O157:H7 infections. *Pediatrics* 100:e12, 1997. (Available at www.pediatrics.org/cgi/content/full/100/1/e12.)
   The following were associated with increased rate of HUS: antimotility agent (three-fold increase); vomiting in children younger than 5 years (four-fold increase); and white blood cell count >13,000 in first 3 days of illness (seven-fold increase). Sadly, nothing was found that correlated with a reduced rate.
7. Trachtman, H., and Christen, E. Pathogenesis, treatment, and therapeutic trials in hemolytic uremic syndrome. *Curr. Opin. Pediatr.* 11:162–168, 1999.
   An update of possible pathogenetic mechanisms (51 references). See also Arch. Dis. Child. *1998;78:190–193.*

Non–Diarrhea-Associated Hemolytic-Uremic Syndrome

8. Fitzpatrick, M., et al. Atypical (non-diarrhea-associated) hemolytic-uremic syndrome in childhood. *J. Pediatr.* 122:532–537, 1993.
   Report of 20 children with D-HUS, "a heterogeneous yet distinct subgroup" that differs from D+HUS on "epidemiologic, clinical, laboratory, histologic, and prognostic grounds." Plasma exchange appears to have improved the initial outcome in this form of HUS.
9. Neuhaus, T., Calonder, S., and Leumann, E. Heterogeneity of atypical haemolytic uraemic syndromes. *Arch. Dis.Child.* 76:518–521, 1997.
   Children with a recurrent, familial, or neonatal course have worse outcomes; infants not requiring dialysis in the acute phase have a better prognosis.
10. Cabrera, G., et al. Hemolytic uremic syndrome associated with invasive *Streptococcus pneumoniae* infection. *Pediatrics* 101:699–703, 1998.
    A series of seven patients plus a review. Pneumococcal neuraminidase appears to initiate a cascade in infants that can lead to HUS and the need for dialysis.
11. Siegler, R., et al. Atypical hemolytic-uremic syndrome: A comparison with postdiarrheal disease. *J. Pediatr.* 128:505–511, 1996.
    In contrast to reports from most other regions, patients with atypical disease in this area of the western United States had milder acute nephropathy and, with the exception of those with recurrence, did not experience worse outcomes.
12. Gordon, L., and Kwaan, H. Cancer- and drug-associated thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. *Semin. Hematol.* 34:140–147, 1997.
    Part of a symposium on thrombotic thrombocytopenic purpura (TTP) HUS (pp. 81–166), that is heavily oriented toward TTP, but this article is particularly useful for the list of conditions and

drugs. (For a reminder that inborn errors of metabolism may present with HUS, in this case cobalamin C defect, see J. Pediatr. *120:934–937, 1992.)*

von Willebrand Factor-Cleaving Protease

13. Furlan, M., et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. *N. Engl. J. Med.* 339: 1578–1584, 1998.
The activity of von Willebrand factor–cleaving protease activity is decreased in patients with TTP and normal in those with HUS.

Complications

14. Sheth, K., Swick, H., and Haworth, N. Neurological involvement in hemolytic-uremic syndrome. *Ann. Neurol.* 19:90–93, 1986.
Neurologic involvement was recorded in one third of children with HUS; complete neurologic recovery occurred in less than half of those affected. Children with neurologic involvement had a higher incidence of residual hypertension, chronic renal damage, and death.
15. Cimolai, N., Morrison, B., and Carter, J. Risk factors for the central nervous system manifestations of gastroenteritis-associated hemolytic-uremic syndrome. *Pediatrics* 90:616–621, 1992.
Of 91 patients, 27 (30%) had central nervous system (CNS) manifestations. Multivariate analysis suggested the following risk factors: female gender, prolonged use of an antimotility agent, and increased hemoglobin level.
16. Schlieper, A., et al. Neuropsychological sequelae of haemolytic uraemic syndrome. Investigators of the HUS Cognitive Study. *Arch. Dis. Child.* 80:214–220, 1999.
Children discharged from the hospital without apparent neurologic injury after an episode of acute HUS did not have an increased risk of subclinical problems with learning, behavior, or attention.

17. Ogura, H., et al. Reversible MR findings of hemolytic uremic syndrome with mild encephalopathy. *Am. J. Neuroradiol.* 19:1144–1145, 1998.
The reversible magnetic resonance imaging findings in a 7-year-old girl with hemolytic-uremic syndrome and mild encephalopathy, who recovered without CNS impairment.
18. Saltzman, D., et al. Timing of colonic necrosis in hemolytic uremic syndrome. *Pediatr. Surg. Int.* 13:268–270, 1998.
Colon perforation, a complication in 1–2% of patients with HUS, tends to occur toward the end of the second week of symptoms.

Prevention

19. Rowe, P., et al. A phase II randomized controlled trial of SYNSORB Pk for the prevention of hemolytic uremic syndrome in children with verotoxin producing *E. coli* (VTEC) gastroenteritis. *Pediatr. Res.* 41:283A, 1997.
This preliminary study has led to an ongoing trial: SYNSORB Pk was associated with a 54% reduction in HUS when given during the first 3 days of illness.
20. Konadu, E., et al. Investigational vaccine for *Escherichia coli* O157: Phase 1 study of O157 O-specific polysaccharide-*Pseudomonas aeruginosa* recombinant exoprotein A conjugates in adults. *J. Infect. Dis.* 177:383–387, 1998.
Results of this phase I trial are sufficiently encouraging to warrant a phase II study in young children.

Therapy

21. Schulman, S., and Kaplan, B. Management of patients with hemolytic uremic syndrome demonstrating severe azotemia but not anuria. *Pediatr. Nephrol.* 10: 671–674, 1996.
Suggests that management of D+HUS patients without dialysis is appropriate when the only abnormality is increased blood urea nitrogen (i.e., the patient is not anuric and has normal acid-base and serum electrolyte concentrations, and fluid balance).
22. Perez, N., et al. Steroids in the hemolytic uremic syndrome. *Pediatr. Nephrol.* 12:101–104, 1998.
Oral steroids did not modify hematologic, neurologic, or renal parameters during the acute phase, except for a more rapid decline in serum creatinine levels.

Long-Term Renal Outcome

23. Gagnadoux, M., et al. Long-term (15–25 years) outcome of childhood hemolytic-uremic syndrome. *Clin. Nephrol.* 46:39–41, 1996.
Long-term outcome (mean 18 years, range 15–28 years) of 29 patients: 10 had no renal abnormality; 12 had residual abnormalities (hypertension in 7, proteinuria in 4, and mildly reduced glomerular filtration rate [GFR]in 1); 3 were in chronic renal failure; and 4 had reached end-stage renal failure (2 of whom had normal GRF at 10 year follow-up!). Outcome correlates with renal histology but not with initial clinical severity.
24. Siegler, R., et al. Long-term outcome and prognostic indicators in the hemolytic-uremic syndrome. *J. Pediatr.* 118:195–200, 1991.
Anuria was the best predictor of disease at follow-up. Abnormalities sometimes appeared after an interval of apparent recovery. Of 61 patients followed a mean of 9.6 years, 5% had hypertension, proteinuria, and low creatinine clearance.

76. NEPHROTIC SYNDROME

Richard A. Cohn

The nephrotic syndrome (NS) consists of (1) heavy proteinuria (>1 g/m^2/d); (2) hypoalbuminemia (<2.5 g/dL); (3) edema; and (4) hypercholesterolemia (>250 mg/dL). The primary abnormality is an alteration in the structural or functional integrity (or both) of the glomerular filter, which ordinarily permits less than 0.03% of plasma albumin to reach the tubules. A small increase in permeability, while still restricting more than 99% of plasma albumin, can overwhelm the resorptive capacity of the tubules and result in heavy proteinuria. The features of NS are either a direct consequence of protein loss or a result of compensatory mechanisms.

Edema (periorbital, peripheral, scrotal, or abdominal) is the usual presenting complaint and may be massive. The pathogenesis is related to (1) decreased plasma oncotic pressure and transudation of water into the extravascular compartment, and (2) decreased effective plasma volume, causing enhanced salt and water resorption in distal nephron sites via secondary hyperaldosteronism, and the release of both antidiuretic hormone and atrial natriuretic peptides.

The incidence of NS is estimated at 2 new cases per 100,000 children/year. In contrast to adults with NS, children with NS usually have primary renal disease rather than systemic disorders such as systemic lupus erythematosus (SLE), acquired immunodeficiency syndrome (AIDS), or diabetes mellitus. Renal biopsy studies have permitted the characterization and differentiation of several primary renal disorders leading to NS in children.

By far, the most common cause of NS in children is *minimal change nephrotic syndrome* (MCNS). More than 75% of children with NS and more than 90% of those 1–6 years old have this form of NS. The term *minimal change* refers to the paucity of abnormalities seen by light microscopy; terms formerly used include *nil lesion* and *lipoid nephrosis*. It is this disorder that determines the overall epidemiology of NS in childhood: The majority of affected patients are symptomatic by age 6, and boys predominate 2:1.

Blood pressure is elevated transiently in 20% of children with MCNS. Gross hematuria is rare, but microscopic hematuria occurs in 25% of patients when proteinuria is present. Histologically, the glomeruli are normal or minimally abnormal by light microscopy; no immunoglobulin or complement component deposits are seen by immunofluorescence microscopy. Fusion of epithelial podocytes is detected by electron microscopy.

Treatment consists of medication to reduce proteinuria, salt restriction to control edema, and measures to prevent and treat complications. Proteinuria remits in more than 90% of children with MCNS within 4 weeks after initiating prednisone therapy (often within 7–10 days). Two thirds of those whose NS responds to prednisone will have a relapsing course, however, usually for several years; most children ultimately achieve prolonged or permanent remissions, particularly by early adolescence. In some children, the NS becomes resistant to steroids after earlier responses or requires intoxicating doses to maintain remission; for these patients, immunosuppressive medication (cyclophosphamide, cyclosporine or levamisole) has been used, but there is concern about the undesirable associated effects, particularly sterility and the threat of malignancy with cyclophosphamide, and nephrotoxicity with cyclosporine.

Dietary sodium should be restricted, but vigorous fluid restriction is not helpful and may be dangerous in these children because their intravascular volumes may already be low. Moreover, children with MCNS are predisposed to vascular thromboses, particularly when taking steroids. Patients with respiratory embarrassment, skin breakdown, or massive edema may benefit from infusions of intravenous albumin followed by furosemide.

The most common serious complication of MCNS is bacterial infection (e.g., cellulitis, peritonitis, pneumonia, sepsis), especially at sites of edema. Contributing factors include hypoimmunoglobulinemia and reduced opsonic activity from loss of properdin factor B in the urine, and other immunologic abnormalities caused by both the disease and the treatment. Children should receive pneumococcal vaccine, and appropriate precautions should be taken when steroids are being administered, such as avoidance of live viral vaccines and administration of varicella-zoster immune globulin (VZIG) following exposure to chickenpox, if the dose of prednisone is high and the child is not already immune. Bacterial infection should be treated early and aggressively; *Streptococcus pneumoniae* and *Escherichia coli* are the most frequently seen organisms.

The prognosis for children with MCNS is excellent. Renal function remains normal in those who respond to medication, whether relapses are frequent or not.

Of children with NS, 10% (or nearly half of those who do not have minimal-change disease) have *focal segmental glomerular sclerosis*. As in MCNS, most are boys, have apparent disease by age 8, and are normocomplementemic; hypertension and hematuria are more common than in MCNS. Histologic examination reveals a portion of glomeruli with a segment of hyalinosis, devoid of nuclei and adherent to Bowman's capsule; capillary lumens are obliterated. The remaining tufts in an involved glomerulus may be normal. Juxtamedullary glomeruli are often affected earliest, but progression to generalized involvement occurs commonly. Immunoglobulin M, C3, C4, and often properdin can be demonstrated by immunofluorescence microscopy in sclerosing segments; collapse of capillary loops and sclerosis are evident on electron microscopy. The relationship of this lesion to “minimal change” is unsettled: Some believe that sclerosis may develop over time in a child with MCNS; others think that the sclerotic lesion is present at the onset but that, since it is focal in nature, it may be missed on examination of early biopsy specimens, particularly if juxtamedullary glomeruli are not sampled.

In 20% of patients with focal segmental glomerular sclerosis, the NS responds to steroids and to cytotoxic drugs. Relapses may be frequent, but a complete remission is often achieved; in some, progression to end-stage renal disease (ESRD) occurs, despite the initial response. In 80% of patients, however, the NS does not respond initially to either oral steroid therapy or cytotoxic drugs. However, two treatment modalities may be useful in patients with focal segmental glomerulosclerosis: In one, high-dose intravenous methylprednisolone combined with oral chlorambucil may induce remissions in many patients; in the second, high-dose oral cyclosporine has resulted in improvement and, in many cases, remission. Patients unresponsive to medication with persistent nephrotic-range proteinuria, usually progress to renal insufficiency, often within 2 years of diagnosis. Renal transplantation is generally successful, although NS, with focal sclerosis, may recur. In children with AIDS who develop NS, the most common histologic change seen is focal sclerosis.

Approximately 7% of children with NS have *membranoproliferative* (*mesangiocapillary*) *glomerulonephritis*. These patients are usually older children who present with NS or an acute nephritis syndrome (gross hematuria, edema, hypertension), or both; they may present with asymptomatic hematuria and proteinuria. Reduced renal function, hypertension, and hypocomplementemia are common. The characteristic histologic appearance is mesangial proliferation and expansion around capillary walls. The glomeruli are enlarged and lobular, with either subendothelial or intramembranous deposits apparent on electron microscopy. Immunoglobulin and complement are found on capillary loops in a peripheral-lobular distribution by fluorescence microscopy.

Daily prednisone therapy and immunosuppressive agents do not induce remissions in this form of NS and may cause severe toxicity, particularly hypertensive encephalopathy; alternate-day steroid therapy, when started early in the course of renal disease, is usually beneficial. Some patients have a slowly progressive course over many years, often into ESRD. In most patients, renal function stabilizes with persistent proteinuria; complete remissions do occur but are unusual. The lesion may recur after renal transplantation.

Mesangial proliferative glomerulonephritis is present in 5% of children with NS. There usually is an initial remission with steroids, but frequent relapses and steroid dependency are common; in some children, steroids are ineffective from the outset. The response to cyclophosphamide or cyclosporine is highly variable, ranging from none to long-term remission. Immunoglobulin M is often seen in the mesangium by immunofluorescence microscopy, and mesangial electron-dense deposits are present on electron microscopy.

Membranous glomerulopathy (extramembranous glomerulonephritis, membranous glomerulonephritis) is present in less than 5% of children with NS. Neither sex

predominates, and age distribution is scattered. Hematuria and hypertension may or may not be present; renal function and complement levels are generally normal at the time of presentation. Histologic findings include uniformly thickened capillary walls in all glomeruli, lack of proliferative changes in glomeruli, and typical spikes along the basement membrane on silver stain. Electron microscopy reveals deposits on the epithelial side of the thickened glomerular basement membrane. Uniform granular deposits of immunoglobulin G, C3, and often C4 are seen on the outer aspect of the basement membrane by immunofluorescence microscopy. A search for etiologic causes (e.g., SLE, hepatitis B, syphilis, etc.) should be made in these patients.

Although therapy in children with membranous glomerulopathy is generally ineffective, one third to one half have spontaneous clinical improvement over months or years; an equal number continue to have proteinuria but maintain normal renal function. Approximately 10%, primarily older children, continue in a nephrotic state and progress slowly to ESRD.

Congenital NS is a rare familial disorder transmitted in an autosomal recessive pattern, with a higher frequency in families of Finnish ancestry. The gene for this disorder is located on chromosome 19 and codes for a transmembrane protein, nephrin, which is normally expressed solely in glomerular podocytes. These patients have severe proteinuria from birth, have disproportionately more ascites and less peripheral edema than other patients with NS, and generally fail to thrive. Response to steroid therapy is uncommon, and large doses of diuretics are required. Many advocate prophylactic antibiotic therapy, since overwhelming sepsis is common in this group. Hypothyroidism develops in almost all children by age 3. Renal function may remain normal for years, but most patients ultimately develop ESRD. The nephrotic state does not recur after renal transplantation, lending support to evidence that abnormal biochemical structure of the glomerular capillary is the basic underlying defect. Antenatal diagnosis is possible with the gene noted above, as well as elevated levels of alpha fetoprotein present in the amniotic fluid, with concomitantly high levels in maternal blood.

How does one approach a given patient once NS has been diagnosed? Should a renal biopsy be performed initially, or should steroid therapy be started? Most authorities agree that children younger than age 8 who are normotensive, do not have hematuria, and have normal renal function can be given a trial of steroid therapy, with a renal biopsy to be done later if the NS does not respond. Biopsy prior to using prednisone should be considered in patients less likely to have MCNS (older children and those with hypocomplementemia, hypertension, reduced renal function, or a concomitant acute nephritis syndrome). If treatment is prescribed without histologic diagnosis, these patients in particular must be monitored closely to reduce potential morbidity from steroid therapy.

Reviews

1. Clark, A., and Barratt, T. Steroid-responsive nephrotic syndrome. In: Barratt, T. (ed.). *Pediatric Nephrology* (4th edition). Baltimore: Lippincott Williams & Wilkins, 1999:731–747.
   A comprehensive review.
2. Kelsch, R., and Sedman, A. Nephrotic syndrome. *Pediatr. Rev.* 14:30–38, 1993.
   A review of the clinical presentation, pathologic varieties, and therapy.
3. Border, W. Distinguishing minimal-change disease from mesangial disorders. *Kidney Int.* 34:419–434, 1988.
   A discussion (with beautiful pictures) of the histopathology of nephrotic syndrome (NS).

Pathology and Pathogenesis

4. Brenner, B., Hostetter, T., and Humes, H. Molecular basis of proteinuria of glomerular origin. *N. Engl. J. Med.* 298:826–833, 1978.
   A still excellent, readable summary of glomerular permeability.
5. Perico, N., and Remuzzi, G. Edema of the nephrotic syndrome: The role of the atrial peptide system. *Am. J. Kidney Dis.* 22:355–366, 1993.
   Excellent review of mechanisms causing edema, including a role of atrial natriuretic peptide.
6. Ritz, E. Pathogenesis of "idiopathic" nephrotic syndrome. *N. Engl. J. Med.* 330: 61–62, 1994.
   Editorial summarizing what is known and what is not known. (See also Lancet *2:556–560, 1974, for more on T cell changes, and* J. Clin. Invest. *79:257–264, 1987, for a discussion of the "soluble immune response suppressor" in the urine of children with NS.)*

Complications

7. International Study of Kidney Disease in Children. Minimal change nephrotic syndrome in children: Deaths during the first 5 to 15 years' observation. *Pediatrics* 73:497–501, 1984.
   A review of long-term problems. The pattern of response to steroids appears to be of prognostic significance.
8. Freundlich, M., et al. Bone modulating factors in nephrotic children with normal glomerular filtration rate. *Pediatrics* 76:280–285, 1985.
   Undermineralized bone in nephrotic children is a common problem and may be treatable with active vitamin D metabolites.
9. Gorensek, M., Lebel, M., and Nelson, J. Peritonitis in children with nephrotic syndrome. *Pediatrics* 81:849–856, 1988.
   A review of 62 episodes in 37 patients over a 20-year period.
10. Thabet, M., et al. Hyperlipidemia in childhood nephrotic syndrome. *Pediatr. Nephrol.* 7:559–566, 1993.
    A review of lipid metabolism and considerations for therapy (96 references).
11. Petaja, J., et. al. Resistance to activated protein C as an underlying cause of recurrent venous thrombosis during relapsing nephrotic syndrome. *J. Pediatr.* 127: 103–105, 1995.
    A specific cause for recurrent thrombosis was detected in a patient.

Minimal Change Nephrotic Syndrome

12. International Study of Kidney Disease in Children. The primary nephrotic syndrome in children: Identification of patients with minimal change nephrotic syndromes from initial response to prednisone. *J. Pediatr.* 98:561–564, 1981.
    Ninety-two percent of responders and 25% of nonresponders had minimal change nephrotic syndrome (MCNS); additional criteria are needed to justify biopsy in nonresponders.
13. Trompeter, R., et al. Long-term outcome for children with minimal-change nephrotic syndrome. *Lancet* 1:368–370, 1985.
    In a 20-year study, prognosis was favorable but proteinuria and relapses persisted longer in patients who presented at an early age.
14. Berns, J., et al. Steroid-responsive nephrotic syndrome of childhood: A long-term study of clinical course, histopathology, efficacy of cyclophosphamide therapy and effects on growth. *Am. J. Kidney Dis.* 9:108–114, 1987.
    Also see J. Pediatr. *113:996–1001, 1988.*
15. Siegel, N., et al. Steroid-dependent nephrotic syndrome in children: Histopathology and relapses after cyclophosphamide treatment. *Kidney Int.* 19:454–459, 1981.
    Much greater likelihood of long-term remission after cyclophosphamide in MCNS than in focal sclerosis or mesangial proliferative NS. (See also J. Pediatr. *92: 304–308, 1978, and* Pediatrics *57:948–951, 1976. For a review of gonadal dysfunction, see* J. Pediatr. *84:831–836, 1974, and 91:385–394, 1977.)*
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    A series of 19 children who received cyclosporine and benefited, particularly from not being on steroids. Cyclosporine doses were much lower than those used to prevent organ transplant rejection. See also Pediatr. Nephrol. *8:401–403, 1994.*
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Focal Segmental Glomerular Sclerosis

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    Early treatment with high-dose, intravenous steroids (and, later, chlorambucil) benefited children with an otherwise dismal prognosis.
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Other Causes of Nephrotic Syndrome

20. West, C., and McAdams, A. The chronic glomerulonephritides of childhood. *J. Pediatr.* 93:1–12, and 167–176, 1978.
    Still excellent, well-referenced, brief discussions of the various common glomerulonephritides of childhood (two-part review).
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    For a large uncontrolled study suggesting improved survival with alternate-day prednisone therapy, also see Clin. Nephrol. *13:117–124, 1980.*
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24. Kleinknecht, C., et al. Membranous glomerulonephritis with extra-renal disorders in children. *Medicine* 58:219–228, 1979.
    Review of this entity associated with systemic lupus erythematosus, hepatitis, syphilis, etc., in children.
25. Holmberg, C., et al. Congenital nephrotic syndrome. In: Barratt, T. (ed.). *Pediatric Nephrology* (4th edition). Baltimore: Lippincott Williams & Wilkins, 1999:765–777.
    For medical management, see J. Pediatr. *105:549–557, 1984.*
26. Habib, R. Nephrotic syndrome in the first year of life. *Pediatr. Nephrol.* 7:347–353, 1993.
    An excellent review by the foremost pediatric nephropathologist. (See also J. Pediatr. *85:615–621, 1974.)*
27. Ingulli, E., et al. Nephrotic syndrome associated with acquired immunodeficiency syndrome in children. *J. Pediatr.* 119:710–716, 1991.
    For an overview of renal complications of acquired immunodeficiency syndrome (AIDS) in children, see Am. J. Kidney Dis. *11:48–50, 1988. For a discussion of renal disease in adults with AIDS, see* N. Engl. J. Med. *310:669–673, 1984*.

77. URINARY TRACT INFECTION

Richard A. Cohn and Kenneth B. Roberts

Urinary tract infections (UTIs) in children are of concern for two reasons. First, UTIs cause acute morbidity. Second, in young children, UTIs have the potential to produce renal scarring, which can lead to hypertension and decreased renal function. The potential for life-long consequences requires that the diagnosis of UTI be made accurately and that young children be assessed for additional risk factors for scarring. Unfortunately, scarring occurs at the age when the signs and symptoms of UTI are the most nonspecific, obtaining a clean urine specimen is the most complicated, and underlying abnormalities of the urinary system may not yet have been diagnosed.

Clinical manifestations of UTI vary with the age of the patient. Signs in the neonatal period are generally nonspecific and include weight loss, failure to thrive, unexplained jaundice (including conjugated hyperbilirubinemia), diarrhea, and central nervous system abnormalities (hypotonia, hypothermia, absent reflexes, irregular respirations). Sepsis is commonly associated with UTI in this age group, and concomitant maternal infection occurs in one half of affected newborns. Children between 1 month and 2 years of age may present with unexplained fever, failure to thrive, colic (especially before and during voiding), dribbling, vomiting, and abdominal distention. (In this age group, UTI is the most common bacterial cause of unexplained fever; rates as high as 15% have been reported in febrile infant Caucasian girls.) Children over age 2 generally have symptoms referable to the urinary tract: fever, dysuria, urgency, frequency, lower abdominal pain, flank tenderness, and enuresis.

If UTI is being considered, and certainly once UTI has been properly diagnosed, special consideration should be given on the physical examination to detecting hypertension, funduscopic changes, abdominal masses, vertebral anomalies, and neurologic disturbances associated with a neurogenic bladder. In males particularly, observation of the urinary stream should be made: A weak stream despite straining suggests the possibility of posterior urethral valves. In older children, particularly girls, inquiry should be made regarding completeness of voiding. Children with bladder dyssynergia may indicate the presence of residual urine when they explain that they have to void “twice” each time they urinate.

It is essential that the diagnosis of UTI be established properly by culture of a suitable specimen of urine. Specimens collected in a bag affixed to the perineum are subject to contamination, which may be unavoidable, particularly in girls and uncircumcised boys whose urine is “rinsed” through the vagina or under the prepuce. Bacteriuria is considered significant when culture demonstrates more than 50,000–100,000 organisms of a single species per milliliter (or more than a few colonies if the specimen is collected by suprapubic aspiration). In most UTIs, in fact, there are more than 1 million organisms/mL, whereas contaminated specimens contain less than 10,000/mL. If the colony count is difficult to interpret, another urine sample should be obtained and cultured. False-negative results can occur with high urine volumes of low osmolality, prior antibiotic therapy, extreme urinary acidity, or obstruction of the infected kidney or ureter. Specimens need to be plated soon after being obtained (or refrigerated until plated) to avoid bacterial multiplication in vitro, since the duplication time of enteric organisms is less than 30 minutes at room temperature.

“Dipstick” tests, leukocyte esterase and nitrite, can be used to raise or lower the probability of UTI, but their sensitivity and specificity are insufficient to substitute for culture. Leukocytes and unstained bacteria seen on light microscopy are unreliable indicators of UTI. The presence of bacteria on gram-stained smears of fresh, *uncentrifuged* urine correlates well with colony counts in excess of 100,000/mL, but microscopy does not replace culture as the diagnostic procedure.

Escherichia coli is the pathogen in approximately 75% of childhood UTIs; *Klebsiella, Proteus* (especially *Proteus mirabilis), Pseudomonas*, enterococcus, and *Staphylococcus* species account for most others, particularly in patients who have had recent antibiotic therapy, prior surgery, or a condition that results in immunocompromise.

Uncomplicated first episodes are treated with trimethoprim-sulfamethoxazole (TMP-SMX), a cephalosporin, or amoxicillin; amoxicillin has been demonstrated to be less effective than TMP-SMX. Antibiotic treatment of recurrent or complicated infections is based on the sensitivity of the responsible organisms. Treatment of febrile UTI is for 7–14 days, but older children with presumed cystitis may be treated effectively with shorter courses. Patients with anatomic abnormalities or frequent recurrences may benefit from long-term, low-dose suppressive therapy with nitrofurantoin or TMP-SMX in a single daily dose.

A major structural abnormality of the urinary tract may underlie a UTI, and radiologic evaluation is therefore indicated after an initial infection in preschool children. (Imaging protocols for older children are less clear.) The abnormalities being sought are obstruction and reflux. Underlying obstruction anywhere along the urinary tract, from collecting ducts to urethral meatus, predisposes to stasis, infection, and scarring. Vesicoureteral reflux (VUR) permits retrograde flow of urine from bladder to ureter and, when severe, to the kidney. Severity is graded on a scale of I to V. Grades I and II reflux (from bladder to low- or midureter without dilatation) usually resolve spontaneously with time. Grades III and higher represent increasing ureteral dilatation and tortuosity accompanied by caliceal clubbing. Grades IV and V generally are corrected surgically. Children with grade III reflux are treated medically at first; those who continue to have “break-through” infections may require operative repair. Antireflux procedures are indicated for (1) recurrent infections despite continuous antibiotic therapy; (2) failure of renal growth on sequential radiologic studies; (3) the development or progression of renal scarring despite adequate medical management; or (4) persistent, high-grade VUR that does not subside on follow-up, particularly in a young child. Long-term follow-up and study of all patients with urologic, neurologic, and reflux problems is mandatory if chronic renal failure on an infectious basis is to be avoided.

To detect obstruction and reflux, both an upper tract study and a lower tract study need to be performed. Ultrasonography is the upper tract study performed most widely; it does not involve radiation and is capable of identifying major structural abnormalities. Radionuclide renal scans are more sensitive for identifying changes of pyelonephritis and renal scars, but this information is generally not needed for acute decision making, and nuclear scans expose the patient to radiation. Voiding cystourethrography (VCUG) is the lower tract study of choice to identify (and permit quantitation of) VUR, lower tract obstruction, and bladder abnormalities. It should be performed after the urine has been sterilized by medication.

In addition to anatomic changes, other factors that are frequently associated with UTI in children include constipation; infrequent voiding with large bladder capacity causing stasis; the use of crude soap or bubble bath; and foreign bodies in the vagina or urethra. In pubertal girls, as in adult women, intercourse may predispose to cystitis, and pregnancy to cystitis and pyelonephritis. Children with neurogenic bladders need to be identified and a program of bladder emptying established.

Management includes careful follow-up of the patient. Renal function in children with anatomically and functionally *normal* urinary tracts rarely deteriorates to renal insufficiency if recurrences of UTI are appropriately managed. Recent studies of patients with renal transplants show a very low incidence of pyelonephritis as the cause of renal failure, and patients in whom pyelonephritis is the cause of end-stage renal disease usually have a major underlying structural abnormality of the urinary tract.

Screening healthy children for UTI is no longer done, since asymptomatic bacteriuria is now recognized to be a benign condition largely of Caucasian girls and women. It does not represent “silent pyelonephritis.” The major difficulty is in the interpretation of a “positive” urine culture in a child with unexplained fever. At the time of the acute illness, it may be impossible to distinguish asymptomatic bacteriuria with fever of another cause from true UTI. If pyuria is present, the episode is more likely to be a true UTI, and multiple asymptomatic “recurrences” shortly after antibiotics are discontinued may be an indication of the propensity to mucosal colonization with coliform bacteria.

Collection, Practice Parameter, and Review

1. Lohr, J. (ed.). Pediatric urinary tract infections. *Pediatr. Ann.* 28;639–699, 1999.
   A recent collection of brief articles that cover the various aspects well: pathogenesis (pp. 639–642); epidemiology and clinical presentation in children younger than 2 years (pp. 644–649) and 2 years through adolescence (pp. 653–658); diagnostic testing strategies (pp. 670–676); imaging (pp. 678–686); treatment (pp. 688–692); and long-term consequences (pp. 695–699).
2. American Academy of Pediatrics Committee on Quality Improvement, Subcommittee on Urinary Tract Infection. Practice parameter: The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 103:843–852, 1999. (Published errata appear in *Pediatrics* 103:1052, and 104:118, 1999.)
   In addition to the 11 recommendations, the committee has made available the 66-page technical report summarizing the literature that formed the basis for the recommendations: Pediatrics *103:e54, 1999. (Available at: www.pediatrics.org/cgi/content/full/103/4/e54.)*
3. Hellerstein, S. Urinary tract infections. Old and new concepts. *Pediatr. Clin. North Am.* 42:1433–1457, 1995.
   Don't be put off by a 1995 publication date or presume that something more recent is either better or more up-to-date.

Epidemiology and Natural History

4. Hannson, S., et al. The natural history of bacteriuria in childhood. *Infect. Dis. Clin. North Am.* 11:499–512, 1997.
   Focuses separately on symptomatic urinary tract infections (UTIs) and asymptomatic bacteruria.
5. Hoberman, A., et al. Prevalence of UTI in febrile infants. *J. Pediatr.* 123:17–23, 1993.
   Of febrile infants, 5% had UTIs; 24% of them had abnormalities on radiologic examination, and the findings were significant in almost all. See also Pediatrics *102:e16, 1998. (Available at: www.pediatrics.org/cgi/content/full/102/2/e16.)*
6. Wiswell, T., and Hachey, W. Urinary tract infections and the uncircumcised state: An update. *Clin. Pediatr.* 32:130–134, 1993.
   Confirms a 12-fold increase in UTIs associated with being uncircumcised; the rate of bacteremia in infant males with UTIs was 22.7%.
7. Kemper, K., and Avner, E. The case against screening urinalyses for asymptomatic bacteriuria in children. *Am. J. Dis. Child.* 146:343–346, 1992.
   Reviews the natural history of asymptomatic bacteruria and concludes that it is benign; screening should not be performed.
8. Vernon, J., et al. New renal scarring in children who at age 3 and 4 years had had normal scans with dimercaptosuccinic acid: Follow-up study. *B.M.J.* 351:905–908, 1997.
   The "action" is before age 3 or 4: New scars do not appear to form later if scans at this age are normal.

Diagnosis

9. Gorelick, M., and Shaw, K. Screening tests for urinary tract infection in children: A meta-analysis. *Pediatrics* 104:e54, 1999. (Available at: www.pediatrics.org/cgi/content/full/104/4/e54.)
   Confirms the sensitivity of bacteria seen on Gram-stained specimens and the lack of sensitivity/specificity of pyuria. Is somewhat more positive about leukocyte esterase and nitrite than reference 2.

Reflux

10. Elder, J., et al. Pediatric Vesicoureteral Reflux Guidelines Panel summary report on the management of primary vesicoureteral reflux in children. *J. Urol.* 157:1846–1851, 1997.
    This panel, convened by the American Urological Association, reviewed the literature and concluded that most children should receive continuous antibiotic prophylaxis initially. Indications for surgery are specified.

Controversial Issues

11. Dick, T., and Feldman, W. Routine diagnostic imaging for childhood urinary tract infections: A systematic overview. *J. Pediatr.* 128:15–22, 1996.
    After reviewing 463 studies on diagnostic imaging, the authors question whether the benefit of identifying abnormalities is justified.
12. Elder, J., et al. Variations in practice among urologists and nephrologists treating children with vesicoureteral reflux. *J. Urol.* 148:714–717, 1992.
    The opinion you receive may depend on whom you ask. For a debate on operative vs. nonoperative treatment, see B.M.J. *300:1391–1392, and 1393–1394, 1990.*
13. Benador, D., et al. Cortical scintigraphy in the evaluation of renal parenchymal changes in children with pyelonephritis. *J. Pediatr.* 124:17–20, 1994.
    One of many studies demonstrating the superiority of nuclear imaging over ultrasound in diagnosing pyelonephritis (and the presence of reflux in only 39% of children with pyelonephritis). The reason the article is listed under "Controversial Issues" is that it is not clear when and how nuclear scans should be used.

Treatment

14. Hoberman, A., et al. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics* 104:79–86, 1999.
    An all-oral regimen was as effective as a sequential intravenous-oral regimen.
15. Bergstrom, T., et al. Studies of urinary tract infections in infancy and childhood: Short or long-term treatment in girls with first or second-time urinary tract infections uncomplicated by obstructive urological abnormalities. *Acta Pediatr. Scand.* 57:186–194, 1968.
    In terms of 1-year cure rate, 10 days was as good as 2 months.
16. Shapiro, E. Short course antimicrobial treatment of urinary tract infection in children: A critical analysis. *Pediatr. Infect. Dis.* 1:294–297, 1982.
    Review of eight studies concludes that while some children need only a single dose, they cannot be distinguished accurately from those who should receive a longer course, precluding endorsement of single-dose regimens.

Constipation, Infrequent/Dysfunctional Voiding

17. Wan, J., Kaplinsky, R., and Greenfield, S. Toilet habits of children evaluated for UTI. *J. Urol.* 154:797–799, 1995.
    Constipation and infrequent voiding are common contributing factors. (UTI and incontinence resolve with treatment of the constipation: Pediatrics *100:228–232, 1997.)*

Outcome

18. Sreenarasimhaiah, S., and Hellerstein, S. Urinary tract infections per se do not cause end-stage kidney disease. *Pediatr. Nephrol.* 12:210–213, 1998.
    Can't be more succinct than the title.
19. Hellerstein, S. Long-term consequences of urinary tract infections. *Curr. Opin. Pediatr.* 12:125–128, 2000.
    The role of reflux is downplayed. "Acquired" renal damage may really be congenital. Old concepts are being reconsidered.

78. CHRONIC RENAL FAILURE

Richard A. Cohn

Chronic renal failure (CRF) is a permanent, generally progressive reduction in renal function. Four major categories encompass the major definable causes in children, each representing approximately 20–25% of the total. The most common cause in older children and adolescents is *glomerulonephritis*. Both primary renal diseases (e.g., hemolytic-uremic syndrome, focal glomerular sclerosis, and membranoproliferative nephritis) and systemic disorders (e.g., Henoch-Schönlein syndrome, systemic lupus erythematosus, and vasculitis) may cause CRF. Notably, acute poststreptococcal glomerulonephritis *rarely* causes CRF. *Hereditary nephropathies* include medullary cystic disease, hereditary nephritis with sensorineural deafness (Alport syndrome), cystinosis, oxalosis, autosomal recessive polycystic kidney disease, and congenital nephrotic syndrome. Renal *hypoplasia-dysplasia* causes renal insufficiency early in infancy and may present as failure to thrive, often with rickets and acidosis. Patients with *obstructive or reflux nephropathy* commonly present with recurrent infections of the urinary tract or hypertension. Urinary tract infections, in the *absence* of anatomic or functional abnormalities, rarely cause CRF.

Most children with creatinine clearance values in excess of 30 mL/min/1.73 m^2 are asymptomatic, although growth may be impaired; below this level of renal function, anorexia, pallor, polyuria, weakness, fatigue, and, in adolescents, delayed puberty may be noted. With clearance values below 15 mL/min/1.73 m^2, medical intervention is usually necessary to correct metabolic disturbances; below 5 mL/min/1.73 m^2, dialysis and transplantation are generally required, and the condition is termed *end-stage renal disease* (ESRD).

The uremic syndrome (uremia) refers to the group of clinical signs and symptoms that are due to both reduction in functioning renal mass and compensatory mechanisms elicited in response to the altered physiology. A normocytic normochromic *anemia* accompanies advanced CRF, primarily caused by deficient production of erythropoietin; parenteral administration of recombinant human erythropoietin effectively ameliorates the anemia. *Hypertension*, commonly a feature in the glomerulopathies, is related to salt and water retention, and occasionally to excessive renin release. In patients with obstructive nephropathy, hypoplasia-dysplasia, and medullary cystic disease, hypertension may be absent, even in the late stages of CRF because of salt wasting. *Acidosis* results from urinary bicarbonate wasting, diminished tubular production of bicarbonate and other buffers, and impaired excretion of dietary acid. *Neurologic* disturbances include changes in mental status, peripheral neuropathies, and seizures that may precipitate the need for, and are often relieved by, dialysis. *Gastrointestinal* manifestations are nausea, vomiting, ulceration and bleeding, hiccups, and pancreatitis. The most consistent immune change is diminished T lymphocyte function. *Dermatologic* phenomena include pruritus, dry skin, easy bruisability, and terminally, uremic “frost.” *Cardiac* complications include hypertrophic cardiomyopathy, congestive heart failure, and pericarditis.

Osteodystrophy and disordered calcium metabolism result from diminished synthesis of 1,25-dihydroxycholecalciferol (calcitriol) by the failing kidney and from phosphorous retention in proportion to the fall in glomerular filtration rate. Inadequate calcitriol results in diminished intestinal calcium absorption, which leads to hypocalcemia, stimulating parathyroid hormone (PTH) release and calcium mobilization from bone. Skeletal resistance to PTH develops in uremia with calcitriol deficiency. Lack of calcitriol is, in part, responsible for the rachitic changes seen in prepubertal children. Hyperphosphatemia additionally aggravates this sequence by directly suppressing calcitriol synthesis, which causes reciprocal depression of serum calcium levels and further increases PTH production. Therapy must be directed at both reducing intestinal phosphate absorption (by lowering dietary intake and using phosphate-binding drugs) and administering potent synthetic vitamin D preparations (e.g., dihydrotachysterol or calcitriol) and calcium.

Alterations in *salt and water metabolism* allow for urinary excretion of up to one third of filtered sodium and water, in contrast to the less than 1% normally excreted. Atrial natriuretic plays a role in this regulation. Hyperkalemia rarely occurs until very late stages except in the event of acidosis, infection, excess dietary intake of potassium, or inappropriate use of spironolactone and angiotensin-converting enzyme inhibitors.

Uremic toxins, including nitrogenous wastes (e.g., urea, ammonia, guanidine), magnesium, fluoride, cadmium, and possibly middle-sized molecules of unknown composition, natriuretic factors, PTH, and other hormones contribute to the nausea, anorexia, and lack of well-being in patients with CRF. Dietary therapy directed toward reducing nonessential amino acid intake, the use of ketoanalogues, and high caloric loads aid in symptomatic improvement.

Anticipation of the potential metabolic problems that may arise, with their correction whenever possible, is important in reducing morbidity from ESRD. Institution of early dialysis or, preferably, preemptive renal transplantation minimizes complications from developing when it becomes clear that a patient's native kidneys are becoming serious liabilities.

Because of the refinements in pediatric dialysis and transplantation over the last 2 decades, ESRD in children is no longer an inevitably fatal condition. Both peritoneal dialysis (PD) and hemodialysis are now technically feasible for long periods, even in infants. Dialysis is as successful in children as it is in adults, but in contrast to its use in adults, dialysis should be viewed as a temporary procedure in children, preparatory to transplantation or until recovery from acute renal failure (ARF).

The decision to initiate dialysis in children with ARF or ESRD is dependent on many variables and must be individualized with each patient. In ARF, determinants include the levels of serum potassium, calcium, phosphorus, uric acid, urea, creatinine, and bicarbonate; the degree of fluid overload; and the likelihood of rapid or spontaneous recovery. In ESRD, in addition to these factors, the availability of a kidney transplant donor, distance of the dialysis center from the patient's home, and the effect on other family members are considered. Most important in both situations is the overall quality of life and the likelihood of significant change on dialysis. For example, initiating dialysis can be delayed in a patient with ESRD despite serum creatinine levels of 10 mg/dL if symptoms are tolerable and stable, but should be started earlier in children experiencing serious uremic complications or complete failure to thrive despite optimal medical management. One must remember that the normal levels of serum creatinine in infants and small children are lower than in older children and adults; the former may require dialysis and transplantation when the serum creatinine level approaches 5–6 mg/dL.

Hemodialysis requires access to the circulation via external cannulas or internal arteriovenous fistulas, systemic anticoagulation, sophisticated mechanical equipment, and highly trained personnel. In units where these are available and in regular use for children, hemodialysis, as compared with PD, is the more efficient and preferred technique because of the high clearance rates, shorter treatment periods, and greater precision in the chemical control of the patient. Dialyzers and tubing can be tailored to the size and needs of infants. Treatments generally are given for 4 hours, 3 times weekly, with frequent monitoring of vital signs, weight, coagulation values, hematocrit, and dialyzer function. In centers in which the staff has extensive experience with dialysis, morbidity from the procedure is extremely low.

Peritoneal dialysis can be performed in a child of any size and is preferable in patients in whom cardiovascular function is seriously compromised, who cannot tolerate anticoagulation, or in whom vascular access is unavailable or difficult. The clearance of electrolytes, metabolites, and toxins is lower than with hemodialysis, and thus 24 hours are required to achieve results comparable to 4 hours of hemodialysis. Therapy can be instituted on pediatric wards with regular nursing personnel.

Continuous PD has been adapted to pediatric patients and permits home dialysis by the parent or patient. Through a permanent, Silastic peritoneal catheter, 4–5 exchanges are performed daily, each “dialysis” lasting 4–8 hours, termed continuous ambulatory peritoneal dialysis (CAPD) or, alternatively, 8–10 exchanges are performed at night, each cycle lasting 45–90 minutes, using an automated cycler machine, termed continuous cycling peritoneal dialysis (CCPD). Commercially available dialysis solutions are available in bags ranging from 250 to 5,000 mL. By being dialyzed “continuously,” patients on PD avoid the large swings in blood pressure, body chemistry, and fluid status experienced when on hemodialysis. Most patients feel better on PD, in part because of improvements in diet, fluid intake, medications needed, and avoidance of hemodialysis needles and psychological dependence on the machine. Peritonitis and parental “fatigue” are factors that may limit usefulness in certain patients. Peritoneal dialysis is most useful in patients who are *not* likely to undergo imminent transplantation, who live great distances from

hemodialysis centers, and who have motivated caretakers.

Children on dialysis generally have impaired growth and altered nutrition, and may be weak and tired, and psychologically debilitated by their total dependence. When deterioration of function has progressed toward ESRD, transplantation is, at present, the best long-term therapeutic choice. Once accepted into a transplantation program, the child undergoes a thorough pretransplantation evaluation, including HLA-A, -B, and -DR typing, voiding cystourethrogram, serologic and psychological testing, completion of immunizations, a dental evaluation, and an assessment of the compliance by the patient and the family. If urinary tract infection, hypertension, reflux, or nephrotic syndrome has complicated the clinical course, nephrectomy may be necessary prior to transplantation. A relative with the closest HLA match (HLA-identical sibling or HLA partially matched parent or sibling) is the most preferable donor to minimize the time on dialysis and provide a kidney with the greatest likelihood of long-term function; however, living unrelated kidney transplantation with little or no HLA antigen sharing between donor and recipient achieves results as good as or better than cadaveric transplantation. Almost 85% of kidneys from related donors and 70% of cadaveric kidneys transplanted into children are functioning well 5 years later.

The availability of newer and better transplant immunosuppressive medications now allows for tailoring of protocols depending on various factors, including live versus cadaveric donor, degree of mismatching, sensitization of the patient, and initial versus repeat graft. Corticosteroids, calcineurin inhibitors (cyclosporine or tacrolimus), and lymphocyte antiproliferative agents (azathioprine, mycophenolate mofetil, or sirolimus) are usually administered as “maintenance” therapy; in most centers, humanized monoclonal antilymphocyte antibodies (basiliximab or daclizumab) are given as induction treatment. Despite immunosuppressive treatment, acute rejection episodes may occur and are usually treated by temporarily increasing corticosteroid therapy or monoclonal antibody administration directed against T lymphocytes. Other complications that may arise include opportunistic infections, growth retardation, diabetes mellitus, gastrointestinal bleeding, and hypertension. Infections that occur may be bacterial (especially in splenectomized hosts), viral (particularly herpes viruses: zoster, simplex, and cytomegalovirus), fungal (*Candida*, *Nocardia*, *Aspergillus*), or protozoan (*Pneumocystis carinii*). Prophylactic use of antiviral antibiotics, trimethoprim-sulfamethoxazole, clotrimazole, and H_2 blockers can minimize the incidence of the above complications, especially during the initial 100 days after transplantation. Immunosuppression predisposes to an increased incidence of malignancy, notably of the skin and lymphoid organs, the latter termed posttransplant lymphoproliferative disease, or PTLD. Psychological problems arise even when graft function is excellent. Finally, recurrence of the original renal disease in the transplanted kidney has been noted, particularly in patients with nephrotic syndrome with focal segmental glomerular sclerosis, hemolytic-uremic syndrome, immunoglobulin A nephropathy, and primary hyperoxaluria.

Renal transplantation is the preferred mode of therapy for children with ESRD.

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    Renal transplantation is not a cure! Major potential problems exist, including hypertension, vascular disease, infection, liver disease, malignancy, musculoskeletal abnormalities, and cataracts.

79. THYROID DISORDERS

Craig A. Alter and Rosalind S. Brown

Disorders of the thyroid are relatively common in childhood. Thyroid disorders usually present because of either an enlargement of the gland (goiter) or an abnormality in thyroid hormone function, or as congenital hypothyroidism. It is important for the pediatrician or practitioner to understand thyroid function tests (TFTs) because they are frequently included in the broad evaluation of many diseases. Certain groups are at risk for thyroid diseases. These include children with type 1 diabetes mellitus, several syndromes (e.g., Down, Turner, Klinefelter, Noonan), cystinosis, and post–radiation therapy for cancer (e.g., Hodgkin disease). Thyroid disease may coexist with adrenal insufficiency, vitiligo, and other autoimmune diseases. It is common to have families with multiple members with varying types of autoimmune thyroid disease.

The most common presentation of thyroid disease is a *goiter*, which occurs in 2–5% of school-aged children in North America, where iodine is plentiful. Thyromegaly can be due to stimulation, infiltration, or inflammation of the gland. The enlargement is classified as either diffuse or focal (nodular). While some families seek attention for thyroid enlargement, many cases are detected on routine examination. The initial assessment consists of determining whether the child is euthyroid, hyperthyroid, or hypothyroid.

Hypothyroid children tend to complain of increased fatigue, poor growth with relative increased weight despite a low appetite, increased sleep, dry skin, constipation, and, occasionally, cold intolerance. School performance is often normal, in contrast to hyperthyroidism. Menses may become irregular, often with heavy bleeding. Precocious puberty may be seen rarely, but delayed puberty and poor growth are more typical.

Physical examination of the child with hypothyroidism confirms the poor growth with an increasing weight for height (plotting the weight-for-height curve is useful). The thyroid should be palpated carefully. A common approach is to have the practitioner stand behind the sitting patient, or to have the patient tilt the head backwards. Other features include a lethargic appearance, periorbital edema, dry skin, coarse hair and voice, and a delayed relaxation phase of Achilles reflex.

Chronic lymphocytic thyroiditis, or Hashimoto thyroiditis, is the most common cause of hypothyroidism (with or without a goiter). Alternatively, a goiter may be due to a defect in synthesizing thyroid hormone (“dyshormonogenesis”), which is usually autosomal recessive, or due to medications (e.g., lithium, propylthiouracil, methimazole). The thyroid in chronic lymphocytic thyroiditis may be smooth, lobulated, or “pebbly,” in contrast to a smooth enlargement seen in other disorders. Initial work-up includes measurement of thyroid-stimulating hormone (TSH), thyroid antibodies (Abs), and rarely, thyroid uptake and scan. Antibodies include thyroid peroxidase (TPO, formerly “microsomal”), and thyroglobulin antibodies (Tg). It should be noted that Abs serve as markers, and do not cause the disease. A bone age is useful and is characteristically delayed.

The child with a diffuse goiter who is euthyroid is often discovered on a well-visit physical examination. After confirmation of a euthyroid state by history, physical examination confirms that the goiter is diffuse. Laboratory studies consist of measurement of TSH and Abs. Positive Abs confirm chronic lymphocytic thyroiditis. Negative antibodies do not rule out chronic lymphocytic thyroiditis, but may, alternatively, suggest a colloid goiter, mild dyshormonogenesis, ingestion of a goitrogen, or rarely, generalized thyroid hormone resistance. Excessive intake of certain substances and vegetables (e.g., broccoli, sweet potatoes, and cauliflower), particularly in iodine-deficient patients, can cause benign thyromegaly. Colloid goiter, in contrast to chronic lymphocytic thyroiditis, does not carry a risk of developing hypothyroidism. Treatment is usually not necessary, but the thyroid size and TSH should be followed in 3–6 months, then, if negative, every 6–12 months.

The child who presents with a diffuse goiter and hyperthyroidism tends to complain of anxiety, decreased school performance, emotional lability, tremors, decreased ability to fall asleep, weight loss with an increased appetite, proximal muscle weakness, tachycardia and palpitations, and sensitivity to heat. There may be lethargy in context of the above symptoms. Most children with hyperthyroidism have Grave disease, an autoimmune disease caused by Abs that stimulate the TSH receptor. A smooth, diffuse goiter is almost always present. A hot nodule (focal goiter), subacute thyroiditis, an initial hyperthyroid phase of chronic lymphocytic thyroiditis, selective pituitary resistance to thyroid hormone, and the very rare TSH-secreting pituitary adenoma may also produce hyperthyroidism. Infiltrative ophthalmopathy and pretibial myxedema are considerably less common in children as compared to adults with Grave disease.

Physical examination consists of vital signs focusing on heart rate, blood pressure, and growth parameters. Tachycardia, initially present, may be useful in following the patient under treatment. Growth acceleration is sometimes seen, but weight loss or poor weight gain is more common. The characteristics of the goiter, presence or absence of a flow murmur, assessment for proximal muscle strength and hyperreflexia, warmth of the skin, search for pretibial edema, presence or absence of tongue and/or hand tremor, and examination of the eyes should be documented. The eye examination focuses on proptosis (bulging outward), as well as a “stare” (sclera visualized completely around the iris). The former is associated with Grave disease, but the stare can be seen with all types of hyperthyroidism.

Initial laboratory studies should include a free T4 or free thyroxine index (see below) and TSH. The total T3 is useful, especially in milder cases when the T3 may be elevated without a concomitant rise in total T4. Measurement of TSH receptor Abs may be helpful when the diagnosis is unclear. Thyroid peroxidase and Tg Abs are seen in the thyrotoxic phase of chronic lymphocytic thyroiditis, as well as in many cases of Grave disease, and are neither as sensitive nor as specific for Grave disease as are TSH receptor Abs. A suppressed TSH rules out TSH-secreting tumor or thyroid hormone resistance, rare causes of hyperthyroidism. Thyroid scan may be useful in distinguishing Grave disease from the thyrotoxic phase of chronic lymphocytic thyroiditis.

Focal enlargement of the thyroid may be caused by an adenoma, cyst, chronic lymphocytic thyroiditis, unilateral agenesis of a thyroid lobe, or by nonthyroidal tissue such as lymphadenopathy. However, the main concern is that of thyroid cancer. A thyroid nodule found in a child has a higher incidence of malignancy (one third of cold nodules) than a nodule observed in an adult.

Evaluation of the nodule consists of a detailed family history, as some forms of thyroid cancer (e.g., medullary thyroid carcinoma) are familial. The finding of a decreased iodine uptake (cold nodule) on thyroid scan indicates the need to perform a thyroid biopsy. In a center with experience both in the procedure and interpretation, fine-needle aspiration biopsy may be useful and is often the initial approach, depending on the age of the child.

Thyroid disease may also present because of symptoms of hyper- or hypothyroidism without general or focal enlargement of the gland on physical examination. While weight gain is a common sign of hypothyroidism, increased weight gain with a normal or high growth velocity suggests strongly that the diagnosis is exogenous obesity and not hypothyroidism. Severe hypothyroidism (primary myxedema) is typically not accompanied by a goiter. In these cases, the autoimmune destruction of the gland prohibits TSH-induced tissue growth. In addition, there may be TSH-receptor blocking Abs further inhibiting the effect of TSH. Similarly, central hypothyroidism, and postsurgical and radiation-induced hypothyroidism are usually not associated with a goiter.

Measurement of TSH by third generation (ultrasensitive) assay remains the most sensitive test for detecting hypo- and hyperthyroidism. This assay allows for the distinction of low normal, as compared to below normal levels. Thus, determination of the TSH level is valuable in the work-up of hyperthyroidism, as well as hypothyroidism. TSH levels do not aid significantly in the work-up of central hypothyroidism. Because T4 is over 99% protein-bound and only the free fraction is biologically active, knowledge of the free T4 (FT4) is necessary. Many institutions have available assays of FT4 and free T3 (FT3); however, if direct measurement is not possible, indirect assessment can be done. This is usually accomplished by measuring the total T4, and measuring the binding capacity with either T3 resin uptake (T3RU) or thyroid-binding globulin (TBG). An estimate of the FT4 (FT4 index) is calculated by multiplying the total T4 by a T3RU and a correction factor. A low T3RU indicates an increased binding capacity, implying much of the T4 measured is bound and not biologically active. Inversely, a high T3RU indicates a low-binding capacity. A high T4 and low T3RU is seen in states of increased TBG, such as with pregnancy and birth control use. Other TFTs, such as reverse T3, iodine scan with

perchlorate discharge, and thyrotropin-releasing hormone (TRH) stimulation, are beyond the scope of this review.

Hypothyroidism is treated with L-thyroxine, the goal being to normalize TSH and reverse symptoms. The typical replacement dosage of L-thyroxine is approximately 100 µg/m^2/d, or 4–6 µg/kg/d for children 1–5 years old, 3–4 µg/kg/d for children 6–10 years, and 2–3 µg/kg for children 11 years and older. In patients with a goiter, a somewhat higher dosage of L-thyroxine is used to keep the TSH in the low normal range. The goiter will shrink if it is TSH dependent, but not if it is due to lymphocytic infiltration. Thyroid suppression of a euthyroid child with a goiter and normal TSH is controversial.

Treatment of hyperthyroidism usually begins with one of the thiouracil derivatives, propylthiouracil (PTU) or methimazole. A b-blocker may be added for pronounced adrenergic symptoms. Certain endocrinologists advocate administering L-thyroxine along with a higher dose of medical suppression. One study showed that there was a higher rate of remission with dual therapy, but this has not been confirmed. Both approaches have their advantages and disadvantages. Approximately 25% of children with Grave disease will enter remission every 2 years. A smaller goiter, older age, lower dosage of antithyroid medication, and less severe thyrotoxicosis are associated with a higher ability to wean off therapy. Radioablation and subtotal thyroidectomy are usually reserved for patients in whom medical management fails. Radiotherapy has gained greater acceptance in children in recent years, particularly in adolescents who are noncompliant or in whom surgery is contraindicated. Thyroid storm (hyperthyroidism with mental status changes, hypertension, and other findings), rare in children, requires treatment in a pediatric intensive care setting.

Congenital hypothyroidism (CH) occurs in 1/4,000 newborns and is one of the most common treatable forms of mental retardation. The most common causes are agenesis or dysgenesis (75–90%), and thyroid hormone dyshormonogenesis (10–15%). As many as 10% are transient, and are due to iodine, maternal medication, or maternal TSH receptor-blocking antibodies. Secondary or tertiary CH (i.e., TSH deficiency due to pituitary or hypothalamic disease) occurs in 1 in 50,000 to 150,000 infants, and is almost always accompanied by evidence of other pituitary hormone deficiencies.

Infants with CH are rarely recognized at birth. Only occasionally does a neonate present with the classic features of a large tongue, hoarse cry, umbilical hernia, hypotonia, poor peripheral circulation (mottling, cold hands and feet), or lethargy. Other findings include large fontanelles (especially posterior fontanelle >0.5 cm in a full-term infant), feeding difficulties, delayed passage of stools, unexplained hyperbilirubinemia, gestation longer than 42 weeks, and respiratory distress in a full-term infant.

The United States and most countries in Europe perform neonatal thyroid screening. Most states measure T4 initially using dried blood spots; TSH is measured subsequently only if the T4 is low. In Europe and Japan, TSH is screened initially. Note that the normal values for T4 in the first few months of life are considerably higher than in older children or adults. The diagnosis is confirmed by an elevated TSH (>20 mU/L) in serum; in most children with permanent CH the TSH will be >50 mU/L. A falsely elevated TSH may be seen if the screen is done prior to 48 hours of life, as a result of the TSH surge at birth. Premature, low-birthweight, or sick babies may have a low T4 and a “normal” TSH; in these cases, thyroid function should be repeated every 2 weeks until it normalizes because of the rare occurrence of delayed elevation of TSH. Any infant suspected clinically of having CH should have TFTs repeated, despite a normal neonatal screen, because of the possibility of either a rare error in the screening process, or a delayed rise in TSH.

All infants with confirmed CH should have a radionuclide scan (preferably ^{123}I) to verify that a permanent thyroid abnormality is present, and to distinguish thyroid agenesis/dysgenesis, sporadic conditions, from dyshormonogenesis, which is autosomal recessive. Babies with a lack of thyroid tissue visualized on scan, or those born to mothers with autoimmune thyroid disease should be checked for TSH receptor-blocking antibodies. These antibodies cause transient CH and, if present in a sufficiently high titer, block TSH-induced iodine uptake, thus mimicking agenesis.

Replacement therapy with L-thyroxine should be started as soon as the diagnosis is confirmed. A high initial dosage of 10–15 µg/kg orally is recommended to normalize the T4 as soon as possible. Therapy is with small tablets; thus, the family must learn how to give a neonate a crushed tablet. Detailed recommendations for therapy and follow-up have been published (see references). Studies suggest that early, adequate treatment will allow for normal brain and neurologic development. Treatment of premature infants with a low T4 but normal TSH is controversial.

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80. HYPOGLYCEMIA

Andrea Kelly and Craig A. Alter

Glucose homeostasis is critical for meeting the metabolic demands of the brain. Glucose serves as the predominant brain fuel; its oxidation by the brain accounts for greater than 99% of the brain's energy production. Acutely, an inadequate glucose supply can cause seizures, while chronic recurrent hypoglycemia can cause permanent brain damage. Particularly vulnerable to hypoglycemia is the infant whose brain is undergoing rapid growth and development. Because of the infant's relatively larger brain-to-body size, an infant's glucose requirement of 6–8 mg/kg/min exceeds that of the adult's 1–2 mg/kg/min.

Defining “normal” blood glucose values in the neonate has generated much controversy because low blood glucose concentrations are not uncommon in this population. Historically, the parameters for hypoglycemia were based on statistical grounds; the criterion for hypoglycemia for the preterm infant was a whole blood glucose value less than 20 mg/dL, while that for the term infant was less than 30 mg/dL.

However, a maturing infant brain is not known to be less sensitive to hypoglycemia than that of an older child or adult. Accepting the same therapeutic standard for an infant as that held for an adult would be more reasonable. The blood glucose goal for an infant should be greater than 60 mg/dL; a blood glucose less than 50 mg/dL is abnormal.

Because in childhood hypoglycemia is almost always a failure of fasting adaptation, an understanding of normal fasting physiology can provide a framework for diagnosing and treating the various hypoglycemia disorders. The elements of fasting include (1) glycogenolysis; (2) gluconeogenesis; (3) lipolysis; and (4) fatty acid oxidation and ketogenesis. These systems are controlled hormonally by (5) insulin, which suppresses the fasting systems; and (6) counterregulatory hormones (glucagon, cortisol, epinephrine, and growth hormone), which act redundantly to stimulate them. In the initial phase of normal fasting, insulin secretion is suppressed, allowing access to glucose from glycogen and from muscle-derived amino acids. By 12–16 hours of fasting, glycogen stores are depleted. To prevent the consumption of all muscle stores to meet the metabolic demands of the body, a transition to fat utilization occurs. Lipolysis provides the substrates for muscle fatty acid oxidation and hepatic ketogenesis. The former allows diversion of glucose away from muscle to brain, while the latter provides an alternate fuel source for brain. Gluconeogenesis remains constant, but its substrates are supplemented by glycerol derived from lipolysis. A normal infant can fast 24–30 hours before becoming hypoglycemic, at which time (1) glycogen stores will be depleted and no glycemic response to glucagon will occur; (2) lactate will be low, reflecting exhaustion of gluconeogenic stores; (3) free fatty acids and ketones will be elevated; and (4) plasma insulin will essentially be undetectable.

Laboratory studies performed at the time of hypoglycemia are thus invaluable for determining the integrity of the fasting metabolic and hormonal systems and, ultimately, establishing the etiology of hypoglycemia. A hypoglycemia evaluation includes assessing for (1) various fasting system metabolites (free fatty acids, ketones, lactate); (2) hormones (insulin, growth hormone, cortisol); (3) the glycemic response to glucagon; and (4) additional clues (ammonia, bicarbonate, and acylcarnitine and urine organic acid profiles). Obtaining this “critical” sample during a spontaneous hypoglycemic episode is preferable to performing a formal diagnostic fasting study.

Serum bicarbonate and urinary ketones are readily obtained and can be used to devise a classification scheme for hypoglycemia. Acidemia, defined as a serum bicarbonate less than 15–17 mmol/L, may be due to lactate or ketone accumulation. Acidemia primarily due to lactate characterizes a gluconeogenic defect, as well as the neonate on day of life one. Acidemia due to ketones typifies a normal fasting child, ketotic hypoglycemia, and cortisol/growth hormone deficiencies. No acidemia with free fatty acid and ketone suppression characterizes insulin excess, but can also be seen with congenital hypopituitarism. No acidemia with elevated free fatty acids but suppressed ketones exemplifies disorders of fatty acid oxidation and ketogenesis.

Acidemia due to lactate at the time of hypoglycemia is consistent with a disorder of gluconeogenesis (unless the child is less than 24 hours old). In addition, at the time of hypoglycemia, a glucagon challenge causes a rise in lactate but not glucose because of the block in conversion of gluconeogenic substrates to glucose. A child with glucose-6-phosphatase deficiency, a glycogen storage disease (GSD type I), has a fasting tolerance of 2–4 hours and is likely to present later in the first year of life, when feeding intervals are increased and invoke gluconeogenesis. Glucose-6-phosphatase deficiency typically presents with failure to thrive and hepatomegaly rather than symptoms of neuroglycopenia, which are attenuated by the brain's ability to use lactate as an alternative fuel source. The child with fructose 1,6-diphosphatase deficiency has a fasting tolerance of 8–10 hours and often first presents to medical attention with an acute life-threatening event .

Lactic acidosis–associated hypoglycemia can occur in the neonate who is forced to fast during the first 12–24 hours of life. This predisposition to nonketotic hypoglycemia occurs because the gluconeogenic and ketogenic systems are immature at birth.

Acidemia primarily associated with ketones typifies a normal response in a child who has fasted excessively, as well as ketotic hypoglycemia, disorders of glycogenolysis, and growth hormone or adrenal insufficiency. Ketotic hypoglycemia describes a relatively normal child with a blunted fasting tolerance. This entity typically occurs in the underweight child, aged 1–4 years, and is thought to result from a decreased muscle mass limiting the gluconeogenic substrate supply. Symptoms occur after a prolonged overnight fast or during periods of poor feeding. An affected child generally outgrows this fasting intolerance. Disorders of glycogenolysis, such as GSD types III (debrancher), VI (liver phosphorylase), and IX (phosphorylase kinase) are distinguished by hepatomegaly, failure to thrive, and fasting tolerances of 4–6 hours. These disorders represent an accelerated fasting state with ketogenesis activated earlier than normal because of limited access to glycogen stores. Because the glucose stores of glycogen are not completely inaccessible, glucagon stimulation will mount a glycemic response in the fed but not the fasted state. A child with hypopituitarism or adrenal insufficiency can present with ketotic hypoglycemia when stressed or fasted beyond 12–14 hours. Clues to the diagnosis of hypopituitarism include short stature, midline defects, and micropenis. A child with primary adrenal insufficiency may be hyperpigmented.

Normal serum bicarbonate and no urinary ketones are consistent with hyperinsulinism (HI). Serum free fatty acids and ketones will be suppressed. Unfortunately for diagnostic purposes, the serum insulin concentration may not be greatly elevated. Insulin-like growth factor–binding protein-1, a binding protein for growth factors, however, is suppressed by insulin and can serve as an additional marker for inappropriate insulin activity. A brisk glycemic response (>30 mg/dL) to glucagon at the time of hypoglycemia is present with HI. An additional feature of HI is the need for a high rate of glucose infusion (>12 mg/kg/min).

Hyperinsulinism in the newborn period can be transient or permanent. Transient dysregulated insulin secretion occurs in the newborn stressed, for example, from asphyxia or from maternal hypertension. Such hypoglycemia occurs within the first few hours of life and can last weeks unless treated. More familiar is the infant of the diabetic mother; the fetus upregulates insulin secretion in response to maternal hyperglycemia. At birth, the infant is large for gestational age due to the growth factor effects of insulin and suffers from hypoglycemia when the excessive maternal glucose supply is acutely withdrawn.

Recent insights into the genetic defects responsible for congenital HI have greatly expanded our appreciation of various, including more subtle, forms of HI. The severe phenotype is typical of genetic defects of the b-cell sulfonylurea receptor/potassium channel complex (SUR1/Kir6.2), which transduces the energy state of the b-cell to the cell membrane to effect insulin release. These defects can be transmitted autosomal recessively and affect the pancreas diffusely. Alternatively, a focal lesion expressing a SUR1 mutation can arise from b-cells affected by loss of heterozygosity; loss of the normal maternal SUR1 allele and tumor suppressor genes on chromosome 11 permit the clonal expansion of a b-cell carrying a paternal SUR1 mutation. Both inheritance patterns typically fail medical therapy with diazoxide and octreotide, necessitating pancreatectomy whose success is assured only if a focal lesion is identified and completely removed. Autosomal-dominantly inherited defects in glucokinase lower the glycemic threshold for insulin secretion to cause a mild form of HI. Finally, the hyperinsulinism-hyperammonemia syndrome (HI/HA) often presents later in infancy and is less severe, diazoxide-responsive, and associated with protein-sensitive hypoglycemia. An affected individual is asymptomatic from the hyperammonemia. Hyperinsulinism/hyperammonemia arises from an autosomal-dominantly or sporadically inherited gain of function mutation in glutamate

dehydrogenase.

In the newborn, congenital hypopituitarism can mimic congenital HI with early severe hypoglycemia, a high glucose requirement, suppressed free fatty acids and ketones, and a glycemic response to glucagon. However, the infant with congenital hypopituitarism demonstrates a normal or low birth weight. Additional clues to this diagnosis are midline facial (cleft palate) or brain (absent septum pellucidum) defects, micropenis, and prolonged hyperbilirubinemia.

In an older child with insulin excess, either a mild form of previously undiagnosed HI, or exogenous insulin administration or sulfonylurea ingestion must be considered. An insulinoma is an uncommon cause of insulin excess in this age range. A C-peptide level inappropriately low in the face of elevated insulin will identify exogenous insulin. Other medications associated with hypoglycemia include alcohol, quinine, propranolol, and pentamidine.

Normal serum bicarbonate and no urinary ketones in the face of hypoglycemia suggest a fatty acid oxidation disorder. Further evaluation reveals elevated serum free fatty acids without ketones. The acylcarnitine and urine organic acid profiles are abnormal. Because infants feed frequently, fatty oxidation disorders do not typically present in infancy unless unsuccessful breast-feeding or an intercurrent illness imposes a fasting state. Instead, the defect manifests when the fasting tolerance of about 12 hours is exceeded or when a significant stress invokes ketogenesis. Because fatty oxidation disorders are life-threatening and account for some cases of sudden infant death syndrome, their identification and appropriate management are crucial.

Although the etiologies of hypoglycemia are numerous, their potential complications demand that the immediate diagnostic evaluation and management be consistently prompt and complete. At the time of hypoglycemia, even before glucose is administered, a blood sample should be collected and reserved so that once the child is stable the exact studies of interest can be determined. At minimum, measurement of urinary ketones and serum bicarbonate can provide a wealth of information regarding the possible etiologies. Meanwhile, restoring euglycemia can be attempted with oral intake if the child's mental status allows, or with intravenous dextrose if a reduced level of consciousness is present or if hypoglycemia is unrelenting or expected to recur. An intravenous bolus of 10% dextrose, 2 mL/kg, followed by a constant infusion and frequent reevaluations of response to therapy is an appropriate starting regimen.

Reviews

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Neonatal Hypoglycemia

2. Dunvanel, C., et al. Long-term effects of neonatal hypoglycemia on brain growth and psychomotor development in small-for-gestational-age preterm infants. *J. Pediatr.* 134:492–498, 1999.
   With differing opinions regarding the definition of neonatal hypoglycemia, this study supports the commonly held view among endocrinologists that hypoglycemia is not normal in neonates and is associated with long-term neurologic sequelae.
3. Stanley, C., and Baker, L. Hyperinsulinism in infancy: Diagnosis by demonstration of abnormal response to fasting hypoglycemia. *Pediatrics* 57:702–711, 1976.
   Classic article describing how measurements of biochemical parameters after a fast can be used to differentiate hyperinsulinism from other hypoglycemia syndromes.

Hyperinsulinism

4. Glaser, B. Hyperinsulinism of the newborn. *Semin. Perinatol.* 24:150–163, 2000.
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5. de Lonlay-Debeney, P., et al. Clinical features of 52 neonates with hyperinsulinism. *N. Engl. J. Med.* 340:1169–1175, 1999.
   A few of the world experts on hyperinsulinsim review their novel diagnostic approach and the surgical outcomes in children requiring pancreatectomy for hyperinsulinism.
6. Levitt-Katz, L., et al. Insulin-like growth factor binding protein-1 levels in the diagnosis of hypoglycemia caused by hyperinsulinism. *J. Pediatr.* 131:193–199, 1997.
   Hyperinsulinism arises from dysregulated insulin secretion and may not be accompanied by greatly elevated insulin levels. Insulin-like growth factor binding protein-1 is an alternative marker for inappropriate insulin secretion/activity.

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Hypoglycemia: Physiology and Counterregulation

9. Cryer, P.. Glucose counterregulation: Prevention and correction of hypoglycemia in humans. *Am. J. Physiol.* 264:E149–E155, 1993.
   This article addresses the body's hierarchy of protective mechanisms against hypoglycemia.

Drug-Induced Hypoglycemia

10. Seltzer, H. Drug-induced hypoglycemia: A review of 1418 cases. *Endocrinol. Metab. Clin. North Am.* 18:163–179, 1989.
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11. Quadrani, D., Spiller, H., and Widder, P. Five-year retrospective study of sulfonylurea ingestion in children. *J. Toxicol. Clin. Toxicol.* 34:267–270, 1996.
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81. DIABETES MELLITUS

Craig A. Alter and Adda Grimberg

Type 1 diabetes mellitus (formerly called insulin-dependent diabetes or juvenile diabetes) is a chronic metabolic disease resulting from a lack of insulin. It is characterized by hyperglycemia, a tendency towards the development of ketoacidosis, and associations with severe long-term complications. Type 1 diabetes may present at any age, but the peak incidence is around 12 years of age. The incidence of type 1 diabetes appears to be increasing. The current prevalence in the United States is approximately 1 in 600 children by age 18 years. Type 2 diabetes mellitus (formerly called noninsulin-dependent diabetes or adult-onset diabetes) differs from type 1 diabetes in that type 1 is due to an absolute insulin deficiency, whereas type 2 stems from insulin resistance often associated with obesity. The incidence of type 2 diabetes seems to be increasing as well and may represent around 5% of cases of diabetes in children. While some of this may be due to greater recognition of the diagnosis, especially in the pediatric-aged group, the concern is that the rise in incidence is due to the higher prevalence of obesity in our society. Because an individual can develop either type of diabetes at any age, and many patients with type 2 diabetes require insulin therapy, the old nomen clatures can be misleading and should be replaced by the pathophysiologic-based terms. The presence of obesity; family history of diabetes, especially in adults; and acanthosis nigricans (a hyperpigmented velvety change in the skin appearance, most readily apparent on the posterior neck and creases, which is due to a direct effect on skin growth by high insulin levels) are all clinical clues suggesting type 2 rather than type 1 diabetes. The pancreas of the newly diagnosed child with type 1 diabetes is characterized by extensive lymphocytic infiltration with destruction limited to the insulin-secreting beta cells; alpha and delta cells, which secrete glucagon and somatostatin, respectively, are spared. Although the precise etiology of this immune destruc tion is unknown, genetic, immunologic, and environmental factors have been implicated. A genetic component is suggested by the higher incidence in certain racial groups and the 25–50% concordance rate in identical twins as compared to the 5% risk of developing diabetes in the fraternal twin or sibling of an affected proband. A greater percentage of children with type 1 diabetes than unaffected children have major histocompatibility complex haplotypes DR3 and DR4; a point mutation involving aspartate in the 57 position of the DQ beta chain has also been associated with disease susceptibility. Since T lymphocytes, the major initiators of the immune response, can recognize antigen only in the context of their major histocompatibility complex, these observations may have implications with regard to the ability of certain predisposed individuals to interact with the putative antigenic trigger. Viral infections have been shown experimentally to cause diabetes mellitus in animals, and there are some epidemiological data suggesting an increased incidence of diabetes in humans following rubella, Coxsackie virus, and mumps virus infections. It is possible that in certain children with a genetic predisposition, viruses (or other environmental agents) trigger an anti–beta cell response that results in diabetes.

Without adequate insulin, children with type 1 diabetes generally have a normal to increased appetite (polyphagia), but because carbohydrate calories are “wasted” in the urine, these children lose (or do not gain) weight. Increased intake of fluids (polydipsia) is caused by the glucose-induced osmotic diuresis (polyuria). Occasionally, the development of enuresis in a previously toilet-trained child or glucosuria on a routine urinalysis will lead to the diagnosis. A clear history of polyuria and polydipsia, with or without polyphagia, and the finding of hyperglycemia and glucosuria are sufficient for the diagnosis of diabetes mellitus. Recently, the American Diabetes Association revised the criteria for establishing the diagnosis of diabetes: a fasting blood glucose above 126 mg/dL or a value at any time over 200 mg/dL plus the classic symptoms of diabetes establish diagnosis. In borderline cases, repeat testing is indicated. Occasionally, in the setting of an acute intercurrent illness, elevated stress hormones may lead to high blood sugars in the “diabetes range”; stress hyperglycemia spontaneously corrects when the illness resolves. Eliciting a prior history of polydipsia and polyuria will distinguish diabetes from stress hyperglycemia. A glucose tolerance test is necessary for diagnosis only rarely in a child with suspected diabetes. Often the diagnosis is not made until ketosis and acidosis develop; at that point, the history, hyperglycemia, and large amounts of ketones in the urine and blood serve to differentiate diabetic ketoacidosis (DKA) from such disorders as salicylate intoxication and Reye syndrome. Approximately 20% of children with type 1 diabetes present in DKA at the time of diagnosis.

Once the diagnosis is established and the child is in reasonable metabolic balance, the child and family require extensive education. The emotional state of the family makes learning an inefficient process. Often a family focuses so much on the challenges of administering “needles” to their child that discussions of other aspects of care need to be temporarily postponed.

The goals of therapy are: (1) maintenance of optimal blood glucose control, (2) normal physical and psychological growth and development, (3) prevention of acute metabolic decompensation (DKA), and (4) amelioration, and possibly prevention, of the long-term vascular complications (i.e., diabetic retinopathy, nephropathy, neuropathy, and atherosclerosis). After many years of controversy, the Diabetes Control and Complications Trial (DCCT) demonstrated clearly that the degree of hyperglycemia is directly related to the development of the vascular complications, particularly retinopathy and nephropathy. Unfortunately, a significant increase in the number of severe hypoglycemic episodes was also observed in the more tightly controlled group. Thus, it is important that what constitutes “optimal control” for the younger infant and child who is unable to recognize and treat a hypoglycemic reaction is less stringent than that for an older, compliant adolescent. It should be evident that the same degree of metabolic control will not be achievable in all patients, and it is important, therefore, to set reasonable therapeutic goals on a case-by-case basis, depending on the patient's age, family, intelligence, lifestyle, etc.

Successful treatment of children with diabetes includes not only subcutaneous insulin injections, but also a family-oriented approach that encompasses nutrition, exercise, and the general psychological well-being of the child. Since the DCCT, many children are now receiving three or more shots of insulin daily. One such regimen includes a mixture of long-acting (i.e., NPH or Lente) and short-acting insulin prior to breakfast, a short-acting insulin presupper or in the afternoon, and a long-acting insulin at bedtime. Lispro insulin (Humalog) was introduced in 1996, and many children choose this instead of regular insulin for their short-acting treatment. Lispro insulin offers the advantage of a quicker onset and shorter duration than regular insulin. More and more children are now using the portable insulin pump.

The strategy of the diabetic meal plan has evolved over the past decade. Initially, the food selections were limited to a menu of exchanges. However, because the carbohydrate content of the meal has the most important effect on the blood glucose, the trend has changed to counting carbohydrates in many diabetes centers. The recent food labeling laws allow for a family to count the grams of carbohydrate ingested. Many families will change the dose of insulin in response to the grams of carbohydrate in the meal.

The supportive aspects of care cannot be overemphasized. The inescapable responsibilities of blood testing, dietary restrictions, injections, and protective parents combine to produce greater tensions for both the child and the family; in adolescents, who do not wish to differ from their peers, the situation is especially difficult and may lead to rebellion. Supportive medical and psychological guidance, continuing detailed education, open communication, and opportunities to enjoy activities with other children with diabetes (such as support groups and summer camps) help the child maintain a good self-image. The psychological health of children with diabetes ultimately depends in large part on the realization that they can control the disease and need not be controlled by it.

Patients and/or caretakers are taught to monitor the fasting blood glucose, typically four times daily, as a measure of metabolic control. Urinary ketones are measured whenever the child is sick or the blood glucose is greater than 240 mg/dL. Patients and their families are taught “sick-day rules” to prevent the development of DKA. While the progress of the child and family with diabetes is reviewed about every 3 months, most families are taught to problem-solve and make adjustments in food, exercise, and insulin to maintain optimal blood sugar control. Overall control is assessed by reviewing the blood glucose records, as well as measurement of glycosylated hemoglobin. In pubertal children who have had diabetes for several years, screening for evidence of long-term complications is important. Periodic blood pressure measurement and urinalysis to detect low levels of protein (urinary microalbumin) are performed to screen for diabetic nephropathy. Yearly ophthalmologic examinations to detect retinopathy are performed. Thyroid function and thyroid antibodies are evaluated periodically because of the increased incidence of autoimmune thyroid disease in patients with type 1 diabetes. Cholesterol and other lipid profiles are checked periodically because of the effects of diabetes on both lipids and the vascular system.

Because of the devastating medical and financial costs related to diabetes, intensive research is in progress to improve treatment methods and, ultimately, to prevent

the disease. Cadaveric pancreatic transplantations are performed in some centers in patients with diabetes requiring kidney transplantation. Isolated pancreatic transplantation is not currently offered as treatment due to the nephrotoxicity of the transplantation-associated immunotherapy, which may be worse than the potential for acquiring nephrotoxicity due to the diabetes itself. Research continues on the prospect of transplanting cultured islet cells. Progress has been made in the area of diabetes prevention with the development of immunological markers (antibodies to glutamic acid decarboxylase-65k, islet cell antibodies, and insulin antibodies) that help target a high-risk population. The large, multicenter Diabetes Prevention Trial-1 (DPT-1) is investigating whether diabetes can be prevented using subcutaneous insulin in family members (of a known patient with type 1 diabetes) who are declared high risk because of these markers.

General Articles

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   In 1998, the criteria for making the diagnosis of diabetes mellitus were modified by this expert panel. The article also nicely describes the different forms of diabetes mellitus.
2. Kaufman, F. Diabetes in children and adolescents. *Med. Clin. North Am.* 82: 721–738, 1998.
   Easy to read chapter covering all aspects of diabetes mellitus in children.
3. Scott, C., et al. Characteristics of youth-onset noninsulin-dependent diabetes mellitus and insulin-dependent diabetes mellitus at diagnosis. *Pediatrics* 100:84–91, 1997.
   This article describes features of type 2 diabetes in children.
4. American Diabetes Association: Clinical Practice Recommendations. *Diabetes Care* 22(Suppl. 1):S1–S114, 1999.
   Each year in the supplement to the January edition of Diabetes Care, *experts give position statements on issues ranging from diabetes and exercise and nutrition to pancreatic transplantation.*
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   In this important study of nonobese diabetic mice, the authors show that cell-specific glutamic acid decarboxylase is required for the development of autoimmune diabetes. The implications in humans should be seen over the next decade.
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   Detailed and organized basic description of the immunopathogenesis of diabetes mellitus, and brief coverage of prevention strategies.
8. Bosi, E., and Sarugeri, E. Advances and controversies in etiopathogenesis of type 1 (insulin-dependent) diabetes mellitus. *J. Pediatr. Endocrin. Metab.* 11:293–305, 1998.
   This article is for those wishing for a more in-depth immunological discussion about current theory and controversies on the development of diabetes.

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10. Santiago, J. Intensive management of insulin dependent diabetes: Risks, benefits, and unanswered questions. *J. Clin. Endocrinol. Metab.* 75:977–982, 1992.
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    The hemoglobin A_{1c} has remained the gold standard for monitoring patients' diabetes control.
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    This is the landmark study that confirmed that intensively treated type 1 diabetes leads to a markedly reduced incidence of long-term complications, and that the relationship between long-term blood glucose levels and the incidence of complications is linear. The results of this study imply that the complications are due to hyperglycemia and not diabetes per se, so we can improve the natural course of diabetes with better glucose control. See also Pediatr. *Clin. North Am.* 44:285–300, 1997.
13. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J. Pediatr.* 125:177–178, 1994.
    In this very important paper, the authors present the results of the Diabetes Control and Complications Trial (DCCT) when considering only adolescent patients from the original study. The results are similar to the standard DCCT, although the adolescents were not able to attain the same overall level of blood glucose control as did the adults.
14. The DCCT Study Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am. J. Med.* 90:450–459, 1991.
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15. Shapiro, A., et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N. Engl. J. Med.* 343:230–238, 2000.
    Highly publicized trial of seven adults with type 1 diabetes who underwent islet cell transplantation in conjunction with a glucorticoid-free immunosuppressive regimen. All achieved insulin independence, but the follow-up was only a year. Exciting news for the future but doesn't yet change current therapy.

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    This article summarizes recent advances in behavioral diabetes research, and focuses on six areas: self-treatment, psychosocial impact, diabetes-specific assessment, psychological stress, neuropsychological effects, and weight loss.
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19. Rafkin-Mervis, L. Carbohydrate counting. *Diabetes Forecast* 48:30–37, 1995.
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Complications

21. Lestradet, H. Long-term study of mortality and vascular complications in juvenile-onset (type l) diabetes. *Diabetes* 30:175–179, 1981.
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22. Rosenbloom, A. Skeletal and joint manifestations of childhood diabetes. *Pediatr. Clin. North Am.* 31:569–589, 1984.
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23. Ryan, C., Vega, A., and Drash, A. Cognitive defects in adolescents who developed diabetes early in life. *Pediatrics* 75:921–927, 1985.
    Poor cognitive development also has implications for the adolescent's ability to manage his or her disease.
24. Chiarelli, F., et al. Diabetic nephropathy in children and adolescents: A critical review with particular reference to angiotensin-converting enzyme inhibitors. *Acta Paediatr.* 425(Suppl.):42–45, 1998.
    While nephropathy is uncommon in children with diabetes, it can occur. Studies in adults show the value of angiotensin-converting enzyme inhibitors. The authors review the pharmacology of this class of medication and present a strategy for its use in diabetic children with nephropathy.
25. Gorman, D., Sochedtt, E., and Daneman, D. The natural history of microalbuminuria in adolescents with type 1 diabetes. *J. Pediatr*. 134:333–337, 1999.
    The authors study 76 adolescents to demonstrate the importance of screening children with diabetes for microalbuminuria. Of those with initial positive urine studies for microalbumin, about one third regressed, one third remained persistent, and one third progressed over a 6-year period.

Prediction and Prevention of Diabetes

26. Knip, M., and Karjalainen, J. Islet cell antibodies are less predictive of IDDM among unaffected children in the general population than in sibs of children with diabetes. *Diabetes Care* 21:1670–1673, 1998.
    This article looked at the predictive value of having islet cell antibodies in the general population in comparison to a high-risk population (siblings of a known patient with type 1 diabetes). They conclude that random screening of children with islet cell antibodies will yield many false-positive results (positive antibodies, but not likely to develop diabetes). See also Bingley, P., et al. Can islet cell antibodies predict IDDM in the general population? Diabetes Care 16:45–50, 1993.
27. Rabinovitch, A., and Skyler, J. Prevention of type 1 diabetes. *Med. Clin. North Am.* 82:739–755, 1998.
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28. Bougneres, P., et al. Factors associated with early remission of type I diabetes in children treated with cyclosporine. *N. Engl. J. Med.* 318: 663–670, 1988.
    Initial article that prompted excitement about the possible use of immunosuppression with cyclosporine to prevent IDDM. Unfortunately, this initial enthusiasm has been tempered by the finding of cyclosporine-induced nephrotoxicity, and the clinical relapse when therapy is discontinued.
29. Keller, R., Eisenbarth, G., and Jackson, R. Insulin prophylaxis in individuals at high risk of type I diabetes. *Lancet* 341:927–928, 1993.
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82. METABOLIC ERRORS

Pamela J. Reitnauer

Inborn errors of metabolism result in abnormalities in the synthesis, metabolism, transport, or storage of biochemical compounds. In general, these disorders, resulting from a gene product (e.g., an enzyme) that is missing or abnormal, cause a wide variety of nutritional, developmental, and physical growth abnormalities. Some general categories of metabolic disorders include: (1) organic acidemias, (2) fatty acid oxidation disorders, (3) aminoacidopathies, (4) urea cycle defects, (5) lysosomal storage diseases, (6) carbohydrate metabolism disorders, (7) peroxisomal disorders, (8) mitochondrial disorders, and (9) purine and pyrimidine metabolism disorders.

An inborn error of metabolism should be considered in any infant or child with acute onset of lethargy, seizures, or vomiting, but the age of onset of symptoms may provide a clue to the specific metabolic diagnosis. Often, symptoms occur as a result of physiologic stress, such as infection and/or fasting. Many inborn errors of metabolism present in the newborn period. Symptoms in infants include poor feeding, vomiting, tachypnea, apnea, irritability, lethargy, altered tone, and seizures. Usually, there are no dysmorphic features. Storage diseases usually present in late infancy or early childhood, with slowly progressive symptoms. Signs of conditions such as glycogen storage disease type I or fatty acid oxidation disorders become apparent when the time between meals is lengthened, e.g., when affected infants begin sleeping through the night. If energy demands exceed available energy stores (e.g., due to illness, stress, decreased oral intake), patients with impaired energy metabolism are unable to maintain homeostasis, which may lead to hypoglycemia, metabolic acidosis, and/or hyperammonemia. Patients with inborn errors of metabolism that involve impaired energy production or accumulation of toxic metabolites can have evidence of multiple organ dysfunction. Symptoms of some conditions, such as fatty acid oxidation disorders, can occur at any age.

Laboratory evaluation should be done while the patient is symptomatic since diagnostic compounds may be diluted or their production diminished once the substrate has been removed or treatment has begun. Blood studies include glucose, electrolytes, blood urea nitrogen, blood pH, serum bicarbonate, lactate, plasma ammonia, and hepatocellular enzymes. In addition, a urinalysis (urine ketones), urine reducing substances, and complete blood count should be performed. If there is a high suspicion for a metabolic disorder, additional analysis of plasma or urine depends on where the metabolites are concentrated, i.e., plasma for amino acids, carnitine and acylcarnitine analysis and urine for qualitative metabolic screen and urine organic acids. The qualitative urine screen usually includes pH, specific gravity, ketones, glucose, protein- reducing substances, ferric chloride (color reaction depends on organic compound present), dinitrophenylhydralazine (for a-ketoacids), nitrosonaphthol (for tyrosine metabolites), nitroprusside (for sulfhydryl groups), and a mucopolysaccharide spot test. Biochemical abnormalities result from a block in a metabolic pathway; the accumulation of substrate behind the metabolic block or deficiency of product can be measured in many cases. Measurement of metabolites often requires specialized techniques such as ion-exchange chromatography and tandem mass spectrometry. Further studies include assaying enzymatic activities in specific tissues (e.g., red cells, neutrophils, skin fibroblasts, or liver or muscle biopsies).

Some of the biochemical abnormalities that may provide a clue to diagnosis of some metabolic disorders are included in Table 82.1. Infants with *organic acidemias* generally exhibit a metabolic acidosis with an increased anion gap and hyperammonemia, whereas those with a *urea cycle defect* will develop severe hyperammonemia and no significant acidosis. Examples of organic acidemias associated with severe metabolic acidosis in infancy include methylmalonic acidemia, propionic acidemia, and isovaleric acidemia. The presence of neutropenia and thrombocytopenia may provide a clue to the presence of an organic acidemia. The abnormalities of organic acidemias are associated with energy metabolism. Lactic acidosis results when NADH accumulates and the lactate-pyruvate equilibrium is shifted in favor of lactate. Acidosis is usually a feature of the *mitochondrial disorders* exemplified by pyruvate carboxylase deficiency or the *oxidative phosphorylation conditions* associated with elevations of lactate and pyruvate.

Acidosis	Hypoglycemia	Ketosis	Hyperammonemia	Disorder to consider
+	±	+	±	Organic acidemia
±	±	-	±	Fatty acid oxidation disorder
-	-	±	+	Urea cycle disorder
±	±	±	±	Amino acid disorder
±	+	-	-	Glycogen storage disease type I
+	±	-	±	Mitochondrial disorder

+, Usually Present; ±, May Be Present; -, Usually Not Present.

Table 82.1. Metabolic errors

A feature of *amino acid disorders* is that there can be a genetic defect in factors that mediate conversion to another amino acid, resulting in an accumulation of substrate. By-products of energy metabolism may or may not be present. Children with the disorder of the branched-chain amino acids, maple syrup urine disease (branched-chain oxoaciduria), will have acidosis, hypoglycemia, and hyperammonemia. Those with nonketotic hyperglycinemia can have acute encephalopathy and no metabolic acidosis and no hyperammonemia. Hepatic dysfunction may occur with tyrosinemia. Phenylketonuria (PKU), a condition associated with slowly progressing and irreversible encephalopathy and/or seizures, occurs because high levels of phenylananine are toxic to the central nervous system.

Fatty acid oxidation disorders can be evident at any age, from birth to adult as noted above. Some signs and symptoms include hypoketotic hypoglycemia, skeletal myopathy, cardiomyopathy, and transient to fulminant liver disease. The medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common fatty acid oxidation disorder. Molecular studies have shown that there is a common mutation (K329E) in at least 90% of affected Caucasians.

The signs of *storage diseases* usually evolve over time, but certain peroxisomal storage conditions such as Zellweger syndrome may be apparent at birth. Hepatosplenomegaly may be the first presenting sign of lysosomal storage diseases such as Gaucher disease, Niemann-Pick disease, or GM_1 gangliosidosis in a child. Features of the mucopolysaccharidoses (MPS), such as Hurler (MPS I) and Hunter (MPS II) syndrome, include hepatosplenomegaly, coarse facial features, skeletal anomalies (dysostosis multiplex), and hernias.

Deficiency of specific enzymes involved in *carbohydrate metabolism* can result in a variety of conditions. Type 1 glycogen storage disease is characterized by significant hypoglycemia with lactic acidosis at times of fasting, whereas signs of glycogen storage disease type II (Pompe disease) include cardiomyopathy, hypotonia, and muscles that feel hard, but neither hypoglycemia nor acidosis. Infants with galactosemia manifest symptoms of growth failure, vomiting, and liver disease after lactose feeding has begun.

Purine and pyrimidine disorders are sometimes difficult to recognize. They should be considered in a patient with a history of recurrent infection, unexplained developmental delay, failure to thrive, and a strong family history of similar features. The autosomal recessive adenosine deaminase (ADA) deficiency and X-linked

recessive Lesch-Nyhan syndrome are examples.

Some metabolic conditions have distinctive clinical features such as an associated odor or physical dysmorphisms. For example, maple syrup urine disease is associated with a maple syrup odor. The odor of sweaty feet characterizes isovaleric acidemia and glutaric acidemia type II. A few metabolic disorders have characteristic dysmorphic features, such as Smith-Lemli-Opitz syndrome (7-dehydrocholesterol deficiency), glutaric acidemia type I, and Zellweger syndrome. Offspring of women with PKU can have significant birth defects, such as congenital heart disease, if there is hyperphenylalanemia during pregnancy.

The treatment of inborn errors of metabolism includes restriction of dietary components that are associated with clinical manifestations. When acute presentation of symptoms leads one to consider a metabolic condition in the differential diagnosis, a brief restriction of protein may be necessary until a diagnosis is evident. Prevention of a catabolic state involves frequent feedings and intravenous glucose at times of illness. Occasionally, dialysis is required to remove toxic metabolites such as for a hyperammonemic coma in an individual with a urea cycle disorder. Supplementation with cofactors/vitamins or biochemicals that take advantage of an alternative pathway to the metabolic block may be required. Transplantation has been used in therapy of metabolic disorders to replace end organs such as livers and kidneys. Bone marrow transplantation has been utilized in a limited way to prevent sequelae of some of the storage diseases. Gene therapy may be the ultimate treatment of some conditions such as ADA deficiency.

Most inborn errors of metabolism are inherited as autosomal recessive disorders: Parents are obligate carriers and the risk of recurrence is 1 in 4 for any pregnancy. However, some metabolic conditions are inherited in an X-linked recessive fashion, with a recurrence risk of 1 in 2 for male offspring. Female carriers of X-linked metabolic disorders may partially express the condition. In the assessment of family history, the clinician should determine whether there is consanguinity and whether there is a history of unexplained neonatal deaths of siblings or males within the family. Prenatal diagnosis is available for many of the metabolic disorders, but many times testing is predicated on an accurate diagnosis in the index case. Extracted DNA from amniotic fluid fibroblasts or chorionic villi can be used to identify a mutation prenatally if a specific mutation has been discovered, as, for example, in a family with MCAD deficiency.

Prevention of the serious consequences of selected metabolic diseases has been the goal of newborn screening programs. The criteria for an effective screening program include (1) identifying a disorder in which symptoms would not be present until irreversible damage occurs, (2) that a disorder has a relatively high prevalence in the population, (3) there is some means of effective treatment or intervention, and (4) early treatment is better than late treatment. Routine population screening of newborns for conditions such as PKU, hypothyroidism, galactosemia and hemoglobinopathies generally involves collection of a blood sample on filter paper for analysis. Most newborn screening programs are administered through state departments of public health. All states report universal screening of infants for PKU and congenital hypothyroidism. Some states are now expanding the screening programs to include tandem mass spectrometry to test for aminoacidemias, organic acidemias, and fatty acid oxidation disorders. One should remember that despite the efficacy of newborn screening programs, metabolic testing should always be repeated if there is any suspicion of a metabolic disorder at any later time.

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83. THE DYSMORPHIC CHILD

Pamela J. Reitnauer

Major anomalies occur in 3% of births, and minor anomalies in 3–15%. Minor anomalies may be normal variants seen in other individuals in a family. Minor variants are considered minor anomalies when they occur as part of an underlying syndrome. There are four major morphologic mechanisms to consider in the evaluation of an individual with birth defects: deformation, disruption, dysplasia, and malformation. Deformations represent external compression and eventual distortion of a normally formed body part (e.g., transient cranial molding in the newborn). Disruptions occur with destruction of tissue that is normally forming. Examples of disruption occur with amniotic bands that constrict a portion of the body and affect further development. Dysplasias are intrinsic abnormalities of developing tissue, with one or several body systems affected. Examples include the bony dysplasias such as osteogenesis imperfecta (type I collagen abnormality) and achondroplasia (fibroblast growth factor receptor 3, [FGFR3] abnormality). Malformations are intrinsic developmental structural abnormalities that occur *in utero*. Examples of malformations include cleft lip and/or palate, congenital heart defects and syndactyly. The term “malformation syndrome” applies to recognizable conditions such as Down syndrome, trisomy 18 syndrome, and Rubinstein-Taybi syndrome, as examples.

If multiple anomalies are present, one question to consider is whether all of the child's abnormalities can be explained on the basis of a single problem that leads to a cascade of subsequent structural defects. A *sequence* is the occurrence of effects stemming from a single localized abnormality in early morphogenesis. Examples include the oligohydramnios sequence (Potter syndrome) or Pierre Robin sequence. An *association* is the clustering of the same multiple anomalies more frequently than would occur by chance. Examples are designated by acronyms: VATER association (*V*ertebral defects, *A*nal atresia, *T*racheo-*E*sophageal anomalies, and *R*enal dysplasia), and CHARGE Association (*C*oloboma, *H*eart defect, *A*tresia choanae, *R*etarded growth, *G*enital hypoplasia, *E*ar anomalies/deafness).

Genetic diseases can also be classified into chromosomal, single gene, multifactorial, mitochondrial, and somatic cell disorders. The chromosomal disorders include all conditions associated with visible changes in chromosomes. Usually, individuals with chromosomal abnormalities will have a recognizable constellation of dysmorphic features. Chromosomal disorders occur in 1 in 150 to 200 births. It is estimated that 60% of first trimester miscarriages have an associated chromosome abnormality. The birth incidence of trisomy 21 is 1 in 700 live births, and is the most common chromosomal condition. The chromosome deletion and microdeletion syndromes account for an expanding number of identifiable genetic syndromes. The detection of the microdeletion syndromes requires the use of specialized high-resolution banding techniques and/or fluorescence in situ hybridization (FISH) analysis. Some of the conditions associated with microdeletions include DiGeorge syndrome/velocardiofacial syndrome (del 22q11), Williams syndrome (del 7q11) and Angelman/Prader-Willi syndromes (del 15q11–12). As genetic deletions are identified in the delineation of certain conditions, it is expected that the FISH technique will become an increasingly useful diagnostic tool.

There are thousands of single gene disorders. Single gene disorders associated with malformations include some of the skeletal dysplasias. Skeletal dysplasias may first be evident when it is recognized that there is reduced length or height when compared with normal relatives. Disproportion of certain body areas may be a key factor. Specific mutations in the fibroblast growth factor receptor (FGFR) genes have been discovered in achondroplasia, hypochondroplasia and some of the craniosynostosis syndromes.

The multifactorial and somatic cell disorders account for about 20% of all congenital malformations, most of adult chronic conditions, and most cancer. Conditions associated with dysmorphic features and mitochondrial gene mutations include Leigh disease.

A fascinating aspect of genetic diagnosis is the notion that some conditions occur in a nontraditional inheritance pattern. *Anticipation* is the term that is applied to explain a condition that worsens in subsequent generations. One well-known mechanism to explain anticipation is the phenomenon of trinucleotide repeat expansion. Trinucleotide repeat expansions are responsible for fragile X syndrome, myotonic dystrophy, and some other specific neurologic disorders. Another complex phenomenon is the occurrence of genetic imprinting errors. *Imprinting* is another genetic mechanism associated with the parent of origin. One type of imprinting error is uniparental disomy (inheritance of both genes or chromosomal regions from one parent or deletion of one parental gene). Angelman syndrome and Prader-Willi syndrome are now classic examples of this type of genetic error. Angelman syndrome is most often caused by loss of maternally contributed chromosome 15q11–15q13 region, and the clinically distinct Prader-Willi syndrome results from the loss of the paternally contibuted 15q11–15q13 region.

Toxic environmental exposures during gestation can be associated with anomalies. Physical agents such as maternal exposure to heat (high fever or sauna) have been associated with birth defects. A constellation of physical and developmental features have been associated with fetal alcohol exposure and called fetal alcohol syndrome. Maternal insulin-dependent diabetes is associated with sacral dysgenesis and other anomalies, and maternal phenylketonuria has been associated with congenital heart defects.

The approach to evaluation includes a comprehensive assessment. Complete medical history involves obtaining and reviewing all available medical records. Examination of growth patterns is essential. Prenatal and perinatal history is an important component and includes history of uterine malformations, fetal movement, fetal presentation, and gestational age. Detailed family history includes at least a three-generation pedigree of medical problems, birth defects, miscarriages, or consanguinity. The developmental history should include the temporal progression of development and occurrence of any developmental regression. The physical examination should be very complete, with measurements, skin evaluation, and qualitative and quantitative description of features. Behavioral traits may provide a clue to diagnosis (e.g., obsessive eating and skin picking with Prader-Willi syndrome, and frequent laughing and excitability with Angelman syndrome). Comparison of physical features with parents or others in the family is helpful. Diagnosis depends on the recognition of a pattern of anomalies. Often, features of a particular syndrome will become more apparent as a child grows and develops.

Diagnostic techniques can include chromosome studies, and/or molecular tests to determine microdeletions or methylation patterns, mutation analysis, and direct sequencing. Radiographs may be necessary. Occasionally, metabolic testing may be helpful.

In the evaluation of a child with malformations or developmental delay, families want and need to know answers as to why and how it happened. Accuracy of clinical diagnosis is important. Unfortunately, it is estimated that 60% of individuals referred for genetics evaluation do not have a clear diagnosis. Reevaluation over time is warranted as some traits are more striking with age (e.g., Noonan syndrome). New syndromes are delineated yearly and new genetic tests are becoming available at an amazing rate. Accurate identification of a genetic syndrome is important in the determination of medical issues and the genetic counseling of families. Information about the natural history of a particular syndrome will help in understanding the prognosis, and in the treatment and management of that individual. The American Academy of Pediatrics has published guidelines for management of some common genetic conditions, such as Turner syndrome, Down syndrome, fragile X syndrome, and Marfan syndrome. Parental support groups are valuable, and many groups have registered Internet sites for information exchange.

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84. SEIZURE DISORDERS

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A seizure is an “abnormal, sudden, excessive electrical discharge of neurons (gray matter), which propagates down the neuronal processes (white matter) to affect an end organ in a clinically measurable fashion.” Such events may be subtle or dramatic, and affect 5% of children at one time or another during childhood. Most children who experience a seizure do not have epilepsy, however; the term should be reserved for the disorder affecting only 0.5–1.0% of children in whom seizures are recurrent and unprovoked by metabolic derangements such as hypoglycemia.

The most frequent precipitant to seizures in children who do not have epilepsy is fever, and approximately 3% of children between the ages of 6 months and 5 years have a “febrile seizure” unassociated with central nervous system (CNS) infection or other explainable cause. The event usually occurs early in a febrile illness, during the initial rapid rise in body temperature. The child loses consciousness and has generalized tonic-clonic movements; although the convulsion is frightening to behold and appears to the parents to last a long time, the duration is characteristically on the order of several minutes.

Approximately 30% of children who have a febrile seizure will have at least one recurrence; onset before age 12 months, a family history of febrile seizures, and a seizure early in illness or with lower temperature are predictive of an increased recurrence risk. Risk factors for future afebrile seizures (epilepsy) include a family history of epilepsy; evidence of neurologic damage or impaired development prior to the febrile seizure; and a “complex” febrile seizure, such as one that is focal, prolonged beyond 30 minutes, or recurrent within the same illness. If none of the risk factors is present the risk of epilepsy is 2–3%, but if multiple factors are present this may rise to as high as 50%.

Daily therapy with phenobarbital or valproate (Depakene, Depakote) is effective in preventing recurrences, but routine use of these drugs is not appropriate because of the toxicity and side effects; moreover, there is no evidence that prophylactic therapy has an effect on the ultimate prognosis. Administration of diazepam (Valium) during febrile illnesses can decrease recurrences, but is poorly tolerated by many children.

Nonfebrile seizures are classified into different types on the basis of clinical manifestations and the electroencephalogram (EEG). Knowledge of the various types is important (1) when eliciting a history to determine that an episode was in fact a seizure, (2) when selecting therapy, and (3) when counseling about prognosis.

The International League Against Epilepsy has classified seizures into two main groups, depending on how much of the brain is affected at the onset of the seizure: partial seizures begin clinically or on the EEG in a localized focus; generalized seizures involve both hemispheres simultaneously. Partial seizures are further subdivided into three types: simple partial, in which consciousness is preserved; complex partial, in which consciousness is impaired (formerly called psychomotor or temporal lobe); and partial seizures which spread to become generalized. Generalized seizures are subdivided into six types: absence (formerly petit mal), tonic-clonic (formerly grand mal), tonic or clonic, myoclonic, atonic, and infantile spasms.

In simple partial seizures, the symptoms produced depend on the area of the brain affected, and may be motor, sensory, autonomic, or psychic. Complex partial seizures consist of altered behavior for which the patient is amnestic but during which some interaction with the environment may occur. An aura (simple partial seizure) may usher in the more intense portion of the seizure, during which semipurposeful movements occur. The seizure usually lasts several minutes and is followed by postictal depression and at times focal neurologic deficits (Todd paralysis). Carbamazepine (Tegretol), phenytoin (Dilantin), valproate, and rarely primidone (Mysoline) are the main anticonvulsants currently prescribed to treat partial seizures. Gabapentin (Neurontin), topiramate (Topamax), lamotrigine (Lamictal), and tiagabine (Gabitril) are newer medications that may be considered if first-line medications are ineffective. If several medications alone or in combination fail, surgical options include the vagal nerve stimulator or excision of the epileptic focus.

Absence seizures are episodes of momentary loss of awareness. Often, no motor activity other than rolling or blinking of the eyes is noted. The attacks are brief, 5–10 seconds in duration, appearing without an aura and with no postictal depression; there may be many attacks per day, sufficient to impair learning or cause injury. The child may be accused of “daydreaming” and misbehaving, creating additional pressure for the affected child. The EEG is characteristic, with a spike-wave discharge at a rate of 3 per second. It is thought that such activity originates from the diencephalon or thalamic area. Pure absence seizures are usually limited to school-aged children and adolescents; are amenable to treatment with ethosuximide (Zarontin), valproate, clonazepam (Klonopin), and lamotrigine; and have a good prognosis. Other seizure types may be associated with absence, however.

Tonic-clonic seizures are characterized by stiffness, followed by rhythmic shaking of the trunk and extremities. Consciousness is lost, and incontinence is frequent. The convulsive stage is followed by postictal drowsiness and, often, by confusion. The anticonvulsants most commonly used for tonic-clonic seizures include valproate, phenytoin, carbamazepine, and phenobarbital. Mixed seizures consist of a combination of any of the preceding disorders. These often require the administration of several anticonvulsants simultaneously for control. It is generally preferred to “push” a single drug to efficacy or toxicity before changing medication or adding a second, however.

Three convulsive disorders that are less common but distinctive deserve special attention because of the difficult management and poor prognosis: myoclonic, infantile spasms, and atonic seizures.

Myoclonic seizures are characterized by single or repetitive contractions of an isolated group or groups of muscles. These seizures are most often part of a genetic trait (juvenile myoclonic epilepsy), but they may indicate a degenerative, metabolic, infectious, or progressive disease of the CNS such as subacute sclerosing panencephalitis.

Infantile spasms consist of a sudden flexion or extension of the body resembling an exaggerated Moro reflex. These often occur in clusters, affect infants between 3 and 9 months of age, and are associated with an EEG pattern described as hypsarrhythmia. Although at times idiopathic, infantile spasms usually are symptomatic of an early insult (e.g., infection or birth asphyxia) or an underlying CNS disorder, such as tuber ous sclerosis, CNS dysgenesis, metabolic disease, or chromosomal abnormality. In 90%, the prognosis for intellectual development is poor. By age 3 the spasms are often replaced by atonic or tonic-clonic seizures. To control myoclonic attacks and infantile spasms, adrenocorticotrophic hormone (ACTH) or corticosteroids are usually given. Clonazepam (Klonopin) and valproate have also been tried, but the seizures are usually exceedingly refractory to medication.

Atonic spells are sudden momentary loss of posture and tone without aura or postictal depression. These spells, often multiple during the day, occur in children 1–7 years old and are often associated with brain damage. Valproate, lamotrigine, and topiramate may be effective for these attacks. A very high fat diet sufficient to induce a state of chronic continuous ketosis (the “ketogenic diet”) may also be an option with this, as well as other difficult seizure types.

A child who has a seizure deserves a thorough initial evaluation in an attempt to define an underlying cause. A clear description of the ictal event is important. In addition, a detailed account of any acute illness, the child's medical history, development, and family history should be elicited. The general examination should be thorough, with particular attention to the possibility of acute (e.g., meningitis) or chronic (e.g., tuberous sclerosis) disease, and to the neurologic examination. An EEG may assist in better defining the abnormality. Supplementary investigation may include determination of blood sugar, calcium, electrolyte levels, and urine toxologic screening. Unless the etiology of the child's epilepsy is evident from the history or examination, magnetic resonance imaging (MRI) is now a standard part of the

evaluation.

Since 60–70% of children with a single afebrile seizure will not have a recurrence, anticonvulsant therapy may not be indicated. In 70–80% of children with recurrent seizures, anticonvulsant therapy is effective. Each anticonvulsant has associated toxicity and side effects, however, such as behavioral difficulties with phenobarbital, hypertrichosis and gingival hyperplasia with phenytoin, hepatotoxicity with valproate, and Stevens-Johnson syndrome with lamotrigine. Recent series have demonstrated that most children with epilepsy who, with medication, are seizure free for 2 years, can successfully have their medication tapered and stopped. If seizures recur, they are most likely in the first year after cessation of therapy. The group at highest risk of recurrence includes those with numerous seizures prior to control and those whose EEG is abnormal prior to termination of anticonvulsant treatment.

Convulsive disorders often have a devastating emotional impact on the child and the family; the emotional “morbidity” may far outweigh the physical danger. Thus, a comprehensive approach must be taken by the clinician caring for the child with a seizure disorder: Support and guidance may be needed in many matters of lifestyle, such as participation in sports, driving an automobile, and choosing a career. The ultimate goal of management is to minimize disability and maximize developmental potential.

Texts

1. Aicardi, J. *Epilepsy in Children.* New York: Raven Press, 1994.
   Concise chapters on the various forms and syndromes of pediatric epilepsy.
2. Wylie, E. (ed.). *The Treatment of Epilepsy: Principles and Practice* (2nd ed.). Baltimore: Williams & Wilkins, 1997.
   A 1200-page text covering topics from basic mechanisms and diagnostic testing to medical and surgical approaches. An excellent place to start when researching a subject.

Review and Collections

3. Zupanc, M. Update on epilepsy in pediatric patients. *Mayo. Clin. Proc.* 71:899–916, 1996.
   Brief but thorough review of the various forms of epilepsy, as well as their management.
4. Neville, B. Epilepsy in childhood. *B.M.J.* 315:924–930, 1997.
   Very concise, and also outlines medications that are in common use outside the United States.

Classification

5. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 22:489–501, 1981.
   The various types of seizure events are defined. The same commission published a classification of the epilepsies and epileptic syndromes in Epilepsia *30:389–399, 1989. People argue over details, but these two documents are the cornerstones of current nosology.*

Evaluation

6. Holmes, G. Electroencephalographic and neuroradiologic evaluation of children with epilepsy. *Pediatr. Clin. North Am.* 36:395–420, 1989.
   A good synopsis of electroencephalogram (EEG) terminology and techniques aimed at the pediatric generalist. Then go to J. Clin. Neurophysiol. *16:100–110, 1999, for a discussion of video-monitored EEG.*
7. Sperling, M. Neuroimaging in epilepsy: Contribution of MRI, PET and SPECT. *Semin. Neurol.* 10:349–356, 1990.
   Argues strongly for magnetic resonance imaging over computed tomography in nonemergent situations.
8. Rosenow, F., et al. Staring spells in children: Descriptive features distinguishing epileptic and nonepileptic events. *J. Pediatr.* 133:660–663, 1998.
   A good history can sometimes distinguish between petit mal and daydreaming.

Neonatal Seizures

9. Mizrahi, E., and Kellaway, *P. Diagnosis and Management of Neonatal Seizures.* Philadelphia: Lipincott-Raven, 1998.
   A 192-page monograph on the subject, nicely divided into individual chapters on topics from epidemiology to therapy.

Febrile Seizures

10. Knudsen, F. Febrile seizures: Treatment and prognosis. *Epilepsia* 41:2–9, 2000.
    A good introduction to the topic, but it should be complemented with a review of controversial areas in Curr. Probl. Pediatr. 27:6–13, 1997.
11. American Academy of Pediatrics Provisional Committee on Quality Improvement, Subcommittee on Febrile Seizures. Practice parameter: The neurodiagnostic evaluation of the child with a first simple febrile seizure. *Pediatrics* 97:769–775, 1996.
    A well-reasoned algorithm outlining what, if any, diagnostic tests to perform in that situation.
12. Nelson, K., and Ellenberg, J. Prognosis in children with febrile seizures. *Pediatrics* 61:720–727, 1978.
    One of the most important documents in pediatric neurology in the 20th century, emphasizing the benign nature of febrile seizures when data are collected prospectively across a large population.
13. Berg, A., et al. Predictors of recurrent febrile seizures: A metaanalytic review. *J. Pediatr*. 116:329–337, 1990.
    Onset before 12 months and a family history of febrile seizures each raise the recurrence risk of further febrile seizures to 45–50%. See also Epilepsia *37:126–133, 1996, for a discussion of increased risk of repeat bouts of febrile status in children with complex febrile seizures.*
14. Webb, D., et al. Retrospective study of late febrile seizures. *Pediatr. Neurol.* 20:270–273, 1999.
    Most children with occasional febrile seizures beyond age 5 still have a good outcome. Also see Ann. Neurol. *45:75–81, 1999, for a description of children with self-limited febrile and afebrile seizures (“febrile seizures plus” syndrome).*
15. VanLandingham, K., et al. Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile convulsions. *Ann. Neurol.* 43:413–426, 1998.
    Although febrile seizures are not harmful in general, focal febrile status may lead to temporal lobe injury and seizures. Fernandez, G., et al. (Neurology *50:909–917, 1998) argue that some of these children have preexisting temporal lobe malformations that cause the seizures to be prolonged in the first place. A chicken-or-egg debate waiting for a prospective study. In the meantime, febrile status needs to be treated vigorously.*

Specific Seizure Types

16. Loiseau, P. Idiopathic and benign partial epilepsies of childhood. In: Wylie, E. (ed.). *The Treatment of Epilepsy: Principles and Practice* (2nd ed.). Baltimore: Williams & Wilkins, 1997:442–449.
    A good introduction to the course and management of rolandic epilepsy.
17. Wheless, J., and Constantinou, J. Lennox-Gastaut syndrome. *Pediatr. Neurol.* 17:203–211, 1997.
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18. Serratosa, J., et al. Clinical and genetic analysis of a large pedigree with juvenile myoclonic epilepsy. *Ann. Neurol.* 39:187–195, 1996.
    Genetic mapping of a common form of idiopathic generalized epilepsy to chromosome 6p.

Natural History

19. Nelson, K., and Ellenberg, J. Antecedents of seizure disorders in early childhood. *Am. J. Dis. Child.* 140:1053–1061, 1986.
    Risk factors could be identified, but they carried a high rate of false-positive labeling.
20. Hirtz, D., and Ellenberg, J. The risk of recurrence of nonfebrile seizures in children. *Neurology* 36:637–641, 1984.
    In an old but large population-based study, 60% of children with a first afebrile seizure had a recurrence by age 7, with 90% occurring within 1 year. See also Neurology *40:1163–1170, 1990, and* Neurology *35:1657–1660, 1985, where recurrence risks of 34–50% are found, depending on the clinical presentation.*
21. Shinnar, S., et al. Sleep state and the risk of seizure recurrence following a first unprovoked seizure in childhood. *Neurology* 43:701–706, 1993.
    A first seizure in sleep carries a higher recurrence risk than one while awake.
22. Ellenberg, J., Hirtz, D., and Nelson, K. Do seizures in children cause intellectual deterioration? *N. Engl. J. Med.* 314:1085–1088, 1986.
    Apparently not, comparing children with seizures to their siblings and to themselves prior to onset of seizures. But see Paquier, P., et al. Arch. Neurol. *49:354–359, 1992, for a discussion of the Landau-Kleffner syndrome of acquired epileptic aphasia.*

Management

23. Greenwood, R., and Tennison, M. When to start and stop anticonvulsant therapy in children. *Arch. Neurol.* 56:1073–1077, 1999.
    An excellent risk/benefit analysis of the major treatment decisions.
24. American Academy of Pediatrics Committee on Drugs. Behavioral and cognitive effects of anticonvulsant therapy. *Pediatrics* 76:644–647, 1985.
    A review of the effects of phenobarbital, phenytoin, carbamazepine, and valproate concludes that behavioral effects may be apparent, but less obvious cognitive impairments are also common; the decision to treat should weigh these risks against the risk of recurrent seizures.
25. Pellock, J. Treatment of seizures and epilepsy in children and adolescents. *Neurology* 51(Suppl. 4):S8–S14, 1998.
    Relates medication choice to the child's specific seizure type and/ or epileptic syndrome.
26. Pellock, J. (ed.). New antiepileptic drugs in childhood epilepsy. *Semin. Pediatr. Neurol.* 4:1–67, 1997.
    Individual chapters on pediatric use of four of the newest medications: felbamate, lamotrigine, topiramate, and tiagabine.
27. Camfield, C., et al. Asymptomatic children with epilepsy: Little benefit from screening for anticonvulsant-induced liver, blood or renal damage. *Neurology* 36:838–841, 1986.

The title gives it away.
28. Parker, A. Vagal nerve stimulation in epileptic encephalopathies. *Pediatrics* 103:778–782, 1999.
The mechanism is far from clear, but vagal nerve stimulation can be effective in children with severe epilepsy.
29. Swink, T., Vining, E., and Freeman, J. The ketogenic diet. *Adv. Pediatr.* 44:297–329, 1997.
A good review of another intriguing alternative to medication.
30. Duchowny, M. Surgery for intractable epilepsy: Issues and outcome. *Pediatrics* 84:886–894, 1989.
The indications, risks, and benefits of neurosurgical intervention are discussed. Also see J.A.M.A. *264:729–733, 1990, for a National Institutes of Health Consensus Conference Report on epilepsy surgery.*

85. SPINA BIFIDA

Beth A. Rosen

The term *spina bifida*, which literally means “open spine,” is used to describe a spectrum of disorders involving the spinal column. In *spina bifida occulta*, there is failure of fusion of the posterior vertebral arches. This occurs in at least 5% of the population and is usually discovered as an incidental finding on radiographs. Most children remain asymptomatic, but a small percentage have abnormalities affecting the underlying spinal cord, such as a lipoma, a dermoid cyst, or a tethered cord, and may develop neurologic deficits during childhood. These deficits are most frequently incontinence and gait disturbance. When spina bifida occulta is associated with a spinal cord abnormality, but the overlying skin is intact, it is known as *occult spinal dysraphism*. Often a clue to its presence can be found, such as a tuft of hair, a skin tag, or a dimple over the affected area. Ultrasound of the spine is a useful tool to evaluate the infant spine, especially prior to 6 months of age, before ossification of the dorsal elements of the spinal column.

The term *spina bifida cystica* describes a lesion involving not only disruption of the bony structures of the spine, but also of the soft tissue above them, leading to cystic protrusion of the underlying structures. A *meningocele* consists of protruding meninges alone and is not usually associated with any abnormal neurologic findings. More common is a *myelomeningocele*, which includes not only meninges, but also neural elements of the spinal cord in the protruding sac, and is often accompanied by major neurologic deficits. The remainder of this chapter is devoted to the topic of myelomeningocele.

Myelomeningocele is one of the most common congenital neurologic malformations. The incidence in the United States is approximately 1 per 2,200 births, with a recurrence rate of up to 8% after the birth of an affected child. The defect most likely occurs during the fourth week of gestation, secondary to incomplete closure of the embryonic neural tube. Genetic, environmental, and nutritional factors are all believed to play a role in the etiology of myelomeningocele. It has been shown that supplemental folic acid administration at a dose of 0.4 mg/d around the time of conception decreases both the incidence and the recurrence rate. A genetic defect involving homocysteine metabolism is postulated in some cases.

Prenatal diagnosis of myelomeningocele is available through the use of maternal serum a-fetoprotein screening in the second trimester. If the level is increased, amniocentesis can be done to confirm that there is an elevated level in the amniotic fluid, and ultrasound can be used to attempt to visualize the myelomeningocele, as well as to rule out other causes of elevated a-fetoprotein, such as twin gestation.

Myelomeningocele is a complex disorder, and affected individuals are faced with lifelong disabilities. Some of the disabilities are related directly to the spinal lesion and others to associated brain malformations that commonly occur. Because the myelomeningocele lesion is usually in the lumbar, lumbosacral, or thoracolumbar area, two major problems are paralysis of the lower extremities and incontinence of bladder and bowel. In general, the higher up the spine the lesion is, the greater the neurologic deficit will be. The level of the lesion is not an absolute predictor, however, and initial examination is of great importance in assessing the level and degree of disability. A determination of the spinal cord level of motor and sensory deficits is aided by noting the posture of the lower limbs, since the deformities result from imbalance of normally and abnormally innervated muscle groups.

The most common problem related to associated brain malformation is hydrocephalus. This is secondary to the Arnold-Chiari malformation, also known as the Chiari II malformation in the hindbrain, which is nearly always present, causing caudal displacement of the cerebellum and brain stem. Children with Arnold-Chiari malformation can experience respiratory and swallowing difficulties from brainstem dysfunction. Endocrine abnormalities, most notable growth hormone deficiency, can occur.

Most children with myelomeningocele are in the range of normal intelligence, but learning disabilities are very common. Because of their disabilities, many have difficulties with socialization and are often quite isolated from their peers.

Treatment of the child with myelomeningocele usually begins in the neonatal period, though some centers are attempting repair of the lesion in utero. Parents are often overwhelmed and need continued emotional support and counseling. Early treatment is directed at closing the spinal defect, preventing infection, and if necessary, placing a ventriculoperitoneal shunt to treat hydrocephalus. Later treatment is directed at maximizing the potential of the child both by addressing existing problems early and by actively preventing potential problems. Comprehensive care of the child with myelomeningocele is best achieved in a multidisciplinary setting, where care can be both well coordinated and efficient. Various specialists include a pediatrician, neurologist, neurosurgeon, orthopedic surgeon, physical and occupational therapist, orthotist, urologist, nurse, social worker, and nutritionist. Neurosurgical care is required to address shunt malfunction and infections, as well as the late complications of myelomeningocele repair, including tethered cord and syringomyelia. Orthopedic care is directed at strengthening working muscles and treating deformities to achieve functional ambulation, if possible. Habilitation includes physical and occupational therapy, bracing, and surgery. Children with myelomeningocele are at great risk for renal dysfunction because of their neurogenic bladders, and urologic care must be directed both at preserving renal function and achieving a socially acceptable level of continence. The introduction of clean intermittent catheterization in the 1970s has been a great advance in this area. An acceptable regimen must also be found for bowel incontinence. A new surgical procedure known as the ACE procedure (anterior continence enema) is achieving some success is this area. Amid all the medical and surgical attention, it is critical that the educational and emotional needs of both the child and the family are continually addressed.

Spina Bifida

1. Byrd, S. Developmental disorders of the pediatric spine. *Radiol. Clin. North Am.* 29:711–752, 1991.

Myelomeningocele Reviews

2. Botto, L., et al. Neural tube defects *N. Engl. J. Med.* 341:1509–1519, 1999.
   A good overview of current knowledge and recent advances (100 references).
3. Blum, R., and Pfaffinger, K. Myelodysplasia in childhood and adolescence. *Pediatr. Rev.* 15:480–484, 1994.
   An excellent practical overview of multiple aspects. See also Clin. Perinatol. *16:311–329, 1989.*
4. Alexander, M., and Steg, N. Myelomeningocele: Comprehensive treatment. *Arch. Phys. Med. Rehabil.* 70:637–641, 1989.
   Issues and treatment from a rehabilitation point of view.
5. Lemire, R. Neural tube defects. *J.A.M.A.* 259:558–562, 1988.
   A review of the various types of neural tube defects.

Epidemiology, Prevalence, and Prevention

6. Yen, I., et al. The changing epidemiology of neural tube defects: United States, 1968–1989. *Am. J. Dis. Child.* 146:857–861, 1992.
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7. Lary, J., and Edmonds, L. Prevalence of spina bifida at birth United States, 1983–1990: A comparison of two surveillance systems. *M.M.W.R.* 45(SS-2):15–26, 1996.
   Discusses latest prevalence rates. Cragan, J., et al. suggest that prenatal diagnosis has been a major factor in reducing the prevalence: M.M.W.R. 44(SS-4):1–13, 1995.
8. American Academy of Pediatrics Committee on Genetics. Maternal serum alpha-fetoprotein screening. *Pediatrics* 88:1282–1283, 1991.
   Guidelines for screening for neural tube defects. See N. Engl. J. Med. *323:557–561, 1990, and* Am. J. Obstet. Gynecol. *166:1328–1329, 1992, for opposing views on the need for amniocentesis*

for the prenatal diagnosis of neural tube defects in the presence of elevated maternal serum alpha-fetoprotein and a normal fetal ultrasound.
9. Iqbal, M. Prevention of neural tube defects by periconceptional use of folic acid. *Pediatr. Rev.* 21:58–66, 2000.
A review of the studies that demonstrate the benefit of folate in reducing the incidence of spina bifida.
10. Mills, J., and Conley, M. Folic acid to prevent neural tube defects: Scientific advances and public health issues. *Curr. Opin. Obstet. Gynecol*. 8:394–397, 1996.
One reason why folate works despite normal folate levels. See also Lancet *346: 1070–1071, 1995.*
11. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *M.M.W.R.* 41(RR-14):1–7, 1992.
The Food and Drug Administration, and Centers for Disease Control and Prevention recommend that all women of childbearing age consume 0.4 mg folic acid per day.

Assessment

12. Stark, G. Neonatal assessment of the child with myelomeningocele. *Arch. Dis. Child.* 46:539–548, 1971.
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13. Brunberg, J., et al. Magnetic resonance imaging of spinal dysraphism. *Radiol. Clin. North Am.* 26:181–205, 1988.
What you see.
14. Rohrschneider, W., et al. Diagnostic value of spinal US: Comparative study with MR imaging in pediatric patients. *Radiology* 200:383–388, 1996.
Don't forget this noninvasive test can be done in infancy to evaluate for possible dysraphism.

Neurosurgical Aspects

15. Guthkelch, A. Aspects of the surgical management of myelomeningocele: A review. *Dev. Med. Child Neurol.* 28:525–532, 1986.
A historical perspective on the surgery of myelomeningocele. For more specifics about the surgery, see Neurosurg. Clin. North Am. *6:231–241, 1995.*
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20. Olutoye, O., and Adzick, N. Fetal surgery for myelomeningocele. *Semin. Perinatol.* 23:462–473, 1999.
A controversial new treatment still in its early stages.

Orthopedic Aspects

21. Sarwark, J. Spina bifida. *Pediatr. Clin. North Am.* 43:1151–1158, 1996.
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23. Franks, C., et al. The effect of walking with an assistive device and using a wheelchair on school performance in students with myelomeningocele. *Phys. Ther.* 71:570–577, 1991.
Suggests that the high energy cost of walking may have a negative effect on school performance.
24. Jansen, J., et al. Upper limb function of children with myelomeningocele. *Dev. Med. Child Neurol.* 28:790–798, 1986.
Of 33 children, only two had clinically normal hand function.

Bladder

25. Spindel, M., et al. The changing neurourologic lesion in myelodysplasia. *J.A.M.A.* 258:1630–1633, 1987.
The neurourologic lesion is a dynamic one that can improve or deteriorate over time, requiring close surveillance. See J. Urol. *148:362–365, 1992, as a reminder that children with low lesions who appear neurologically intact are at significant risk for urinary tract deterioration.*
26. Lin-Dyken, D., et al. Follow-up of clean intermittent catheterization for children with neurogenic bladders. *Urology* 40:525–529, 1992.
Concludes that long-term clean intermittent catheterization results in stable renal status and improved social continence and independence. (Wu, H., Baskin, L., and Kogan, J. Treatment should begin in infancy to prevent irreversible bladder dysfunction. J. Urol. *157:2295–2297, 1997.)*
27. Zawin, J., and Lebowitz, R. Neurogenic dysfunction of the bladder in infants and children: Recent advances and the role of radiology. *Radiology* 182:297–304, 1992.
The radiology of the neurogenic bladder is described, as well as surgical procedures to improve function.
28. Cass, A., et al. Sexual function in adults with myelomeningocele. *J. Urol.* 136: 425–426, 1986.
Most in this study had adequate sexual function.

Bowel

29. Younoszai, M. Stooling problems in patients with myelomeningocele. *South. Med. J.* 85:718–721, 1992.
Constipation and incontinence of stool lower self-esteem and limit social interaction. The scope of the problem and various treatments are described. (Also see rch. Phys. Med. Rehabil. *75:243–247, 1994, in which the need is stressed for beginning training before age 7, and for patient education. The authors feel poor compliance and lack of anal reflexes are major barriers to continence.)*
30. Hensle, T., Reiely, E., and Chang, D. The Malone antegrade continence enema procedure in the management of patients with spina bifida. *J. Am. Coll. Surg.* 186:669–674, 1998.
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Endocrine

31. Rotenstein, D., and Breen, T. Growth hormone treatment of children with myelomeningocele. *J. Pediatr.* 128:S28–S31, 1996.
Of those treated, 49% were growth hormone deficient. Improvement in growth symmetry, obesity, and muscle strength are reported. (However, being taller may not be better in this population: J. Pediatr. *129:771, 1996.)*

Latex Allergy

32. Mazon, A., et al. Factors that influence the presence of symptoms caused by latex allergy in children with spina bifida. *J. Allergy Clin. Immunol.* 99:600–604, 1997.
Sensitization ranges from 18–72%, depending on criteria (positive skin test vs. clinical symptoms). A large number of surgical procedures and a history of atopy were the most important predictors. See J. Pediatr. *134:344–348, 1999, for data suggesting that latex allergy is disease associated, possibly through an HLA antigen phenotype.*

Prognosis and Outcome

33. Bier, J., et al. Medical and social factors associated with cognitive outcome in individuals with myelomeningocele. *Dev. Med. Child Neurol.* 39:263–266, 1997.
Unshunted individuals scored in the average range; those with uncomplicated hydrocephalus, in the low average range. Socioeconomic factors also played a role. (Specific deficits in visual-motor activities: J. Pediatr. Psychol. *16:423–428, 1991. Shunt infection as a major factor in the depression of intellectual performance:* Pediatrics *70:338–342, 1982.)*
34. Talwar, D., Baldwin, M., and Horbatt, C. Epilepsy in children with meningomyelocele. *Pediatr. Neurol.* 13:29–32, 1995.
In this study, 17% had seizures; the majority had additional central nervous system pathology.
35. McLone, D. Spina bifida today: Problems adults face. *Semin. Neurol.* 9:169–175, 1989.
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36. Hunt, G., and Poulton, A. Open spina bifida: A complete cohort reviewed 25 years after closure. *Dev. Med. Child Neurol.* 37:19–29, 1995.
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Support

37. Colgan, M. The child with spina bifida: Role of the pediatrician. *Am. J. Dis. Child.* 135:854–858, 1981.
Provider of medical care, coordinator, and advocate.

Spina Bifida Association

38. Spina Bifida Association of America, 4500 McArthur Boulevard N.W., Suite 250, Washington, D.C. 20007.

86. HYDROCEPHALUS

Beth A. Rosen

Hydrocephalus is a disorder that occurs as a result of obstruction to flow of cerebrospinal fluid (CSF), leading to dilatation of the cerebral ventricles. It may be congenital in origin, often as a result of a primary cerebral malformation, or it may be acquired postnatally, secondary to diverse etiologies including tumor, infection, and hemorrhage. Several genetic causes of hydrocephalus have been identified. Children with untreated hydrocephalus usually present with signs and symptoms of increased intracranial pressure.

To understand the pathophysiology of hydrocephalus, it is important to review normal CSF physiology. The CSF is produced by the choroid plexus in the lateral ventricles, and flows to the third ventricle and through the aqueduct of Sylvius into the fourth ventricle; from there, CSF enters the cisterns and ultimately the subarachnoid space, which surrounds the hemispheres of the brain and the spinal cord. There, it is absorbed via the arachnoid villi into the venous system.

A major cause of hydrocephalus is blockage of CSF flow within the ventricular system itself; this is known as *obstructive* or *noncommunicating* hydrocephalus. The most common site of obstruction is in the aqueduct of Sylvius, which connects the third and fourth ventricle, because it is the narrowest part of the system. Varying degrees of narrowing and obstruction may occur and are referred to as aqueductal stenosis. The onset of symptoms may be rapid in the case of an expanding mass, but is often insidious, and may even be delayed until adulthood. A small percentage of cases appear to have a sex-linked pattern of inheritance. Other examples of noncommunicating hydrocephalus involve obstruction of the fourth ventricle. Two examples of this are the Arnold-Chiari malformation and the Dandy-Walker syndrome. The Arnold-Chiari malformation is due to aberrant development of the lower brain stem and cerebellum, and usually accompanies myelomeningocele. The Dandy-Walker syndrome is characterized by cystic dilatation of the fourth ventricle and cerebellar hypoplasia.

If the ventricular system is open, but there is obstruction at the level of the arachnoid villi, so that CSF cannot be absorbed into the venous circulation, this is known as *communicating* hydrocephalus. This obstruction most commonly occurs over the convexities and is usually caused by scarring due to hemorrhage or meningitis. This type of hydrocephalus is the usual etiology of post–hemorrhagic hydrocephalus in the premature infant.

A rare cause of hydrocephalus is choroid plexus papilloma, in which overproduction of CSF rather than obstruction is the problem.

Enlargement of the ventricles can also occur because of loss of brain tissue in the periventricular area. Though this is frequently called *hydrocephalus ex vacuo*, it is not hydrocephalus at all. There is no obstruction to CSF flow and no increase in intracranial pressure. Use of this term should be avoided. Another frequently used term that is also a misonomer is *external hydrocephalus*. This refers to a widening of the subarachnoid space frequently seen in infants with large heads. This may be secondary to abnormal reabsorption through the arachnoid villi. Ventricular size is usually normal. In the majority of cases, it is a self-limited process and rarely requires treatment

The signs and symptoms of hydrocephalus vary with the age of the child and the degree of pressure. In infants and young children, the symptoms may be insidious, with failure to thrive, vomiting, irritability, or somnolence. Examination may demonstrate a tense or large anterior fontanelle, distended scalp veins, a divergent strabismus, or spasticity in the lower extremities. Often, however, concern is prompted by the observation on repeated examination that the head circumference is increasing more rapidly than expected; this is demonstrated by plotting serial measurements of the head circumference on a normative chart. Headache, papilledema, and other symptoms and signs of elevated pressure may develop in older children with fused cranial sutures. As in all children with increased intracranial pressure, diagnostic evaluation for the definition of site and type of pathologic condition should be prompt. In the newborn or infant with an open anterior fontanelle, ultrasound is a useful tool both for initial evaluation and as a method to follow ventricular size serially. Computed tomography (CT), magnetic resonance imaging, or both are necessary to delineate the anatomy. The advantage of CT is that it is quick and easy to perform and is available in many centers on an emergency basis. Magnetic resonance imaging is superior in defining the anatomy, especially in cases of obstructive hydrocephalus. Transillumination of the skull is an all-but-forgotten technique that can be performed in young children to provide a clue to the presence of hydrocephalus.

The current standard of treatment for hydrocephalus is operative diversion of CSF from the cerebral ventricles using a shunt system with a one-way, pressure-controlled valve. Usually, the CSF is diverted into the peritoneum, but the right atrium, the pleura, and the kidney can be used. In most cases, there is adequate connection between the enlarged ventricles so that only a single shunt is required, but in cases where there is extensive scarring, multiple systems may be necessary. The major complications of shunts are infection and obstruction. A shunt is a foreign body; hence, infection may be caused by organisms of low virulence, such as *Staphylococcus epidermidis*, which should therefore not be dismissed as “contaminants.” Diagnosis is made by aspiration of CSF directly from the shunt; most systems have reservoirs for this purpose. Treatment with antibiotics alone is rarely successful; ultimately, the contaminated equipment must be removed and replaced. Malfunction of the shunt is also a serious event. The child may present with acute signs and symptoms of increased intracranial pressure, but presentation may be less clear-cut, both clinically and radiographically. A high index of suspicion is required, as expressed in the maxim: “Anything that goes wrong in a person with shunted hydrocephalus is due to a shunt problem until proved otherwise.” Shunts may have to be revised several times during childhood, though occasionally a single procedure will suffice.

Medical management of hydrocephalus using diuretics and hyperosmolar agents to control CSF production or increase excretion has been advocated by some, but a recent collaborative study in premature infants found no benefits and possibly some negative effects. Premature infants who are too small for shunting procedures often require serial lumbar punctures or placement of a ventricular reservoir to control hydrocephalus.

Despite the problems associated with shunts, at present they are still the best option for most children. Promising new technology includes shunts with valves that can be externally programmed postoperatively and a procedure that uses an endoscope to visualize the blockage and open it, making a shunt unnecessary.

It is difficult to define the prognosis for children with hydrocephalus as a group, since outcome is greatly influenced by the etiology of the hydrocephalus and the presence of associated anomalies. It is clear, however, that to conserve intellectual potential, detection should be early and treatment aggressive. The clinician must withstand the temptation to consider hydrocephalus synonymous with mental retardation. All children with hydrocephalus should be considered at risk, however, and receive appropriate developmental evaluation and services.

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87. CEREBRAL PALSY

Beth A. Rosen

Cerebral palsy (CP) is a nonprogressive disorder characterized by abnormal control of movement and posture due to insult or injury to the developing brain, usually before the age of 5. The manifestations of a given lesion may change as the nervous system matures, but the insult that caused the lesion is no longer present, and there is no active disease at the time of diagnosis.

Many cases of CP are of unknown cause. Several risk factors have been identified, including birth weight of less than 2,001 g, maternal mental retardation, fetal malformation, and breech presentation. Birth asphyxia is a less common cause of CP than is commonly thought. Unless asphyxia is sufficiently significant to create problems for the neonate in the nursery, it is unlikely to lead to CP. Furthermore, many asphyxiated babies are found on closer examination to have contributing prenatal factors. Obstetric and neonatal care has improved, but the frequency of CP appears relatively unchanged and may be related to improved survival of low–birth-weight and other sick infants. Increasingly, metabolic and genetic etiologies are being identified.

There are certain developmental observations, often made first by parents, that suggest a possible diagnosis of CP. The most frequent is delayed motor development, often with “dissociation” between motor and intellectual developmental milestones. Parents may note problems in sucking, swallowing, and excessive drooling. An infant who is strongly right-handed or left-handed before 12 months is at high risk for having hemiplegia. Persistent fisting after 3 months, a paucity of activity, asymmetry in the use of extremities, or unusual crawling warrants suspicion. Cerebral palsy can often be detected clinically by 4 months of age, utilizing expected milestones and assessment of tone, posture, and reflexes. However, some children do change and appear to outgrow the early characteristics that make them look like they have CP.

There are three main types of CP: spastic, extrapyramidal, and mixed. Estimates of the distribution vary, but spastic CP is by far the most common. The incidence of extrapyramidal CP has decreased greatly with control and prevention of hemolytic disease hyperbilirubinemia in newborns. Accurate classification is important information for clinicians, as it alerts them to serious abnormalities associated with particular types (e.g., hearing deficits with athetoid CP) and provides a better basis for counseling and planning therapy.

Findings that should alert physicians to the possibility of spastic CP include decreased range of motion, extensor tone in the supine position, and the presence of pathologic reflexes. Characteristics of the spastic limb include (1) muscular hypertonia of the clasp-knife type, (2) extreme hyperreflexia associated with sustained clonus, (3) a marked tendency to the development of contractures, and (4) extensor plantar reflex (Babinski's sign). The following topographic patterns of spastic CP are defined: (1) hemiplegia, involving two limbs on the same side; (2) quadriplegia, involving all four limbs, usually arms greater than legs; and (3) diplegia, where the lower extremities are affected significantly more than the upper extremities, which may be nearly normal.

The hallmark of extrapyramidal CP is variability with regard to motion, posture, and sleep state of muscle tone. Movement disorders, including athetosis, chorea, dystonia, or any combination of these can be present. When muscle tone is increased, hypertonicity is “lead-pipe” rather than “clasp-knife” rigidity (i.e., there is a steady increase or decrease of tone during flexion and extension rather than a sense of “give” or “catch,” as in spasticity). The child with rigidity is often floppy when asleep. Reflexes may be hyperactive, but rarely is clonus sustained. The plantar reflex is usually flexor (plantar), but involuntary movement may simulate an extensor response.

Comprehensive assessment is necessary for the child with CP because of the multiplicity of associated disabilities. Mental retardation occurs in at least 50%. Psychological testing is often difficult because of the motor disabilities of these children, and often requires the use of specialized tests and experienced examiners. Hypotonic children are often most adversely affected. The child of normal intelligence with CP is at high risk for attention-deficit hyperactivity disorder, and other associated learning and behavioral problems. Visual problems occur in about 50% of children, the most common being strabismus. Hearing acuity is diminished in approximately 10–15%, especially in those with athetoid CP and those with CP secondary to congenital infections such as cytomegalovirus. Epilepsy is also common, affecting 25–33% of children with CP.

The treatment of CP should begin in infancy or as soon as the diagnosis is made. The primary motor disability as well as the associated problems must be addressed, and this involves the input of a team of professionals as well as the child's family. Therapeutic intervention is frequently prescribed or mandated for children under the age of 3 in state-run “early intervention” programs. There is evidence that good infant stimulation may be more effective than extensive physical therapy in improving outcome. The occupational therapist is involved with upper-extremity function, self-help skills, designs for adaptive devices, and seating arrangements. The physical therapist deals with lower-extremity skills, posture, locomotion, and the evaluation of orthotic devices. Children with CP also benefit from careful hearing and language evaluation and, for some, the provision of methods of communication (e.g., language boards, computers). Not to be neglected is a nutritional assessment of caloric needs and methods of achieving adequate growth (supplementation, feeding techniques, and gastrostomy).

Many medications have been used to ameliorate the motor disabilities. Diazepam has been widely used, but sedation may be a major problem. Dantrolene acts directly on skeletal muscle as a relaxant, but weakness and liver toxicity limit its use. Baclofen also acts on the central nervous system (CNS) to relieve spasticity but when given orally is very sedating. It can now be delivered directly into the CNS using an implanted pump, available in a pediatric size, allowing smaller doses to be used. Botulinum toxin can be injected directly into specific muscles at periodic intervals to relieve spasticity.

Various surgical procedures have been employed in the habilitation of children with CP. Orthopedic procedures include adductor tenotomies, Achilles tendon releases, and multiple forms of hip surgery. The results are variable and depend on the type of CP and postoperative habilitative efforts. A neurosurgical procedure called selective dorsal rhizotomy has been used to relieve spasticity, particularly in children with spastic diplegia, but whether there is a benefit to this treatment over intensive physical therapy alone remains controversial.

Special education services are very important to the child with CP. Parents and school personnel must work together to provide the best social and educational environment for the child, and to avoid the feelings of depression and hopelessness that are seen in many adolescents and adults with CP. An important component of this process involves preparation for independent adult living and employment to the greatest extent possible. It is to be hoped that more appropriate intervention will maximize the potential of each person with CP.

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88. ECZEMA-DERMATITIS

Karen Wiss

The terms “eczema” and “dermatitis” are synonymous. They refer to a specific reaction pattern in the skin that is characterized by erythema, edema, vesicles, serous exudate, and scale. Many physicians use the word “eczema” when they are referring to atopic eczema. However, there are many forms of nonatopic eczema or dermatitis, including seborrheic dermatitis, irritant and allergic contact dermatitis, nummular eczema, asteatotic eczema, dyshidrotic eczema, lichen simplex chronicus, autoeczematization, and photoallergic dermatitis. The various types of eczema are classified based on history and the pattern of skin involvement.

Atopic eczema is a very common skin condition, primarily of childhood, that is usually seen in individuals with either a family or personal history of asthma, allergic rhinitis, or atopic dermatitis. The majority of patients have onset of the disorder before the age of one year. Atopic dermatitis is often extremely pruritic. It tends to exacerbate and remit until it resolves spontaneously, usually before adolescence. There are multiple possible triggers, including environmental allergens, foods, temperature extremes, sweating, and stress.

The cause of atopic dermatitis is not known. There is a definite genetic basis to the disease. Two immunologic abnormalities that seem to be involved are the overproduction of immunoglobulin E and T cell dysregulation. A current popular theory to explain many of the abnormalities in atopic dermatitis is that T cells produce decreased levels of g-interferon, which, combined with excessive interleukin-4 production, results in the inflammatory process seen.

Itching is an integral feature. Atopic eczema is the “itch that rashes”: It is widely believed that itching is the primary event, and rubbing and scratching produce the rash. (Atopic patients seem to have a lowered threshold for itch in response to physical stimuli.) The function of environmental and dietary allergens is controversial. It appears that foods such as cow's milk, eggs, nuts, soy, wheat, and seafood can play a critical role in triggering and potentiating atopic dermatitis, especially in infants and young children. However, in many children, elimination of these foods from their diets will not cure the dermatitis. Infants and children with moderate-to-severe disease, or those with disease unresponsive to topical therapy, may benefit from food elimination and should be evaluated for food allergy. In older children, foods seem to play less of a role and inhalant allergens a more critical function. Exposure to pets and to house dust mites may also trigger a flare of the disease. Patients with atopic dermatitis have a very high rate of colonization with *Staphylococcus aureus.* Flares of the disease often correlate with infection and heavy colonization.

Acute flares are represented by poorly defined plaques of erythema, scaling, microvesicles, and crusting. Chronic episodes demonstrate lichenification (thickened skin with accentuated skin markings) and hyperpigmentation. The distribution of skin involvement varies with the age of the patient. Infants frequently have lesions on their faces and extensor extremities. As children approach school age, flexural surfaces such as the antecubital fossae, popliteal fossae, and posterior neck are involved. If the condition persists into the teenage years, the hands and feet are more likely to be affected.

The diagnosis of atopic dermatitis is based on the clinical appearance and a personal or family history of atopy. Certain associated cutaneous clues may aid in the diagnosis: xerosis (dry skin), hyperlinear palms, Dennie-Morgan sign or atopic pleat (infraorbital eyelid folds), ichthyosis vulgaris (inherited fish-like scaling mostly on the extremities), and keratosis pilaris (hyperkeratotic follicular papules with a chicken-skin appearance on the arms and legs). These skin findings are common in patients with atopic eczema.

Treatment of atopic dermatitis is palliative and not curative. Educating the child and family about the disorder is probably the most valuable part of therapy. This includes a discussion of the natural history and the fact that the disease will likely resolve spontaneously. A primary goal of therapy is to relieve itching so that the child is more comfortable. Topical corticosteroids are the mainstay of therapy. However, high-potency topical corticosteroids may interfere with growth and cause local damage, such as thinning of the skin; midpotency topical corticosteroids may produce similar effects when applied to the face or groin. Various tar preparations, antibiotics, antihistamines, and especially avoidance of known triggers are also of value. While frequent bathing may dry out the skin, it also may reduce bacterial colonization. It is best to make decisions regarding bathing based on the individual and family as well as the patient's type of eczema.

Topical macrolides are a very promising group of drugs that are being developed for treatment of atopic dermatitis. They inhibit cytokine transcription in immune and inflammatory cells. One of these macrolides, tacrolimus (FK 506), has been shown to be very safe and beneficial in pediatric clinical trials.

Seborrheic dermatitis is a common problem of infancy, adolescence, and adulthood. It is a usual cause of “cradle cap” in infants, resulting in a yellowish scaling in the scalp. Lesions are pink, poorly defined plaques with a greasy, yellow scale. They are found in areas where sebaceous glands are most prevalent the scalp, nasolabial folds, eyebrows, eyelids, beard area, postauricular region, axillae, groin, and anterior chest. For seborrheic dermatitis to be present, sebaceous glands must be active. Therefore, this disorder is rarely seen between the ages of 1 and 12 years. *Malassezia* yeasts likely play some role in the pathogenesis. Treatment consists of topical antifungal agents; topical corticosteroids; and shampoos containing zinc, selenium, and tar.

Dyshidrotic eczema or *pompholyx* is a very pruritic dermatitis of the hands and feet that overlaps with atopic dermatitis. The majority of affected patients have an atopic personal or family history. It is not common in childhood but rather becomes a problem for teenagers or young adults. Affected persons develop tiny deep-seated vesicles on their palms, soles, and lateral fingers. Scaling and erythema are acute features. Eventually, fissures, lichenification, and pigmentary changes occur. Stress and frequent hand-washing seem to contribute to the problem. Therapy with more potent topical corticosteroids, moisturizers, antihistamines, and decreased hand-washing are helpful, although this can be a very difficult condition to treat.

Contact dermatitis is of two types: allergic or primary irritant. Allergic contact dermatitis occurs only in individuals who have been sensitized to an allergen after repeated exposure. A delayed-type hypersensitivity occurs, resulting in an acute eczematous process with erythema, vesicles, weeping, and crusting. Continued exposure will likely cause more chronic changes. The Rhus antigen found in poison ivy, poison oak, or poison sumac is a common allergen. Nickel found in jewelry is another frequent cause. Because it takes time to develop allergy, infants and young children are rarely affected with allergic contact dermatitis.

Delayed-type hypersensitivity reactions to natural rubber latex proteins as well as an immediate-type allergy to these proteins have become major concerns in the past decade. Atopic individuals with hand eczema, those exposed to latex gloves, and children with spina bifida are at greatest risk.

Primary irritant contact dermatitis is caused by a substance that is irritating to anyone exposed. This substance frequently causes burning or stinging after exposure. Some of the more common causes of irritant dermatitis in children include saliva, urine, stool contents, soaps, and detergents.

The main treatment for either type of contact dermatitis is avoidance of the substance. Topical steroids and occasionally systemic steroids may be necessary.

Nummular eczema is a common, chronic disorder of circular, “coin-shaped” plaques usually on the extensor surfaces of the extremities. While mostly related to dry skin, it is common in atopic individuals. One of the more difficult forms of eczema to treat, nummular dermatitis will often respond to topical corticosteroids.

Asteototic eczema or *xerotic eczema* refers to an eczematous process caused by dry skin. Usually on the extensor arms and legs, affected individuals have very dry, cracked skin, often with erythema and fine fissures. It is seen in adolescents and adults, primarily in the wintertime, and is associated with dry weather and frequent

bathing.

Lichen simplex chronicus, called neurodermatitis in the past, is a very pruritic, localized, chronic form of eczema. Hyperpigmentation, lichenification, and scaling result from repeated rubbing and scratching of the skin. Sites that can be easily reached are usually affected.

An *autoeczematization* reaction occurs in response to an initial eczematous process like a contact dermatitis. The patient has one form of a dermatitis that is usually severe, and develops a secondary eczematous process in response. This same phenomenon is seen in response to a severe dermatophyte infection, especially tinea capitis, and is termed a dermatophytid or id reaction.

Besides the previously mentioned forms of eczema, there are other conditions that can give an eczematous picture that should be considered in the differential diagnosis. Scabies is also a very pruritic eruption that can be eczematous. Clues to this diagnosis are a distribution that involves palms and soles, later age of onset, and possibly involvement of other family members. Cutaneous infection with molluscum contagiosum can cause a surrounding eczematous response. Alternatively, children with atopic dermatitis are particularly susceptible to infection with molluscum. A variety of inherited immunodeficiency syndromes such as hyper–immunoglobulin E syndrome, Wiskott-Aldrich syndrome, and agammaglobulinemia may present with eczematous dermatitis.

Atopic Dermatitis: Reviews

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   An outstanding, comprehensive, recent review.
2. Rothe, M., and Grant-Kels, J. Atopic dermatitis: An update. *J. Am. Acad. Dermatol.* 35:1–13, 1996.
   Everything one would want to know about this subject.
3. Knoell, K., and Greer, K. Atopic dermatitis. *Pediatr. Rev.* 20:46–52, 1999.
   A concise overview with impressive tables.
4. Hanifin, J. Atopic dermatitis in infants and children. *Pediatr. Clin. North Am.* 38:763–789, 1991.
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Atopic Dermatitis: Pathogenesis

5. Leung, D. Pathogenesis of atopic dermatitis. *J. Allergy Clin. Immunol.* 104:S99–S108, 1999.
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Atopic Dermatitis: Food Hypersensitivity

6. Burks, A., et al. Atopic dermatitis and food hypersensitivity reactions. *J. Pediatr.* 132:132–136, 1998.
   Results of this study suggest that food allergy is common in children with atopic dermatitis and that most can be diagnosed by prick testing for seven foods milk, egg, peanut, soy, wheat, cod/catfish, and cashew.
7. Sicherer, S., and Sampson, H. Food hypersensitivity and atopic dermatitis: Pathophysiology, epidemiology, diagnosis, and management. *J. Allergy Clin. Immunol.* 104:S114–S122, 1999.
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   Review of work that supports a role for food hypersensitivity in atopic dermatitis. (For another review of food allergy and dietary management in children with atopic dermatitis, see Pediatr. Dermatol. *9:376–379, 1992.)*

Atopic Dermatitis: Clinical Manifestations

9. Beltrani, V. The clinical spectrum of atopic dermatitis. *J. Allergy Clin. Immunol.* 104:S87–S98, 1999.
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14. Ruzicka, R., et al. Tacrolimus. The drug for the turn of the millennium? *Arch. Dermatol.* 135:574–580, 1999.
    A review of all the published studies of tacrolimus in dermatology.
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    A very practical article that tells us when referral to an allergist is appropriate. Food allergy, aeroallergens, and interpretation of skin and radioallergosorbent testing are addressed.
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Seborrheic Dermatitis: Pathogenesis

21. Hay, R., and Graham-Brown, R. Dandruff and seborrhoeic dermatitis: Causes and management. *Clin. Exp. Dermatol.* 22:3–6, 1997.
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Seborrheic Dermatitis: Treatment

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Dyshidrotic Eczema

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25. Landow, K. Hand dermatitis. The perennial scourge. *Postgrad. Med.* 103:141–152, 1998.
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27. Wakelin, S., and White, I. Natural rubber latex allergy. *Clin. Exp. Dermatol.* 24:245–248, 1999.
    An outstanding review of latex allergy, with emphasis on diagnosis and management.
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29. Hatch, K., and Maibach, H. Textile dye dermatitis. *J. Am. Acad. Dermatol.* 32: 631–639, 1995.
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This is not common in children, but does occur. The most common cause in the Netherlands was nickel.
32. Kalish, R. Recent developments in the pathogenesis of allergic contact dermatitis. *Arch. Dermatol.* 127:1558–1563, 1991.
A review of the pathogenesis with up-to-date clarification of the role of T cells, Langerhans' cells, and adhesion molecules.

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89. EXANTHEMS

Kenneth B. Roberts

The term *exanthem* is generally used to refer to an infectious illness with a rash. It is distinguished from *enanthem,* which refers to lesions on mucosal surfaces such as in the mouth. Literally, the term refers only to the rash, but in common usage it is applied to the diseases as well. The exanthems represent a disparate collection of illnesses, with the common features being the rash and a predilection for children. The diseases are distinguished clinically by the morphology of the rash; epidemiologic features, including season of the year, exposures, and previous immunity; accompanying signs and symptoms; and the course of the illness.

The morphology of the rash is most helpful when the eruption is vesicular or petechial, since the differential diagnosis is relatively limited. Common vesicular eruptions include chickenpox (varicella), herpes simplex virus, and coxsackievirus (hand, foot, and mouth disease). Petechial rashes associated with infection suggest bacterial sepsis, especially meningococcal, but may also be due to rickettsiae (e.g., Rocky Mountain spotted fever) and viruses (especially echoviruses); noninfectious causes, such as thrombocytopenia and vasculitis, must also be considered. Also distinctive are the "sandpapery" rash of scarlet fever, the "sunburn" rash of toxic shock syndrome, and the painful blisters of staphylococcal scalded skin syndrome.

In the majority of rashes, the color is pink to red, and the individual lesions are flat (macular) or palpable (papular); these are what clinicians tend to describe as "erythematous, maculopapular" eruptions. Clinical diagnosis depends on a knowledge of the individual diseases. Measles, as a distinct entity, was distinguished from scarlet fever in the seventeenth century by clinicians such as Sydenham. In the mid-nineteenth century, rubella was recognized to be a separate (third) disease. Late in the nineteenth century, Filatow and Dukes proposed a fourth disease, with features suggestive of scarlet fever and rubella; by the 1930s, fourth disease was no longer considered a distinctive illness separable from scarlet fever and rubella. Erythema infectiosum had already been named fifth disease, however, and the designation persisted, even in the absence of a fourth disease. Fifth disease is the last of the "officially" numbered exanthems, though some authors consider exanthem subitum (roseola) to be sixth disease.

Measles (rubeola) is most prevalent in the winter and spring. Following an incubation period of 10–14 days, an illness develops that appears to be a common upper respiratory infection, with low-grade fever, coryza, mucopurulent conjunctivitis, and cough. By the second or third day, Koplik spots are present on the buccal mucosa; these are blue-white dots on a red base and are pathognomonic for measles. Koplik spots are present the day before the rash and remain for a day or two after the onset of rash. The rash generally begins on the third day of illness, on the neck, behind the ears, and at the hairline; it is accompanied by retroauricular and posterior cervical lymph nodes. The rash spreads quickly to the face and then progresses over days from head to foot. Notably, the rash is cumulative; that is, lesions do not fade from the face before appearing on the chest but accumulate on the face, resulting in the characteristic appearance of a miserable child with mucopurulent conjunctivitis and an edematous face covered with rash. Fever and constitutional illness reach their peak as the rash progresses, generally on the second or third day of rash, corresponding to the fifth day of illness. The illness subsides over the next several days, except for the cough, which lingers for weeks. Complications are common, particularly otitis media and bacterial pneumonia. The most serious complications are measles pneumonia ("giant-cell pneumonia"), particularly in immunocompromised hosts, and encephalitis. Encephalitis occurs in 1 of 1,000–2,000 children with measles during the course of the acute illness. Mortality is 15–25%, and many of those who survive are left with neurologic impairment, a severe seizure disorder, or both. Subacute sclerosing panencephalitis (Dawson encephalitis) is a degenerative disorder following measles in 1 of 1,000 infected children, generally taking a decade to develop. Measles is preventable by immunization (see Chap. 105).

Rubella, also called German measles, is also most prevalent in the late winter and spring but is a much milder clinical disease than measles, particularly in children. Adults tend to experience a prodrome of low-grade fever, malaise, and adenopathy, but these symptoms are generally absent or so mild as to be overlooked in children. The exception is adenopathy; at the onset of rash, retroauricular and posterior cervical nodes are prominent. The rash begins on the face. Unlike measles, however, the rash is not cumulative; as it progresses from head to foot, it leaves the previously affected area. The total duration of rash is generally only 2–3 days. In dark-skinned children, the rash may not be apparent at all.

Arthralgia, and even frank arthritis, accompany rubella in adult women, less often in children. Joint complaints were common with the first rubella vaccines introduced but are not a problem with the current vaccine strain (RA 27/3).

Rubella is such a mild clinical illness that it would not be a candidate for a vaccination program except for its teratogenicity. Primary infection with rubella early in pregnancy is likely to result in damage to organ formation, particularly eye, heart, and brain. Rubella was a common childhood infection prior to the introduction of rubella vaccine, and 85–90% of adults were immune; nevertheless, epidemics occurred every 6–9 years. As a result of the pandemic of 1964–1965, some 20,000–50,000 babies were born with congenital rubella syndrome (CRS) in the United States. Now, with vaccination, there are no large rubella epidemics, and CRS is rare (see Chap. 105).

Fifth disease is also known as erythema infectiosum and, commonly, as the "slapped cheeks syndrome" because the initial phase of the rash is erythema of the cheeks. During the next several days, a rash develops on the trunk, with rapid central clearing; the result is a lacy, reticular appearance. The rash fades but is subject to reappearance in response to various stimuli such as cold or warm temperatures. Children generally have no constitutional signs of illness; adults may have low-grade fever, malaise, and joint complaints.

Fifth disease is caused by parvovirus B19, a virus identified in 1979 during screening of blood for evidence of hepatitis B. It is spread by the respiratory route and multiplies in host red blood cell precursors in bone marrow. Approximately 1 week after infection, a febrile illness may develop during which erythrocyte production is greatly suppressed in the bone marrow. The temporary red cell aplasia is inconsequential in normal individuals but results in aplastic crises in individuals with hemolytic disorders, such as sickle cell disease and chronic anemia in immunocompromised individuals. Moreover, if nonimmune pregnant women contract infection with parvovirus B19, the fetus may suffer fatal aplasia (nonimmune hydrops fetalis). Erythema infectiosum develops approximately 1 week later, as the bone marrow recovers.

Virus is present at the time of the bone marrow suppression, and children with aplastic crisis are infectious. By the time fifth disease develops, however, virus is no longer being shed, and children are no longer infectious. Thus, quarantine measures to protect pregnant women from children with erythema infectiosum are unnecessary and ineffective; exposure will already have occurred during the previous week.

Roseola, or exanthem subitum, is a common illness of early childhood, affecting most children by age 3 years. It is characterized by high fever for 3 or 4 days, followed by the concurrence of rapid defervescence and the appearance of a truncal rash. Suboccipital adenopathy may be prominent and serve as a clue to the diagnosis during the febrile period before the rash. Infants may have a bulging fontanelle; when the cerebrospinal fluid is examined for evidence of meningitis, it is normal. The only other clinical clue is that children are often described as appearing less ill than expected for the degree of fever. Children with roseola characteristically have low white blood cell counts with an absolute neutropenia and relative lymphocytosis, but these findings may not be present early in the illness.

Children with roseola may have a febrile seizure, generally at the onset of the illness when the high fever first appears. Complications are otherwise rare.

Human herpesviruses 6 (HHV-6) and 7 (HHV-7) both appear able to cause roseola. They also cause nonspecific febrile illnesses in young children, similar to roseola but without the rash. In older children, HHV-6 can mimic another member of the herpesvirus family, Epstein-Barr virus, and produce an infectious mononucleosis syndrome; atypical lymphocytes are present, but heterophil antibodies are not.

Additional causes of maculopapular eruptions include other viruses (e.g., enteroviruses, Epstein-Barr virus), *Mycoplasma pneumoniae,* Kawasaki syndrome, collagen vascular diseases, and reactions to drugs, particularly anticonvulsants and antibiotics.

Reviews

1. Cherry, J. Cutaneous manifestations of systemic infections. In: Cherry, J., and Feigin, R. (eds.). *Textbook of Pediatric Infectious Diseases* (4th ed.). Philadelphia: Saunders, 1998:713–737.
   An extensive chapter, listing and tabulating various infectious illnesses with associated rash (24 pages, 18 tables, 24 color plates, 181 references). The same author provides thorough reviews in his chapters on measles (pp. 2054–2074), parvovirus (pp. 1620–1630), enteroviruses (pp. 1787–1839), roseola (pp. 738–741), and rubella (pp. 1922–1949).
2. Frieden, I., and Resnick, S. Child exanthems: Old and new. *Pediatr. Clin. North Am.* 38:859–887, 1991.
   Briefly reviews multiple illnesses: measles, rubella, fifth disease, roseola, varicella, enteroviral and adenoviral exanthems, Epstein-Barr infection, scalded skin syndrome, toxic shock syndrome, scarlet fever, meningococcemia, Rocky Mountain spotted fever, Gianotti-Crosti syndrome, and Kawasaki syndrome. Resnick provides an update of issues with measles, varicella, parvovirus B19 (both erythema infectiosum and papular-purpuric glove and socks syndrome), unilateral laterothoracic exanthem, eruptive pseudoangiomatosis, and Kawasaki syndrome: Dermatol. Clin. *15:257–266, 1997.*
3. American Academy of Pediatrics Committee on Infectious Diseases. *Report of the Committee on Infectious Diseases* (25th ed.). Elk Grove Village, IL: American Academy of Pediatrics, 2000.
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   Very briefly reviews measles, enteroviral infections, rubella, fifth disease, varicella, infectious mononucleosis, roseola, scarlet fever, toxic shock syndrome, Stevens-Johnson syndrome, Kawasaki syndrome, and infections that produce petechiae; includes some color pictures. More recently in Pediatr. Rev. *(17:120–127, 1996), the "almost extinct" diseases, measles and rubella, are briefly reviewed, along with mumps and pertussis.*

Measles

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   Briefly reviews the epidemiology, clinical features, and complications. (For Sydenham's 1693 description of measles, see Pediatrics *77:556, 1986.)*
6. Cherry, J., Cohen, L., and Panosian, C. Diarrhea, fever, hypoxia, and rash in a house officer. *Rev. Infect. Dis.* 12:1044–1051, 1990.
   The resident had measles! (Say, you're immune, aren't you?) (See also Chap. 105.)

Rubella

7. Bakshi, S., and Cooper, L. Rubella. *Clin. Dermatol.* 7:8–18, 1989.
   An excellent overview of both rubella and congenital rubella syndrome (See also Chap. 105.)

"Fourth Disease"

8. Morens, D., and Katz, A. The "fourth disease" of childhood: Reevaluation of a nonexistent disease. *Am. J. Epidemiol.* 134:628–640, 1991.
   The authors review the data from cases between 1892 and 1900 that Dukes used to propose a distinct disease, and conclude fourth disease never to have existed. Also an excellent review of the history of exanthems.

Fifth Disease (Erythema Infectiosum)

9. Chorba, T., and Anderson, L. Erythema infectiosum (fifth disease). *Clin. Dermatol.* 7:65–74, 1989.
   Reviews the history, the virus (parvovirus B19), and the clinical syndrome(s) produced by the virus. (For a beautiful color picture of the "slapped cheeks," see N. Engl. J. Med. *331:1062, 1994.)*
10. Rao, S., Miller, S., and Cohen, B. Transient aplastic crisis in patients with sickle cell disease: B19 Parvovirus studies during a 7 year period. *Am. J. Dis. Child.* 146: 1328–1330, 1992.
    Approximately 70% of the aplastic crises were due to parvovirus B19; antibodies to the organism persisted, and there was no evidence of chronic or recurrent infections.
11. Nocton, J., et al. Human parvovirus B19-associated arthritis in children. *J. Pediatr.* 122:186–190, 1993.
    Of 20 children with arthritis associated with parvovirus B19 infection, 14 had joint symptoms for less than 4 months, but 6 had more persistent arthritis and fulfilled criteria for juvenile rheumatoid arthritis.
12. Cherry, J. Human parvovirus B19 infections in children and adults. *Adv. Pediatr.* 46:245–269, 1999.
    An extensive review with 118 references.
13. American Academy of Pediatrics Committee on Infectious Diseases. Parvovirus, erythema infectiosum and pregnancy. *Pediatrics* 85:131–133, 1990.
    Emphasizes infectiousness of individuals in aplastic crisis and noninfectiousness of children with fifth disease. Estimates risk of fetal death to be 1–2% in women of unknown immunity exposed to parvovirus B19 during the first 20 weeks of pregnancy.

Roseola (Exanthem Subitum)

14. Pryksananonda, P., et al. Primary human herpesvirus 6 infection in young children. *N. Engl. J. Med.* 326:1445–1450, 1992.
    Of 243 febrile children in an emergency department, 34 (14%) had evidence of acute human herpesvirus (HHV)-6 infection; only 2 developed a rash.
15. Suga, S., et al. Clinical features and virological findings in children with primary human herpesvirus 7 infection. *Pediatrics* 99:e4, 1997. (Available at: www.pediatrics.org/cgi/content/full/99/3/e4.)
    HHV-7, as well as HHV-6, associated with roseola.
16. Steeper, T., et al. The spectrum of clinical and laboratory findings resulting from human herpesvirus-6 (HHV-6) in patients with mononucleosis-like illnesses not resulting from Epstein-Barr virus or cytomegalovirus. *Am. J. Clin. Pathol.* 93: 776–783, 1990.
    Of 27 patients with mononucleosislike clinical illness, atypical lymphocytes but no heterophil antibody, and who did not have Epstein-Barr virus or cytomegalovirus, 8 (30%) had serologic evidence of HHV-6 infection.

Other

17. Russo, T., and Chang, T. Eruptions associated with respiratory and enteric viruses. *Clin. Dermatol.* 7:97–116, 1989.
    An extensive review, organized by clinical syndrome (19 pages, 176 references).
18. Mancini, A. Exanthems in childhood: An update. *Pediatr. Ann.* 27:163–170, 1998.
    In addition to the "usual suspects," brief consideration is given to unilateral laterothoracic exanthem, papular-purpuric glove and socks syndrome, and papular acrodermatitis of childhood (Gianotti-Crosti syndrome). Also see another article in the same issue, pp. 129–135. Both articles contain color pictures.

90. ACNE

Karen Wiss

Acne vulgaris is an extremely common skin condition, affecting 85% of teenagers and young adults. While it is not life-threatening, it can be disfiguring and can have a tremendous psychological impact on affected individuals. Multiple factors are involved in the pathogenesis, and effective therapy is targeted at these factors in an attempt to prevent scarring and emotional problems.

Acne is a disease of the pilosebaceous unit, which comprises the hair follicle and associated sebaceous gland. Pilosebaceous units are prominent on the face, chest, and back–the areas typically involved in acne. Four main components are involved in the pathogenesis of acne: abnormal follicular keratinization with obstruction of the follicle; excess sebum production triggered by androgen stimulation; proliferation of *Propionibacterium acnes*, and inflammation. The initial event, caused by unknown factors, is a plugging of the follicle by thickened epithelium. This results in a microcomedone, the precursor lesion of acne. In response to androgen stimulation beginning at the time of puberty, the sebaceous glands produce sebum. Sebum is oily and accumulates in a follicle that is obstructed by keratinocytes (epithelial cells), forming a plug or comedone. The obstructed follicle in acne lacks oxygen and is rich in lipids, forming a perfect environment for the proliferation of *P. acnes*, an anaerobic diphtheroid normally present in pilosebaceous units. The organism activates the complement pathways and promotes chemotaxis. The result is inflammation around the follicle, leading to its rupture. The follicular contents are very irritating to the surrounding dermis, furthering the inflammatory response and resulting in papules, pustules, and nodules.

Two main forms of acne vulgaris exist: noninflammatory, which consists of comedones; and inflammatory, with papules, pustules, and nodules. Comedones are of two types: closed and open. Closed comedones (whiteheads) are dilated, plugged follicles that have a thin epithelial covering. Open comedones (blackheads) have no epidermal roof and have a central black opening. The dark color in open comedones is due to melanin pigment, not to dirt, as is thought by some patients.

Inflammatory papules are small, erythematous, solid lesions. Pustules are more superficial and filled with pus. Acne nodules, which are often called cysts (but are not true cysts), are red, firm, frequently painful, and located in the deep dermis. Postinflammatory hyperpigmentation and erythema are temporary changes in skin color that result from inflammatory acne lesions. Later, there may be scarring in the form of papules, pits, or deep depressions.

The distribution of acne varies with age. Most preteens tend to have centrofacial involvement, while teens have more truncal and lateral face involvement. If acne persists into adulthood, it tends to involve the inferior half of the face, specifically the perioral region, jawline, and chin.

Physical examination of patients with acne should include all acne-prone areas, such as the chest, back, and face. It is important to define the morphology of the lesions and the severity of involvement, since treatment is based on these features. Sebaceous glands typically become active around 8 years of age, and the appearance of comedones at this age or later would not be unusual. However, comedones prior to age 8 years may suggest precocious puberty. In preadolescents, examination should include evaluation of secondary sexual characteristics. In teenaged patients, menstrual irregularity, hirsutism, obesity, and striae may also suggest hormonal dysfunction.

Laboratory studies are generally not useful in evaluating acne patients. Prepubertal children (less than age 8 years) with acne deserve hormonal evaluation. Useful tests include 17-hydroxyprogesterone, dehydroepiandrosterone sulfate (DHEA-S), free testosterone, and bone age. Hormonal evaluation may be appropriate in female patients with severe, difficult-to-manage acne, especially if there is evidence of androgen excess, such as hirsutism and menstrual irregularity. The conditions being sought include polycystic ovarian disease, Cushing disease, congenital adrenal hyperplasia, and adrenal or ovarian tumors. Laboratory tests that may prove useful include free and total testosterone, (DHEA-S), prolactin, follicle-stimulating hormone, and luteinizing hormone.

In addition to the common type of acne seen in teenagers and young adults, there are other less common types. Neonatal acne is seen in the first few months of life as a result of maternal androgen stimulation of the neonate's sebaceous glands. These newborns have comedones, papules, pustules, and rarely nodules. They improve spontaneously with the lack of continued maternal hormone stimulation. Treatment is usually not necessary, but scarring can occur with more severe cases. Infantile acne is less common and appears from age 3 months to 3 years. It tends to be inflammatory and can lead to scarring. Severe or prolonged infantile acne may warrant endocrinologic evaluation.

Pomade acne is seen in individuals who use oily or greasy scalp and skin preparations. Primarily comedones are the type of lesion present. Pomade acne is often successfully treated by avoiding greasy substances on the affected area.

Acne excoriée is the result of a true neurotic compulsion in which individuals excessively pick and squeeze their acne lesions. This can cause significant scarring, and often the habit must be treated along with the acne. *Acne conglobata* is a dramatic form of acne seen primarily in young men. These patients have numerous papules, pustules, nodules, abscesses, and draining sinuses. Scarring can be severe if not aggressively treated. *Acne fulminans* is a rare but serious type of acne seen in teenaged boys. After having mild acne, they have abrupt onset of painful nodulocystic lesions on their backs and chests, with ulceration. They have systemic symptoms such as fever, chills, weight loss, weakness, musculoskeletal pain, leukocytosis, and osteolytic bone lesions.

Certain medications may trigger acnelike eruptions. The most notorious are topical and systemic corticosteroids. Steroid acne has a unique appearance, with monomorphic small papules and pustules mostly on the trunk. Anabolic-androgenic steroids used by body builders and athletes have been recognized as a stimulus for acne. Other medications that can trigger acne include phenytoin, phenobarbital, lithium, bromides, iodides, androgens, and vitamin B_{12}.

Treatment of acne is individualized based on the types of lesions, the age of the patient, the severity of the condition, the distribution of the lesions, and the emotional impact that the disorder has on the patient. Physicians need to be sensitive to the fact that the disfigurement seen with acne can lead to low self-esteem, social phobias, and depression. Treatment should be aimed at improving the quality of the person's life and preventing long-term scarring. Educating patients and parents and giving them realistic expectations is crucial. Discussion should include the fact that acne is not a problem of improper cleansing and that it is a normal part of growth and development. It should be stressed that soaps and food have minimal impact on the disorder. Oily creams, lotions, and cosmetics should be avoided in acne-prone regions. Individuals should avoid vigorous scrubbing, picking, and pressure, which promote rupture of comedones, and increase inflammation and the potential for scarring. Patients must realize that initial improvement with acne treatment takes up to 6 weeks and may take months for dramatic resolution.

The topical agents currently available for treating acne include benzoyl peroxide, azelaic acid, topical antibiotics, tretinoin, and adapalene. Usually a combination approach tailored to the patient will be most effective. Benzoyl peroxide, the most commonly used topical acne medication, is bactericidal for *P. acnes* and is very inexpensive. It can be irritating to the skin, but there are formulations available that reduce this effect. It can also bleach clothing and sheets. Numerous benzoyl peroxide products in various concentrations are available over the counter and by prescription. Topical antibiotics are very valuable in treating inflammatory acne. They are thought to work by reducing the population of *P. acnes* and by inhibiting inflammation. Topical erythromycin and clindamycin are the more popular antibiotics used (gels, lotions, solutions, and pledgets), but tetracycline, meclocycline, and sulfosalicylates are also available in a variety of topical formulations. Azelaic acid cream, a natural dicarboxylic acid, is a newer treatment that is anti-inflammatory and somewhat comedolytic. It is extremely safe, minimally irritating, and effective for postinflammatory hyperpigmentation. It is a good alternative for patients with sensitive skin, those with mild acne, those needing a simple treatment, and those with pigmentary changes. Tretinoin is a vitamin A derivative that allows the keratinocytes plugging the follicle to be shed. It acts on the precursor lesion, the microcomedone, and therefore plays a preventive role in acne. It is useful in most acne patients, but especially in those with a large comedonal component. While it is an effective and safe medication, irritation, redness, and an initial flare of acne can limit its use. It is now available in some other vehicles such as a microsponge and a polyolprepolymer. These newer delivery systems seem to reduce the local irritation that can occur. Tazarotene is a newer retinoid that can be effective in acne and

psoriasis. It is unclear at present how it compares to tretinoin and adapalene. Adapalene is a novel naphthoic acid derivative with anti-inflammatory properties and a mode of action directed against comedones. It may be less irritating than tretinoin for some patients and, in contrast to tretinoin, is stable in the sun.

Systemic antibiotics, hormones, and isotretinoin are the oral agents that have proven useful for acne. Oral antibiotics are appropriate for those patients who have acne that is unresponsive to topical therapy, those with moderate-to-severe inflammatory acne, those with truncal involvement (which is difficult to treat topically), and those with significant scarring. Like topical antibiotics, they are anti-inflammatory and have some inhibitory effect on *P. acnes.* Tetracycline, doxycycline, and minocycline are the most frequently used oral antibiotics. Each has some possible side effects, and while they control the problem, they are not curative. The choice depends on potential sun exposure, cost, and whether the medication can be taken on an empty stomach. Minocycline is considered the superior antibiotic for acne, but some uncommon but concerning side effects include bluish pigmentation of the skin, mucous membranes, and teeth; drug-induced lupus; a hypersensitivity syndrome; serum sickness; pneumonitis; and hepatitis. Some alternatives to the tetracyclines that may be of great benefit in treating acne include erythromycin, trimethoprim-sulfamethoxazole, amoxicillin, ampicillin, cephalexin, cefadroxil, and azithromycin.

Resistance of *P. acnes* to oral and topical antibiotics is an existing and growing concern. Some suggestions to reduce bacterial resistance include avoiding antibiotics if possible, discontinuing them as soon as possible, avoiding concomitant use of dissimilar oral and topical antibiotics, using benzoyl peroxide (which does not develop resistance), and stressing to patients the importance of compliance.

Oral contraceptives containing higher dosages of estrogen can be very helpful in treating acne because of their antiandrogenic effects and ability to reduce sebum production. However, because of side effects associated with high-dose estrogens, most oral contraceptive agents used today have very low amounts of estrogen. Nonetheless, when this low-dose estrogen is combined with a progestin such as norgestimate with minimal androgenic activity, the result can be a dramatic improvement in acne. Spironolactone, a potent antiandrogen, can be useful in treating acne, especially in patients with hirsutism. Hormonal therapies such as estrogens and spironolactone should be used only in females because of their feminizing side effects in men.

Isotretinoin (Accutane), which became available in 1982, was perhaps the most significant advance ever in the treatment of acne. This vitamin A derivative dramatically reduces sebum production, inhibits *P. acnes*, suppresses inflammation, and eliminates the comedone. Because of potentially significant side effects, however, it is indicated for patients with severe, recalcitrant acne that has not responded to conventional therapy. There is dramatic improvement and long-term remission, if not cure, after the typical 20 weeks of treatment at a dose of 1 mg/kg/d. The main concern with the use of isotretinoin is its teratogenicity. The risk to the fetus is estimated at 25 times the normal risk and includes craniofacial, cardiovascular, thymic, and central nervous system malformations. Women must not become pregnant while on isotretinoin, and pregnancy tests are recommended prior to instituting treatment, monthly while on the medication, and at the completion. Common side effects of Accutane are similar to signs of hypervitaminosis A, and include dry lips, dry eyes, dry skin, headaches, nosebleeds, myalgias, and hypertriglyceridemia. Rare side effects such as skeletal hyperostosis, depression, hepatotoxicity, and pseudotumor cerebri may also occur. Isotretinoin should be prescribed only by physicians who are knowledgeable about the side effects and the required laboratory tests, and are able to counsel patients thoroughly and effectively, particularly about the teratogenicity.

Once the damage from acne is done, there are techniques of scar revision, which include excision, dermabrasion, collagen implants, chemical peels, and resurfacing lasers. These are not perfect techniques, nor inexpensive, and they are unnecessary if acne is treated appropriately in the initial stages.

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91. URTICARIA, ERYTHEMA MULTIFORME, AND STEVENS-JOHNSON SYNDROME

Karen Wiss

Urticaria is a common skin disorder that affects 15–20% of the population and has multiple causes. It is characterized clinically by transient edematous pink papules or plaques that are called wheals. Urticaria of less than 6 weeks' duration is termed acute, while that lasting greater than 6 weeks is called chronic.

There exist a few mechanisms for the onset of urticaria. Probably the most common is immunoglobulin E (IgE)-dependent hypersensitivity in which mast cells or basophils that have been sensitized with specific IgE antibody release mediators such as histamine after exposure to antigen. This mechanism is thought to be responsible for urticaria caused by foods, drugs such as penicillin, animal danders, and Hymenoptera venom. The same mechanism has been proposed for the physical urticarias in which various physical stimuli trigger wheals. Urticaria may also be the result of direct mast cell degranulation. This occurs in response to a variety of medications such as opiates, curare, and radiocontrast media. Disorders of the complement system may also trigger urticaria. Some examples include necrotizing venulitis, serum sickness, collagen vascular disease, and underlying malignancy.

The most characteristic feature of the urticarial wheals is the transient, fleeting nature. Individual lesions may last minutes to hours, but rarely longer than 24 hours. If a single wheal persists for more than 24 hours, an alternative diagnosis needs to be considered. Although the lesions are transient, episodes may appear intermittently for years. The lesions are erythematous, often with a pale center, and pruritic. They may be localized or generalized; circular, annular, or serpiginous; and range in size from millimeters to several centimeters. Especially in young children in dependent areas, dusky centers with scattered petechiae may be present. This targetoid appearance may resemble erythema multiforme (EM). Occasionally, large wheals and diffuse swelling occur, representing involvement of the deep dermis. This is known as angioedema. It often affects the face or an extremity. Systemic manifestations may occur; patients may experience dizziness, swelling in the throat, difficulty breathing, wheezing, nausea, vomiting, abdominal pain, and diarrhea.

The diagnosis of urticaria is usually not difficult with a thorough history and physical examination. The difficulty lies with determining the cause. The list of potential causes is extensive. A specific agent is identified in slightly more than 50% of individuals. It may be easier to identify a cause in acute cases. In children, acute urticaria is usually caused by infections, particularly viral upper respiratory tract infections. A variety of other viral infections, including mononucleosis and hepatitis, may be responsible. Bacterial, fungal, and parasitic infections can be triggering factors. Multiple medications have been known to cause urticaria. Penicillin derivatives are the most notorious, but other antibiotics, cold preparations, analgesics, and a long list of other drugs may be involved.

Physical factors are responsible for many chronic cases. Cold, heat, pressure, exercise, vibration, sunlight, and water may provoke episodes in certain individuals. Some persons may develop urticaria in response to more than one physical stimulus. Dermatographism, the most common physical urticaria, refers to a wheal that appears after stroking the skin.

Other important etiologic agents of chronic urticaria include foods and food additives, insect bites, underlying malignancy, vasculitis, and collagen vascular disease.

A few types of urticaria deserve special mention. *Papular urticaria* refers to dramatic wheals around insect bites that occur mostly in young children. Serum sickness occurs in response to a medication or heterologous serum. Seven to 21 days after the exposure, patients develop fever, malaise, arthralgias, lymphadenopathy, myalgias, and usually urticaria.

Hereditary angioedema is an autosomal dominant disorder in which individuals have a functional deficiency of the inhibitor of the first component of the complement system (C1INH). Affected persons have recurrent bouts of angioedema.

The most effective treatment of urticaria and angioedema is to identify the cause and eliminate exposure, if possible. H_1-receptor antagonists such as hydroxyzine and diphenhydramine can be very effective but are sedating. Newer generation H_1-blockers such as fexofenadine, loratadine, and cetirizine are less sedating and often very effective. Addition of an H_2-receptor antagonist such as cimetidine, famotidine, or ranitidine to an H_1-receptor antagonist may be useful. While effective for urticaria, systemic corticosteroids should not be used except for severe cases that are not responsive to any other treatments. Subcutaneous epinephrine is indicated for severe attacks with laryngeal edema.

Erythema multiforme is a hypersensitivity syndrome of the skin in response to a variety of trigger factors. There are two types: EM minor and EM major (Stevens-Johnson syndrome). Toxic epidermal necrolysis (TEN), formerly termed Lyell disease, is considered to be at the severe end of the disease spectrum.

Erythema multiforme minor is common and affects all ages but is unusual before the age of 3 years. There is an exhaustive list of triggering agents, but infection and drugs are responsible for most cases. It has become apparent in recent years that in greater than 60% of patients herpes simplex virus (HSV) is the cause. Recurrent episodes of EM minor are preceded by recurrent episodes of oral or genital HSV infection.

The skin lesions of EM minor appear abruptly, usually without a prodromal illness. Lesions are acral and symmetric in distribution initially, involving the dorsal hands and feet, face, palms, and soles. Lesions may spread centripetally to involve the trunk and proximal extremities. Red macules and edematous papules are seen first. These evolve rather quickly over a few days, and develop purpuric or cyanotic centers with the characteristic target or iris appearance. Lesions may enlarge to up to 2 cm in diameter and frequently develop vesicles or bullae in the center. Erosions may occur on mucous membranes. All lesions usually resolve by 3 weeks. If related to HSV infection, EM usually appears 1–2 weeks after the herpes outbreak.

Laboratory evaluations are usually not necessary in EM minor, although skin biopsy can be useful at times. Histologically, necrosis of the epidermis is seen, which corresponds to the clinical appearance of vesicles, bullae, and erosions

Therapy of EM minor is aimed at treating symptoms. If HSV-associated, early oral acyclovir may shorten the course of EM. Oral acyclovir is very effective at preventing recurrences in those persons with recurrent HSV-associated EM. Recovery of EM minor is complete, without scarring or complications.

Erythema multiforme major, or *Stevens-Johnson syndrome*, is a more severe form of the disease. It commonly occurs in children and young adults. Patients often have a prodrome of fever, malaise, myalgias, and arthralgias, and then have sudden onset of cutaneous and mucous membrane lesions. The cutaneous lesions are similar to those of EM minor but become more extensive and spread more rapidly. Diffuse erythema with widespread erosions may develop. Hemorrhagic crusted erosions are typical of the mucous membrane involvement; oral, conjunctival, and anogenital areas may be affected. Because of widespread skin necrosis, patients are at risk for dehydration and sepsis. Internal organ involvement occurs rarely.

Drugs are the main cause of Stevens-Johnson syndrome, in particular sulfonamides, anticonvulsants, and nonsteroidal anti-inflammatory agents.

Treatment of EM major is supportive. Burn unit management is often indicated, with careful attention to fluid, electrolytes, and infection prevention. Topical treatment with gauze and hydrocolloid dressings is important. The use of systemic corticosteroids is controversial. High doses for 2–3 days may halt some progression of the lesions. However, steroids likely increase the risk of severe infection and may worsen prognosis. Recent preliminary studies have shown intravenous g–globulin to be

of benefit.

Stevens-Johnson syndrome may last up to 6 weeks and has a mortality that approaches 15%. Long-term complications include scarring and strictures of mucous membranes.

Toxic epidermal necrolysis can be considered the most severe form of EM major. Patients are systemically ill with high fever, fluid and electrolyte imbalance, and sometimes hemodynamic shock. Diffuse erythema develops in 1–2 days, with widespread bullae and eventually extensive denuded necrotic skin. Mucous membrane involvement is a prominent feature.

Drugs are usually the culprits in toxic epidermal necrolysis. Similar to Stevens-Johnson syndrome, overwhelming sepsis is the greatest risk acutely. The mortality rate is 25–50%. Long-term sequelae consist of mucous membrane scarring and stenosis.

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92. JUVENILE ARTHRITIS

Lawrence K. Jung

The group of disorders known as juvenile rheumatoid arthritis (JRA) is more appropriately labeled “chronic arthritides of childhood,” as the disease seldom bears any resemblance to classic adult rheumatoid arthritis. This has prompted international efforts to reclassify these disorders, and “rheumatoid” has been restricted only to those resembling the adult-type rheumatoid arthritis. The distinction between the adult and juvenile types of chronic arthritis was first clearly drawn in 1897 by the pediatrician George Frederick Still, whose original paper remains perhaps the best clinical description of the childhood disease.

The incidence of juvenile arthritis(JA) in North America is about 10 per 100,000 children at risk, with a prevalence rate of 60–110 per 100,000; females predominate almost 3:1. The cause of the disease is unknown, although intriguing connections with infection, immunologic abnormalities, genetic factors, and environmental stress have been described.

Diagnosis of chronic arthritis in children is made on the basis of the history, physical examination, and clinical course; it is a diagnosis of exclusion as there are no specific laboratory tests. For the diagnosis of chronic arthritis, the following criteria have to be satisfied. “Arthritis” means the presence of at least two of the following joint signs: pain, swelling, warmth, erythema, and limitation of motion. “Chronic,” in this context, implies at least 6 weeks of arthritis; many authorities suggest a time period of 3 months in the absence of extra-articular manifestations.

Defining a chronic course is necessary to differentiate JA from a confusing multitude of transient arthritides (viral, postdysenteric, traumatic). The differential diagnosis must also include acute rheumatic fever, which may be distinguished by evidence of valvular heart disease and by dramatic relief of joint symptoms with aspirin; septic arthritis, which requires examination and culture of joint fluid for diagnosis; Lyme arthritis, distinguishable on clinical and serological grounds; and other rheumatic disorders, such as systemic lupus erythematosus, which are often differentiated by characteristic clinical and serologic abnormalities.

Juvenile arthritis is further divided into several major subsets: (1) systemic onset; (2) polyarticular (five joints or more), subdivided on the basis of whether rheumatoid factor is present (RF+) or not (RF-); (3) pauciarticular (fewer than five joints involved); (4) extended pauciarticular (five or more joints after 6 months); (5) enthesitis-related arthritis (sacroiliitis, HLA-B27–associated); and (6) psoriatic arthritis.

Systemic onset JA, also known as “Still disease,” begins as an acute febrile illness in 10–20% of children with JA and affects boys as often as girls. It may occur at any age, with a median age of onset of 5 years. Antinuclear antibodies (ANA) and rheumatoid factor (RF) are usually absent. Children with this mode of onset have a characteristic intermittent fever with one or two daily temperature spikes and an evanescent salmon-pink rash, which tends to appear at the height of the fever. Hepatosplenomegaly and generalized lymphadenopathy are common. Pericarditis may be present but is seldom clinically significant; myocarditis, on the other hand, although rare, may result in congestive heart failure and death. The characteristic polyarthritis may not be present at the onset of disease, but will usually appear within 6 months; almost one fourth of these children suffer progressive joint destruction. These patients are prone to macrophage activation syndrome characterized by fever, hepatosplenomegaly, and coagulation defect, with erythrophagocytosis on biopsy. Fatalites can result if this is not adequately treated with steroids, intravenous immunoglobulin and cyclosporine

Polyarthritis, involving five or more of the large and small joints, is the predominant initial manifestation in 25–40% of children with JA; systemic features, when present, are usually limited to mild fever and malaise. Cervical spine involvement may occur and can result in life-threatening atlantoaxial subluxation. The polyarthritis group is further subdivided based on the presence or absence of RF. Two thirds of children with polyarthritis do not have RF (seronegative subset) and respond well to treatment; in almost 90%, the arthritis follows a benign course with eventual complete resolution. Children who are RF^{+} (seropositive subset), are classified as having JRA. More than one half have severe progressive crippling arthritis, unresponsive to drug therapy. Both subsets occur more often in females; the seronegative group often presents in the preschool years, while those who have RF usually present in the second decade.

Pauciarticular or oligoarthritis is seen in 30–50% of patients with JRA, usually girls, and presents in the preschool years with asymmetric arthritis affecting only a few large joints. Well over half of the children in this subgroup have ANA. Sequelae from the typically mild joint disease are rare. However, although only 10–30% of all JA patients develop chronic iridocyclitis, the majority of these have pauciarticular onset and are usually ANA^{+}. Iridocyclitis, a potential cause of blindness, is usually asymptomatic, and its course is unrelated to the activity of the joint disease. Slit-lamp examinations by an ophthalmologist every 3 to 4 months are necessary to detect ocular involvement and prevent disabling complications.

A form of pauciarticular JA is usually found in older boys who are $HLA\text{-}B27^{+}$. Knees and ankles are typically involved initially; hips and sacroiliac joints may eventually be affected in some of these children. There may be significant involvement of the lumbar spine, and many of these children ultimately have disease indistinguishable from ankylosing spondylitis. Antinuclear antibodies and RF are absent. Patients may have bouts of acute, symptomatic iridocyclitis, seldom associated with significant sequelae. The prognosis for maintenance of normal gait and posture depends on the severity of disease in the spine and pelvic girdle, and on the adequacy of treatment.

Optimal treatment of JA requires an aggressive multidisciplinary effort. The major goal of treatment is maintenance of normal joint function. Physical therapy is essential, in view of the rapid development of joint contractures, muscle wasting, and growth retardation in children. The treatment plan should stress regular exercise coupled with adequate rest (*not* complete bed rest); in general, joint immobilization is contraindicated, although resting splints may be needed to relieve pain and increase range of motion.

Although there is little evidence that any drug used to treat JRA directly affects the process of joint destruction, anti-inflammatory agents are used to relieve pain, stiffness, and swelling so that joints will function normally and physical therapy may proceed. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as a first line of therapy and have supplanted the use of aspirin due to its toxic side effects. The majority of children will experience significant improvement in symptoms, although the response may come only after several weeks of treatment. Commonly used NSAIDs include tolmetin, naproxen, and ibuprofen, and they are approved for use in children. Cyclooxygenase-2 inhibitors hold the promise of reduced side effects on gastrointestinal integrity, platelet aggregation, and the kidneys, but have not yet been studied in detail in children.

Children whose articular disease progresses or fails to improve after 3–6 months of adequate NSAIDs and physical therapy are candidates for treatment with second-line agents. Oral methotrexate, used at lower doses than those for cancer chemotherapy (10 $mg/m^2/wk$) has been shown to be effective in treating patients not responsive to NSAIDs. Because of its low toxicity (gastrointestinal and liver toxicity being the main concerns), it has become the standard second-line drug. Gastrointestinal side effects of methotrexate are ususally responsive to daily oral folic acid. Penicillamine and hydroxychloroquine have relative low toxicity in children but showed little advantage over NSAIDS for children with JRA in a double-blind placebo-controlled trial. Nevertheless, the combination of methotrexate, hydroxychloroquine, and sulfasalazine (triple therapy) has been shown to be efficacious in those who have failed methotrexate. Intravenous g-globulin has been used to control the systemic symptoms in systemic JA. Gold is now seldom used because of its toxicity and relative lack of efficacy. Immunosuppressive drugs such as cyclophosphamide and cyclosporine have been used, but only in patients with progressive joint destruction who fail to respond to any other form of therapy. A new antimetabolic agent, leflunomide, has been found to be useful in adults with arthritis. Its use in children is still limited.

Systemic steroids are to be avoided in JA because of their failure to retard joint destruction and their well-known side effects. The only indications for systemic steroid use are (1) severe “toxicity,” especially life-threatening carditis, in patients with acute systemic disease; (2) iridocyclitis unresponsive to topical therapy; and (3) incapacitating joint symptoms unresponsive to NSAIDs and oral methotrexate. Vitamin D and calcium supplement are to be considered if steroid is used for extended

periods. Intra-articular steroid (triamcinolone hexacetonide) is very effective, especially in pauciarticular JA, and has relatively low side effects.

The understanding of the inflammatory cytokines involved in the pathogenesis of arthritis has led the new era of “biologics.” Biological agents used to suppress the inflammatory response are used with success in treating recalcitrant arthritis. Tumor necrosis factor antagonists such as etanercept (Enbrel) have been shown to be effective in adults as well as in children. These agents must be used with caution as the long-term consequence of their use is still not known. Future therapeutic considerations, especially in systemic JA or RF+ polyarticular JA, include autologous stem cell transplant and gene therapy.

In addition to physical therapy and drug treatment, other aspects of management include orthopedic intervention for release of contractures, synovectomy, or arthroplasty when necessary, and ophthalmologic examinations for iridocyclitis (children in the high-risk pauciarticular subset should be examined every 3–4 months). As with most chronic illnesses in children, especially teenagers, compliance can be a major problem that may be better managed if the child and family have a thorough understanding of the disease process and receive thoughtful psychological support.

Mortality for JA is estimated at 1–5%; death is usually due to infection, carditis, or renal failure. Renal failure due to amyloidosis had been the leading cause of death in Europe, but has declined in incidence, probably due to improved medical management. With appropriate treatment, the overall prognosis for JA is good. Ninety percent of pauciarticular JA patients have little or no sequela, although they have a higher risk for uveitis. Patients with juvenile onset of adult rheumatoid arthritis, on the other hand, often have severe disability. About half of the patients with systemic onset enter into remission, while the other half develop progressive disease with polyarticular involvement and moderate-to-severe disability. Optimal use of physical therapy, anti-inflammatory agents, ophthalmologic care, and emotional support can prevent most of the physically and emotionally crippling effects of this disease.

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An important aspect of the problem that is pertinent to the integration of the child into a normal life.

93. SYSTEMIC LUPUS ERYTHEMATOSUS

Lawrence K. Jung

Systemic lupus erythematosus (SLE) is a disorder resulting from the formation of antigen-antibody complexes, and the deposition of these complexes in vessel walls and in tissues such as skin (lupus rash), the renal glomerulus (lupus nephritis), and the choroid plexus in the central nervous system (CNS lupus). The cause of the disease is unknown, but it is probably due to a combination of genetic predisposition with a presumed environmental “trigger,” such as viral infection, drugs, pregnancy, sunlight, or emotional stress.

Childhood SLE, about one tenth as common as juvenile rheumatoid arthritis, usually presents in the second decade; the mean age at diagnosis is 12 years, and the onset is often temporally associated with menarche. Less than 5% of children with SLE will present before the age of 5. The disease has a striking female predominance, although the characteristic adult female-male ratio of 9 : 1 decreases to 4 : 1 in children less than 12 years old.

More than 70% of children with SLE present with fever, rash, and arthritis or arthralgia. Another large percentage exhibit weight loss, fatigue, and malaise with or without an arthritis syndrome. Less commonly, the disease at onset is manifested by involvement—primarily or solely—of a single system, occasionally resulting in diagnostic error; examples of such presentations include thrombocytopenic purpura, hemolytic anemia, acute nephritis, nephrotic syndrome, seizures, carditis, pneumonitis, hepatosplenomegaly, recurrent abdominal pain, and sore throat with lymphadenopathy.

Because of the many varied modes of presentation of this disease, the American Rheumatism Association has proposed classification criteria to standardize the diagnosis for research and reporting purposes. The criteria, as revised in 1982, are (1) malar rash; (2) discoid lesions; (3) photosensitivity; (4) oral or nasopharyngeal ulceration; (5) nonerosive arthritis; (6) the presence of LE cells, anti-DNA and anti-Sm antibodies, or chronic false-positive result of the serologic test for syphilis; (7) persistent protein or cellular casts in the urine; (8) pleuritis or pericarditis; (9) psychosis or convulsions; (10) hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia; and (11) the presence of antinuclear antibody (ANA). The presence, simultaneously or serially, of four or more of these features is highly suggestive of SLE (estimated 96% specificity); however, many patients considered to have SLE have less than four of these manifestations and the proposed standard should not be considered necessary for diagnosis.

Tissue injury and manifestations of disease in SLE are caused by the deposition of immune complexes, the cytotoxic effects of activated components of the complement system, and the action of lysosomal enzymes released by polymorphonuclear leukocytes. The antigens involved in the damaging immune complexes are of nuclear origin and, thus, the major screening laboratory test is an assay for the presence of ANA by indirect fluorescence. The absence of ANA virtually rules out the diagnosis of SLE, but its presence is only suggestive of the disease, as it may be found in several other disease states and occasionally in normal persons. The finding of antibody to native (double-stranded) DNA (anti-dsDNA), on the other hand, is highly specific for SLE; it is probable that most, if not all, of the immune complexes formed in the patient with SLE are dsDNA-anti-dsDNA complexes. The anti-dsDNA titer is useful not only for diagnosing, but also for monitoring the disease, since the quantity of antibody appears to correlate well with disease activity. The participation of activated complement in the process of tissue destruction is reflected in the depressed levels of C3, C4, and CH50 generally found during episodes of active disease, especially nephritis; however, the correlation of disease status with complement level may not be as consistent as with the anti-dsDNA titer

The goals of therapy are to (1) suppress inflammation, (2) prevent formation of immune complexes by blocking production of antibodies to DNA, (3) promote normal growth and development, and (4) avoid unacceptable side effects of the medications used. Patients with mild disease, primarily manifested as arthritis and fever, often respond well to nonsteroidal anti-inflammatory drugs (NSAIDs) alone. Hydroxychloroquine, an antimalarial agent, is helpful for treatment of skin lesions and mild disease unresponsive to NSAIDs. It is also used to modulate the course of lupus. A possible but rare side effect of this drug is ocular toxicity. Methotrexate is used in mild SLE and as a steroid-sparing drug.

The drug of choice for more severe disease is prednisone; indications for its use include severe “toxicity” (e.g., marked weight loss), active nephritis, carditis, or CNS disease. “Flares” of fever or joint symptoms that occur while prednisone is being tapered often respond to NSAIDs, hydroxychloroquine, or methotrexate and may not require an increase in steroid dosage. Rapidly progressive renal disease may respond to intravenous “pulses” of methylprednisolone. The toxic effects of prednisone account for many of the complications seen in children with SLE (such as growth retardation, infection, and aseptic necrosis of bone). The balance between control of the disease and prevention of steroid toxicity is often difficult to attain.

In severe lupus nephritis, the addition of immunosuppressive agents (cyclophosphamide, azathioprine, and chlorambucil) has been found to be superior to the use of prednisone alone. Intravenous pulse cyclophosphamide delays or halts the progression of chronic renal scarring seen when prednisone is used alone; other studies have suggested that it may also be beneficial in CNS disease. Thus, the combination of steroid and intravenous pulse cyclophosphamide has been used to treat patients with the most severe type of lupus nephritis (diffuse proliferative glomerulonephritis) and has resulted in a significantly improved survival rate. In recalcitrant SLE, super-high doses of cyclophosphamide and/or autologous stem cell transplantation offer therapeutic alternatives worthy of consideration. Mycophenolate mofetil has also been used in some cases.

In addition to anti-inflammatory drugs, treatment of the child with SLE must include careful attention to diet, rest, exercise, and psychological support. Patients must be taught to avoid exposure to the sun and to use sun-screening lotions, as direct sunlight may precipitate a flare of skin or systemic disease activities. Hypertension, due to both nephritis and steroid therapy, is a common finding and must be meticulously controlled to prevent additional organ damage.

Although SLE in children was initially described to be a rapidly fatal disorder, it is now apparent that at least 80% survive more than 10 years after diagnosis. The improved outcome is due to wiser use of drugs and improved supportive care, as well as increased success of dialysis and renal transplantation. When death occurs, it is due to either the disease itself or to complication of therapy. Active and intractable disease leads to vasculitis of CNS disease; bowel perforation; and end-organ failure of the kidneys, lungs, and heart. Diffuse proliferative glomerulonephritis is the one of the several types of renal lesions associated most often with azotemia and death. The neuropsychiatric manifestation of lupus may be difficult to distinguish from steroid-induced neurologic or psychological abnormalities, but is usually self-limited. However, stroke and death can result from active disease and CNS vasculitis. Increased susceptibility to infection may be a result of the disease itself, but the major cause is probably the immunosuppressive therapy used; viruses and *Pneumocystis carinii* are the organisms commonly associated with fatalities.

Some patients with SLE are found to have lupus anticoagulants or antiphospholipid antibodies. Despite the artifactual prolongation of the partial thromboplastin time, these patients are at risk for developing thrombotic disorders including strokes, deep vein thrombosis, and fetal wastage. Patients with episodes of thrombosis need to be on anticoagulation therapy on a long-term basis.

Children treated successfully for SLE are at increased risk in adulthood of premature atherosclerotic heart disease (and myocardial infarction) and of malignancies. The former is likely a consequence of lupus vasculitis and prolonged steroid therapy, while the latter is probably a result of immunosuppression.

Two lupus-like syndromes deserve note: “drug-induced lupus” and neonatal lupus. Occasionally, a drug (e.g., hydralazine, or, of more relevance in pediatrics, phenytoin) triggers the clinical expression of true SLE. More often, these drugs and others such as procainamide and isoniazid elicit the development of ANA and mild symptoms of lupus, both of which generally disappear when the drug is discontinued; nephritis and anti-dsDNA are rarely part of this syndrome

Neonates of mothers with SLE may have serologic abnormalities, occasionally accompanied by discoid lupus, hematologic abnormalities, or both. These findings,

which are due to the transplacental passage of pathogenic anti-Ro antibodies, are transient. A more serious concern is an increased incidence of permanent congenital heart block and endomyocardial fibroelastosis in infants of mothers with SLE.

Reviews

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   Contains an excellent, detailed chapter on SLE (62 pages, 562 references).
3. Lehman, T. A practical guide to systemic lupus erythematosus. *Pediatr. Clin. North Am.* 42:1223–1238, 1995.
   A sensible clinical approach used by the author in his practice. It should be emphasized that there are other approaches; see Scand. J. Rheum. *26:241–246, 1997.*
4. ACR ad hoc committee on SLE guidelines. Guidelines for referral and management of systemic lupus erythematosus in adults. *Arthritis Rheum.* 42:1785–1796, 1999.
   The American College of Rheumatology (ACR) ad hoc committee attempts to suggest a management guideline for SLE. Included is useful information, including the ACR classification criteria, differential diagnosis, and treatment plans. See Arthritis Rheum. *25:1271–1277, 1982, for the original criteria for the classification of SLE.*
5. Carreno, L., et al. Immunological and clinical differences between juvenile and adult onset systemic lupus erythematosus. *Lupus* 8:287–292, 1999.
   This study confirms the clinical impression that children with SLE often have more severe disease than adults, with renal and central nervous system (CNS) manifestations as major manifestations in children.

Lupus Immunology

6. Liossis, S., et al. Immune cell biochemical abnormalities in systemic lupus erythematosus. *Clin. Exp. Rheumatol.* 15:677–684, 1997.
   A number of immune abnormalities are found in SLE, but the relationships of these findings to the pathogenesis of lupus are still not clear. Autoantibodies, especially anti-DNA antibodies, and aberrant T cell clones might play significant roles in the pathogenesis of lupus. This article summarizes some of the more recent insights into the immune dysregulation in lupus. See also Semin. Nephrol. *19:67–76, 1999.*
7. Alarcon Segovia, D., and Cabral, A. Autoantibodies in systemic lupus erythematosus. *Curr. Opin. Rheumatol.* 8:403–407, 1996.
   A discussion of the various autoantibodies that might have pathogenetic roles in lupus: anti-DNA in nephritis, anti–ribosomal P in CNS lupus, anti-Ro and anti-La in neonatal lupus, and anti-b_2 glycoprotein I in antiphospholipid syndrome. For an in-depth look at the various autoantibodies, read the May 1992 issue of Rheum. Dis. Clin. North Am.
8. Ting, C., and Hsieh, K. A long-term immunologic study of childhood onset lupus erythematosus. *Ann. Rheum. Dis.* 51:45–51, 1992.
   Looks at immune parameters associated with exacerbation of disease: fall in C4 and rise in anti-DNA antibodies, while T cell phenotype and function remained relatively constant.
9. Barron, K., et al. Clinical, serologic and immunogenetic studies in childhood-onset systemic lupus erythematosus. *Arthritis Rheum.* 36:348–354, 1993.
   Renal involvement was more frequent than adults, while CNS and hematologic involvement less so. Age and race differences were also noted with respect to the HLA antigen type and autoantibody production.

Systemic Manifestations: Nephritis

10. Gloor, J. Lupus nephritis in children. *Lupus* 7:639–643, 1998.
    A review of the treatment and prognosis in children with nephritis. The use of steroid and immunosuppressive drugs has improved the overall outcome but does entail drug-related morbidity, which demands meticulous care by the medical personnel
11. Foster, M., and Kelley, V. Lupus nephritis: Update on pathogenesis and disease mechanisms. *Semin. Nephrol.* 19:173–181, 1999.
    Multiple and independent mechanisms contribute to the pathogenesis of the disease, which may explain the phenotypic and histopathologic heterogeneity seen in this condition.
12. Baqi, N., et al. Lupus nephritis in children: A longitudinal study of prognostic factors and therapy. *J. Am. Soc. Nephrol.* 7:924–929, 1996.
    Changes in therapeutic approaches in early inclusion of immunosuppressive drugs in class III/IV nephritis have significantly improved the outlook of patients with SLE (see Rheum. Dis. Clin. North Am. *20:213–242, 1994). This retrospective analysis helps to identify certain risk factors for progressive renal disease (hypertension, high creatinine, low C3); their presence would indicate aggressive therapy.*

Systemic Manifestations: Central Nervous System

13. West, S. Neuropsychiatric lupus. *Rheum. Dis. Clin. North Am.* 20:129–155, 1994.
    A comprehensive treatment of this complex subject, classifying the syndrome into diffuse and focal involvements of the CNS and peripheral nervous system, and a thorough discussion of the diagnostic approaches. Well worth the time to read this article.
14. Reiff, A., et al. Childhood central nervous system lupus; longitudinal assessment using single photon emission computed tomography. *J. Rheumatol.* 24:2461–2465, 1997.
    *Central nervous system lupus in children includes subtle deficits in cognitive functions that can be difficult to diagnose. Clinical markers such as anti-ribosomal P Ab (*Arthritis Rheum. *39:671–676, 1996) or antineuronal Ab (*Neurology *37:464–467, 1987) have been explored as clinical markers. Neuropsychiatric testing is very useful in follow-up of these patients. The use of CNS imaging techniques such as magnetic resonance imaging and positron emission tomography has a useful role as well. Single-photon emission computed tomography has been found to be useful by several groups (see also* J. Rheumatol. *25:576–582, 1998).*
15. Baca, V., et al. Favorable response to intravenous methyl-prednisolone and cyclophosphamide in children with severe neuropsychiatric lupus. *J. Rheumatol.* 26:432–439, 1999.
    A small sample size (7), but data reflect the common practice of aggressive therapy to treat this disorder among pediatric rheumatologists.

Systemic Manifestations: Miscellaneous

16. Male, C., et al. Clinical significance of lupus anticoagulants in children. *J. Pediatr.* 134:199–205, 1999.
    A retrospective study of 95 patients with lupus anticoagulant. Most patients were symptomatic, and the finding incidental. However, 10% had bleeding tendencies, while 5% had thrombotic events. Only 1 patient had SLE. See also Manco-Johnson, M. Antiphospholipid antibodies in children. Semin. Thromb. Hemost. *24:591–598, 1998, and Ravelli, A., and Martini, A. Antiphospholipid antibody syndrome in pediatric patients.* Rheum. Dis. Clin. North Am. *23:657–676, 1997.*
17. Lockshin, M. Which patients with anti-phospholipid antibody should be treated? *Rheum. Dis. Clin. North Am.* 19:235–247, 1993.
    An excellent review of the interpretation, the clinical manifestations, and treatment of antiphospholipid antibody syndrome by an expert in this field. See Medicine *77:195–207, 1998, for a description of catastrophic antiphospholipid syndrome, which has a high mortality rate.*
18. Moder, K., Miller, T., and Tazelaar, H. Cardiac involvement in systemic lupus erythematosus. *Mayo Clin. Proc.* 74:275–284, 1999.
    The various components of the heart: the coronory arteries, pericardium, myocardium, and valves may be involved in lupus. Antiphospholipid syndrome may lead to significant coronary and valvular diseases. This article is a comprehensive review in this area.
19. Cervera, R., et al Cardiac disease in systemic lupus erythematosus: Prospective study of 70 patients. *Ann. Rheum. Dis.* 51:156–159, 1992.
    Echocardiographic evidence of cardiac involvement was present in 60% of patients, with valvular disease the most frequently seen (44%). Pericardial effusion was present in 27%, and 20% had myocardial involvement. However, the majority of these findings were clinically silent and their significance remains to be determined.
20. Murin, S., Wiedemann, H., and Matthay, R. Pulmonary manifestations of systemic lupus erythematosus. *Clin. Chest Med.* 19:641–665, viii, 1998.
    Pulmonary involvement in SLE includes pleuritis, interstitial lung disease, pneumonitis, pulmonary hemorrhage, and others. Often difficult diagnostic and management problems, which can be fatal without proper intervention. See also Curr. Opin. Pulm. Med. *1:368–375, 1995, and* Rheum. Dis. Clin. North Am. *20:159–193, 1994.*

Therapy

21. Silverman, E., and Lang, B. An overview of the treatment of childhood SLE. *Scand. J. Rheumatol.* 26:241–246, 1997.
    A concise summary of the treatment options available for childhood SLE. However, the authors advocate the use of azathioprine instead of cyclophosphamide in lupus nephritis (see ref. 3). For a review of the basis for use of intravenous cyclophosphamide, see Rheum. Dis. Clin. North Am. *15:455–477, 1989.*
22. Urowitz, M. Is “aggressive” therapy necessary for systemic lupus erythematous? *Rheum. Dis. Clin. North Am.* 19:263–270, 1993.
    *Argues that majority of patients with SLE have mild disease and that aggressive cytotoxic drugs with their potential toxicities are not necessary. More “benign” cytotoxic drugs such as azathioprine and methotrexate are advocated. The companion paper argues that intravenous cyclophosphamide is an effective form of aggressive therapy for the serious complications of lupus (*Rheum. Dis. Clin. North Am. *19: 249–262, 1993).*
23. The Canadian hydroxychloroquine study group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N. Engl. J. Med.* 324:150–154, 1991.
    Hydroxychloroquine can maintain clinical quiescence in mild SLE. It has been useful in treating skin and mucosal lesions, and musculoskeletal complaints.
24. Fox, D., and McCune, W. Immunosuppressive drug therapy of systemic lupus erythematosus. *Rheum. Dis. Clin. North Am.* 20:265–299, 1994.
    Summarizes the use of cyclophosphamide, azathioprine, and others in the various manifestations of lupus. The short- and long-term toxicities of these drugs are also discussed.
25. Burt, R., et al. Treatment of autoimmune disease by intense immunosuppressive conditioning and autologous hematopoietic stem cell transplantation. *Blood* 92:3505–3514, 1998.
    *The authors are the first North American group to apply this technique to treat autoimmune disorders. The results are especially encouraging in patients with recalcitrant lupus. More data are being collected nationally and internationally to determine the role of this procedure in the treatment of autoimmune disorders. Others have argued that intense immunosuppression is the critical element and that autologous stem cell transplantation is not essential (*Ann. Intern. Med. *129: 1031–1035, 1998).*

Prognosis

26. White, P. Morbidity of childhood systemic lupus erythematosus. In: Woo, P., White, P., and Ansell, B. (eds.). *Pediatric Rheumatology Update.* Oxford, England: University Press, 1990:217.
    A review of several studies on the morbidity and mortality in pediatric lupus, discussing infections, renal diseases, atherosclerosis, CNS involvement, growth abnormalities, and aseptic necrosis as areas clinicians will have to deal with in the management of these patients.
27. Lehman, T. Long-term outcome of systemic lupus erythematosus in childhood. What is the prognosis? *Rheum. Dis. North Am.* 17:921–930, 1991.
    It is interesting to compare the survival rate of studies done for the last 40 years (see Pediatrics *42:37–49, 1968, and* Am. J. Dis. Child. *130:929–933, 1976). Undoubtedly, aggressive therapy in patients with severe disease helps to reduce the mortality rate. A treatment protocol with intravenous cyclophosphamide is suggested. See also* Pediatrics *89:240–246, 1992.*

Lupus-Like Syndromes

28. Rubin, R. Etiology and mechanisms of drug-induced lupus. *Curr. Opin. Rheumatol.* 11:357–363, 1999.
Over 30 medications are associated with drug-induced lupus. Of interest to the pediatrician is diphenylhydantoin-related lupuslike syndrome. Also minocycline and related medications are relevant in pediatric practice (see Semin. Arth. Rheum. *28:392–397, 1999). The possible mechanisms leading to drug-induced lupus are discussed.*
29. Silverman, E., and Laxer, R. Neonatal lupus erythematosus. *Rheum. Dis. Clin. North Am.* 23:599–618, 1997.
Reviews the many clinical manifestations of neonatal lupus. Nice discussions on the maternal autoantibodies (SSA/Ro and SSB/La) and the pathogenesis. Also good pictures of the skin findings.
30. Buyon, J., et al. Autoimmune-associated congenital heart block: Demographics, mortality, morbidity and recurrence rates obtained from a national neonatal lupus registry. *J. Am. Coll. Cardiol.* 31:1658–1666, 1998.
The presence of anti-Ro and anti-La antibodies in a pregnant woman poses significant risk to her unborn child, with congenital heart block a permanent and often fatal outcome. For the cutaneous manifestations of neonatal lupus, see J. Am. Acad. Dermatol. *40:675–681, 1999.*

94. OTHER RHEUMATIC AND VASCULITIC DISORDERS

Lawrence K. Jung

Juvenile rheumatoid arthritis and systemic lupus erythematosus represent at least 90% of all rheumatic diseases (excluding acute rheumatic fever) in childhood, but there are a few other disorders that deserve mention.

Dermatomyositis and polymyositis are distinct manifestations of what is probably a single disease entity. Polymyositis, the more common of the two in adults, is a disease of chronic muscle inflammation; dermatomyositis, at least 10 times more common than polymyositis in children, is the same disease with the addition of a characteristic rash. Females predominate and the usual age of onset in children is 5–8 years.

Most children present with insidious symmetrical muscle weakness, which may be manifested as “clumsiness,” difficulty climbing stairs, or, occasionally, an apparent behavior problem in a child who can no longer dress himself or participate in active play. Weakness is generally greater in proximal muscles, and in abductors and extensors. Muscles are sometimes painful and may be swollen or atrophic. Flexion contractures develop rapidly in children and may already be present at the time of diagnosis. Involvement of palatal and respiratory muscles, manifested by a voice change or difficulty swallowing, is ominous; aspiration and respiratory failure may result.

The rash of dermatomyositis typically begins as an erythematous discoloration (with purplish or “heliotrope” hue) and edema of the eyelids; the scaly eruption soon spreads to involve the periorbital and malar areas, and the extensor surfaces of the knees, elbows, and digits (Gottron sign). In case of a prolonged active disease, calcinosis can develop in these sites. The skin lesions are but one sign of the diffuse vasculitis typical of dermatomyositis in children; angiopathic changes may be seen in the nailfolds with periungual erythema, dilated capillary loops and telangiectasia. Similar changes in the gastrointestinal tract may result in perforation or hemorrhage.

Dermatomyositis is diagnosed on the basis of the clinical syndrome of muscle pain and weakness coupled with the typical rash, plus elevated levels in the serum of one or more muscle enzymes (creatine phosphokinase, aldolase, aspartate aminotransferase [previously serum glutamic-oxaloacetic transaminase], lactate dehydrogenase). The sedimentation rate, although often elevated, may be normal in the presence of active disease. Antinuclear antibodies and rheumatoid factor are often absent, but other autoantibodies may be present. Myositis-specific autoantibodies directed against tRNA synthetases define a subset of patients (antisynthetase syndrome) who may develop interstitial lung disease. Magnetic resonance imaging with short tau inversion recovery images is useful for diagnosis and as a guide for muscle biopsy. The electromyogram shows a characteristic, though not diagnostic, mixture of myopathic and neuropathic abnormalities. Histologic studies of muscle reveal nonspecific changes; muscle biopsy is seldom necessary for diagnosis. Differential diagnostic consideration includes systemic lupus erythematosus, other connective tissue diseases, bacterial and viral myositis, steroid-induced myopathy, Guillain-Barré syndrome, and muscular dystrophy.

Treatment includes daily administration of high-dose steroids (1.5–2.0 mg/kg/d of prednisone) until remission is achieved, as indicated by clinical improvement, usually paralleled by the return of muscle enzyme levels to normal. Steroid administration is then tapered and continued at a low dose for 1–2 years. High-dose pulse methylprednisolone may reduce the overall daily prednisone requirement. In cases where steroid resistance or toxicity becomes a problem, methotrexate, cytotoxic drugs, and intravenous g-globulin infusion may be useful. Physical therapy is necessary to increase muscle strength and to prevent or ameliorate flexion contractures.

Death from respiratory failure, gastrointestinal perforation and hemorrhage, and infection occurred in 35–50% of patients prior to the advent of steroids; the majority of survivors were crippled. Now with prednisone and physical therapy, more than 80% of patients recover without sequelae and the mortality is less than 10%. Although most children are free of disease within 2 years after diagnosis, some will go on to have a chronic or relapsing course for several more years, requiring continuous steroid and immunosuppressive therapy. Almost 30% of patients have scattered subcutaneous calcifications unresponsive to chelation therapy; the calcinosis may be somewhat disabling but usually does not correlate with ultimate prognosis. Of adults with dermatomyositis, 20% are found to have an underlying malignancy; this association does not occur in children.

Scleroderma, a very unusual disease in childhood, involves dermal alterations resulting in “hard skin.” In children, the disease most often takes the form of localized scleroderma, which may occur either as morphea or as linear scleroderma. Morphea is a well-circumscribed, variably pigmented, shiny patch of initially edematous, then indurated, and ultimately atrophic skin. Although there may be multiple areas in a single patient, their effect is generally cosmetic only. In contrast, the lesions of linear scleroderma are far more extensive, usually involve underling tissue down to bone, and frequently cross joints, resulting in contractures and limb atrophy. Associations with uveitis and seizures have been reported in cases involving face and scalp (*en coup de sabre*). Thus, localized scleroderma, while not life-threatening, can cause marked dysfunction. Progression of the lesions is variable; complete healing is rare. There is no proven effective treatment, but D-penicillamine and cytotoxic drugs have been used in selected cases. Methotrexate is considered useful in some cases. Physical therapy can be invaluable in maintaining function. Children with scleroderma, especially of the linear type, may present with synovitis; antinuclear antibodies (nonspecific pattern) and rheumatoid factor are often present, and elevated immunoglobulin levels are common. Progressive systemic sclerosis—diffuse scleroderma with visceral involvement—fortunately is rare in children; the mortality is high, with death generally being the result of pulmonary or myocardial fibrosis.

Eosinophilic fasciitis, characterized by pain and induration of the skin from inflammation of deep fascia in association with marked eosinophilia and hypergammaglobulinemia, may resemble scleroderma. Eosinophilia-myalgia syndrome and toxic oil syndrome also shared clinical features similar to eosinophilic fasciitis and scleroderma. Contaminants in the L-tryptophan and rapeseed oil were responsible in these syndromes.

Mixed connective tissue disease, an “overlap” syndrome, combines features of systemic lupus erythematosus, progressive systemic sclerosis, and polymyositis, and is characterized serologically by the presence of antibodies to ribonucleoprotein (U1)snRNP. Over time, however, most of these patients have a clinical course similar to that seen in one of their “component” diseases, usually systemic sclerosis. It is probably most important to recognize that many patients with rheumatic disorders are not easily classified into a specific disease category and are perhaps better considered to have an undifferentiated connective tissue disease, rather than an entirely new syndrome.

The general category of rheumatic disorders also includes syndromes characterized by specific patterns of primary vasculitis. The pathologic process is one of inflammation and necrosis of blood vessels, and the nature of the resulting syndrome depends on the size and location of the vessels involved. Primary vasculitic syndromes in children include Henoch-Schönlein syndrome (see Chap. 95); Wegener granulomatosis, with necrotizing lesions of the face, respiratory tract, and kidneys; polyarteritis nodosa, characterized by fever, arthritis, subcutaneous nodules, and severe hypertension; and infantile polyarteritis nodosa, a uniformly fatal disorder that is clinically and pathologically indistinguishable from fatal cases of Kawasaki syndrome (see Chap. 97).

Textbook Review

1. Cassidy, J., and Petty, R. (eds.). *Textbook of Pediatric Rheumatology* (3rd ed.). Philadelphia: Saunders, 1995.
   Excellent chapters on dermatomyositis, scleroderma, and systemic vasculitis.

Dermatomyositis

2. Rider, L., and Miller, F. Classification and treatment of the juvenile idiopathic inflammatory myopathies. *Rheum. Dis. Clin. North Am.* 23:619–655, 1997.
   A detailed description of the various types of juvenile dermatomyositis and a good summary of treatment options for this disorder.
3. Pachman, L., et al. Juvenile dermatomyositis at diagnosis: Clinical characteristics of 79 children. *J. Rheumatol.* 25:1198–1204, 1998.
   Results of a national registry for juvenile dermatomyositis are described. Twenty-three percent developed calcinosis correlated with delay in therapy. While all patients had muscle weakness,

10% had normal muscle enzymes.

4. Eisenstein, D., Paller, A., and Pachman, L. Juvenile dermatomyositis presenting with rash alone. *Pediatrics* 100:391–392, 1997.
   Also known as amyopathic dermatomyositis, the skin disorder resembles that of dermatomyositis but without the muscle involvement. The usual recommendation is to be conservative in treatment.
5. Reed, A., et al. Immunogenetic studies in families of children with juvenile dermatomyositis. *J. Rheumatol.* 25:1000–1002, 1998.
   The molecular genetics of juvenile dermatomyositis is just starting to be understood. The authors report association of HLA-DQA1-0501. See also Hum. Immunol. *60:255–258, 1999, in which the same investigators report that HLA-DMA-0103 and HLA-DMB-0102 alleles are increased in these patients.*
6. Ng, Y., Ouvrier, R., and Wu, T. Drug therapy in juvenile dermatomyositis: Follow-up study. *J. Child Neurol.* 13:109–112, 1998.
   A summary of the treatment options for dermatomyositis. These authors advocate the use of azathioprine as a second-line drug; others would recommend methotrexate. See next reference.
7. Miller, L., et al. Methotrexate treatment of recalcitrant childhood dermatomyositis. *Arthritis Rheum.* 35:1143–1149, 1992.
   Patients with steroid-resistant disease are a challenge to the clinicians. This retrospective study suggests that oral methotrexate may be of benefit in this situation. See also ref. 19.
8. Roifman, C., et al. Reversal of chronic polymyositis following intravenous immune serum globulin therapy. *J.A.M.A.* 258:513–515, 1987.
   *Patients with steroid resistance or toxicity showed remarkable response to intravenous g-globulin, documented with clinical and serological measurements. Similar findings are reported in adults (*Am. J. Med. *91:162–168, 1991).*
9. Collison, C., et al. Juvenile dermatomyositis and polymyositis: A follow-up study of long-term sequelae. *South. Med. J.* 91:17–22, 1998.
   Ten years after onset of symptoms, half of the patients continue to have residual physical findings. Dermatological findings are common, and fibrotic changes are found in the muscle groups. However, these patients have good muscle functioning and can lead productive lives. See also Shehata, R., et al. Juvenile dermatomyositis: Clinical profile and disease course in 25 patients. Clin. Exp. Rheumatol. *17:115–118, 1999, and Bowyer, S., et al. Childhood dermatomyositis: Factors predicting functional outcome and development of dystrophic calcification.* J. Pediatr. *103:882–888, 1983. The most important predictor of prognosis is early and adequate steroid therapy.*

Scleroderma

10. Lehman, T. Systemic and localized scleroderma in children. *Curr. Opin. Rheumatol.* 8:576–579, 1996.
    A comprehensive summary of clinical presentation of scleroderma in children. Linear scleroderma is by far the more common and less disabling of the various forms of disorders. However, it can be a significant cosmetic problem. See also Laxer, R., and Feldman, B. General and local scleroderma in children and dermatomyositis and associated syndromes. Curr. Opin. Rheumatol. *9:458–464, 1997.*
11. Emery, H. Pediatric scleroderma. *Semin. Cutan. Med. Surg.* 17:41–47, 1998.
    An excellent review of the types of scleroderma, epidemiology, and etiologic factors in children. Management of this problem is difficult, compounded by the lack of controlled studies with significant numbers of patients. A good discussion on the psychosocial impact of the disease in children. See also Curr. Opin. Pediatr. *8:318– 324, 1996.*
12. Nelson, J., et al. Microchimerism and HLA-compatible relationships of pregnancy in scleroderma. *Lancet* 351:559–562, 1998.
    Because chronic graft-versus-host disease presents a clinical picture similar to scleroderma, the possibility exists that persistence of fetal cells in women may result in scleroderma. This report lends support to this hypothesis as scleroderma patients have a higher incidence of persistence of male DNA than controls. While this finding is of interest, other mechanisms must be in play in children and in male patients.
13. Fujita, Y., et al. Systemic sclerosis in children: A national retrospective survey in Japan. *Acta Paediatr. Jpn.* 1997;39:263–267.
    In a 10-year period in Japan, 16 patients with systemic sclerosis were found. Mean age of onset was 8 years when mean age of diagnosis was 10. Eighty percent had Raynaud's phenomenon, while skin and pulmonary symptoms were common. Eighty percent had antinuclear antibodies and 50% had anti–Scl-70 (topoisomerase I) antibodies. This study demonstrates that scleroderma is rare in children, but the clinical manifestations are similar to those in adults.
14. Varga, J., and Kahari, V. Eosinophilia-myalgia syndrome, eosinophilic fasciitis, and related fibrosing disorders. *Curr. Opin. Rheumatol.* 9:562–570, 1997.
    Syndromes related to scleroderma with similar pathologic findings; abnormal cytokine releases may lead to persistent fibrotic changes. Better understanding of these disorders may lead to an understanding of the pathogenesis of scleroderma as well.

Vasculitis

15. Cuttica, R. Vasculitis in children: A diagnostic challenge. *Curr. Probl. Pediatr.* 27:309–318, 1997.
    A summary of the clinical spectrum of the this rather heterogenous group of disorders. See also Curr. Opin. Rheumatol. *8:477–484, 1996.*
16. Blanco, R., et al. Cutaneous vasculitis in children and adults. Associated diseases and etiologic factors in 303 patients. *Medicine* 77:403–418, 1998.
    A comparative study of cutaneous vasculitis in children and adults. Henoch-Schönlein purpura and Kawasaki disease are the predominant vasculitic diseases in children, whereas hypersensitivity vasculitis is the predominant in adults, along with other systemic forms of vasculitis. (See also Chap. 95 and Chap. 97.)
17. Dillon, M. Childhood vasculitis. *Lupus* 7:259–265, 1998.
    A good discussion of the less common but severe forms of vasculitis, such as Wegener granulomatosis, microscopic polyarthritis, primary angiitis, and others. The author draws his experience from the Hospital for Sick Children in London. See also Woo, P., White, P., and Ansell, B. (eds.). Paediatric Rheumatology Update. *Oxford, England: University Press, 1990:227–242.*
18. Rottem, M., et al. Wegener granulomatosis in children and adolescents: Clinical presentation and outcome. *J. Pediatr.* 122: 26–31, 1993.
    Most aspects of Wegener granulomatosis are similar in children and adults, although subglottic stenosis and nasal deformity are more frequent in children. Although 89% of patients responded to therapy (steroid and cyclophosphamide), they have significant morbidity and mortality.
19. Langford, C., Sneller, M., and Hoffman, G. Methotrexate use in systemic vasculitis. *Rheum. Dis. Clin. North Am.* 23:841–853, 1997.
    Methotrexate is found to be very useful in the treatment of vasculitis, including Wegener granulomatosis and Takayasu arteritis. Its use in children with Wegener granulomatosis is documented in J. Pediatr. *129:604–607, 1996. Read also Hoffman's excellent editorial discussion on the standard of therapy for Wegener granulomatosis in* Arthritis Rheum. *40:2099–2104, 1997.*
20. Ozen, S., et al. Diagnostic criteria for polyarteritis nodosa in childhood. *J. Pediatr.* 120:206–209, 1992.
    A retrospective analysis of 31 Turkish children with polyarteritis nodosa to define diagnostic criteria for this disorder. Results from treatment with either corticosteroid alone or in combination with daily cyclophosphamide were similar; significant mortality was seen.

Mixed Connective Tissue Disease

21. Sharp, G., et al. Mixed connective tissue disease: An apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *Am. J. Med.* 52:148–159, 1972.
    The original paper on mixed connective tissue disease (MCTD), with a description of 25 patients. (For a long-term follow-up of these patients, revealing their tendency to follow the course of a specific rheumatic disorder, see Medicine *59:239–248, 1980.)*
22. Michels, H. Course of mixed connective tissue disease in children. *Ann. Med.* 29:359–364, 1997.
    An extensive review of 224 patients reported in the literature, indicating that the majority of these patients develop long-term problems: sclerodermalike skin and Raynaud's phenomenon in 86%, restrictive lung disease in 54%, renal involvement in 47%, arthropathy in 29%, and esophageal dysmotility in 29%. Disease-related mortality was 8%. Thus, while not as disabling as scleroderma or lupus, MCTD remains a management challenge. See also Lupus *5:221–226, 1996, and* J. Pediatr. *122:191–197, 1993.*

95. HENOCH-SCHÖNLEIN PURPURA

Kenneth B. Roberts

The diagnostic designations *Henoch-Schönlein purpura* (HSP) and *anaphylactoid purpura* call attention to the purpuric rash, but it has been the association of the rash with visceral manifestations that has fascinated clinicians for over a century. Schönlein (1837) is credited with relating joint findings to the rash; Henoch added the gastrointestinal complaints (1874) and, incidentally, noted renal involvement (1899). Since Schönlein's report preceded Henoch's, many authors prefer the designation Schönlein-Henoch purpura. As early as 1801, however, Heberden had described the case of a 5-year-old boy with all the cardinal features of HSP: skin, gastrointestinal, renal, and joint involvement, and a course marked by recurrences. The diagnosis of HSP remains the province of the clinician with knowledge of the individual features, since there is no pathognomonic laboratory test.

“Palpable purpura” is considered a sine qua non by most authors, but the lesions first appear as pink, rounded papules, most commonly on the extensor surfaces of the limbs, the buttock, and lower part of the back, and only seldom on the face; they may blanch at this stage. Soon they are red, and by 24 hours are flat and purpuric. As the lesions clear over 3–4 days, the purple color fades to brown and yellow, with residual discoloration persisting for up to 10–14 days. Petechiae or ecchymoses occur in some patients coincident with the purpura but are by no means universally present; more common is urticaria, which precedes the purpura in one third of cases. Subcutaneous edema, particularly of the scalp and eyelids, can be a striking feature of HSP, occurring particularly in younger patients; it is frequently painful. This presentation is usually not associated with severe renal involvement and occurs independent of proteinuria and edema elsewhere on the body. Although rash is present in virtually 100% of cases (essentially by definition), it is the first sign in only one half and may not be purpuric.

Joint involvement is one of the major features of HSP, but the pain and swelling are actually *peri*articular rather than in the joint. The soft tissues around the knees and ankles are most frequently involved. Some disability ascribed to “joint pain” is found in most children with HSP (70–80%) and, particularly when combined with an urticarial rash (mistakenly thought to be erythema marginatum), may suggest the diagnosis of rheumatic fever. The arthralgia is not of the same intensity as that in acute rheumatic fever, however, and the correct diagnosis can usually be made by careful serial observations and attention to clinical detail.

Abdominal pain is as common a finding as joint pain, but the two do not necessarily appear together. Melena occurs in one half of the patients and is usually associated with pain; the stools test positive for occult blood in another 25%. Significant blood loss occurs in 5–15% of children with HSP. Vomiting and hematemesis occur with about the same incidence. Between 3% and 6% of patients have intussusception; this potentially lethal complication can be difficult indeed to diagnose and is made no easier by the ileoileal location in 50% of the reported cases (75% of “usual” intussusceptions in children are ileocolic and therefore easily detected by barium enema). When intussusception occurs in HSP, operative intervention with resection of bowel is commonly required.

Renal manifestations are apparent in about 50% of patients with HSP, but in addition, some children without overt findings show abnormalities on biopsy findings. Renal involvement is usually detected after the onset of skin and joint complaints; less than one half of the patients with urinary findings are identified in the first week of illness, and “new” abnormalities may appear 4–6 weeks after the onset of illness. Hematuria occurs in virtually all children who evidence renal involvement and is more commonly microscopic than gross (1.5:1.0). Children who have only microscopic hematuria have minor focal lesions on biopsy specimens and do not appear to have an impaired prognosis. Rapidly progressive nephritis, nephrotic syndrome, and “nephritis syndrome” (i.e., edema, hypertension, azotemia, urinary abnormalities) are likely to be the manifestations of a proliferative glomerulonephritis of greater import.

While skin, joints, gastrointestinal tract, and kidneys may all be involved (as in Heberden's patient), there is a tendency to “subsyndromes,” based on the age of the patient. Younger children (around age 2) are more likely to have edema and to be free of the serious gastrointestinal and renal complications, which, in turn, are more likely to be present in patients over age 5. There is debate as to whether infants who manifest only the rash and edema have HSP or a different vasculitis named “acute hemorrhagic edema of infancy” (AHEI)

The laboratory is of assistance only in “ruling out” other diagnostic possibilities. Thrombocytopenia is not seen in this syndrome, and the bone marrow, prothrombin time, partial thromboplastin time, and bleeding time are all normal. Renal failure may develop, as evidenced by azotemia and elevated serum creatinine concentration, but the serum complement level is not depressed. The erythrocyte sedimentation rate is generally normal or only slightly increased.

Examination of biopsy specimens of the skin reveals leukocytoblastic vasculitis with neutrophil deposition in venules and arterioles (the former more frequently than the latter); immunofluorescence reveals immunoglobulin A (IgA) deposition. The presence of IgA deposits in the skin is used to distinguish HSP from AHEI. The renal histologic findings correlate well with the degree of proteinuria: The minimal-change pattern is present in mild cases, and a diffuse proliferative glomerulonephritis is present in severe cases. Again, immunofluorescence reveals IgA; its presence in glomeruli helps to distinguish HSP from other forms of nephritis such as poststreptococcal glomerulonephritis, once thought to be related to HSP. The biopsy appearance alone suggests IgA nephropathy (Berger disease), but the other clinical manifestations distinguish HSP. The appearance of fibrotic crescents affecting many glomeruli is a marker for progressive renal disease.

Infections commonly precede HSP, but no relationship has been established. Specifically, the group A streptococcus does not appear to play a causative role in HSP, as was once thought, nor has any other single infectious agent been implicated. Allergy was thought to be the etiology by Sir William Osler and has been proposed as causative in a multitude of case reports; a lack of understanding of possible mechanisms is maintained in the designation “anaphylactoid purpura.” Hypersensitivity vasculitis is more common in adults than in children and usually can be distinguished from HSP by the pattern of organ involvement.

The course of HSP is marked by relapses and remissions in nearly one half of the patients; the rash seems particularly to recur within the first 6 weeks. The joint findings leave no residua and so are of little concern. Similarly, if intussusception or massive hemorrhage does not complicate the acute course, the gastrointestinal manifestations usually resolve completely; some patients will have evidence of small-bowel narrowing later on. Of greatest consequence are the urinary abnormalities. These commonly appear after the first week, as noted, so the urine should be examined at intervals during the first few months after onset. Progressive proteinuria indicates the development of significant glomerulonephritis. The results of follow-up studies suggest that 25% of patients with HSP have chronic urinary findings, but most do well. An assessment at 2 years after the acute episode appears reliable in gauging prognosis, since by that time the ultimate course is more or less apparent, with further deterioration rare and further improvement slow. Follow-up reveals that even in the group with the worst prognosis (“nephritic nephrotics”), 60% do well. Overall, 1–4% progress to end-stage renal disease.

Since the cause is unknown and the course variable, treatment is empiric, symptomatic, and supportive. Corticosteroids continue to enjoy favor for the treatment of abdominal manifestations in the hope of reducing edema and thus preventing intussusception, but data to support this therapy are not conclusive. Corticosteroids may well be effective in hastening the elimination of the edema seen in the younger children. Multiple therapeutic approaches to treating the chronic nephritis of HSP have been proposed and reported, but there is no consensus regarding the most effective regimen. Available data suggest a possible role for high-dose corticosteroids as a preventive measure.

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3. Robson, W., and Leung, A. Henoch-Schönlein purpura. *Adv. Pediatr.* 41:163–194, 1994.
   An encyclopedic catalog (31 pages, 152 references). See also ref. 5.

Series

4. Allen, D., Diamond, L., and Howell, D. Anaphylactoid purpura in children (Schönlein-Henoch syndrome). *Am. J. Dis. Child.* 99:833–854, 1960.
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5. Saulsbury, F. Henoch-Schönlein purpura in children. Report of 100 patients and review of the literature. *Medicine* 395–409, 1999.
   A more modern series than ref. 4, but the real value of this article is as a current review.

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   Surgeons consulted on 47 of 183 children and operated on 10. Indications for laparotomy: nonreducible intussusception, intestinal perforation, and intestinal necrosis.
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   Not only can ultrasonography identify intussusception, it can distinguish between "loose" (which may spontaneously reduce) and "tight" (which requires operative reduction) intussusception!
10. Rosenblum, N., and Winter, J. Steroid effects on the course of abdominal pain in children with Henoch-Schönlein purpura. *Pediatrics* 79:1018–1021, 1987.
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96. RHEUMATIC FEVER

Kenneth B. Roberts and Conrad J. Clemens

The incidence of rheumatic fever has declined dramatically over the past century in this country, but it has not been eliminated as a source of morbidity and mortality, particularly in the third world. Outbreaks in the 1980s suggested the possibility of a resurgence of rheumatic fever in the United States, but these outbreaks appear to have represented localized clusters rather than a nationwide return of the disease to its former levels.

Acute rheumatic fever is a nonsuppurative sequela of group A, b-hemolytic streptococcal pharyngitis, with onset 2–4 weeks after the acute infection; rheumatic fever does not develop following streptococcal skin infection (impetigo). In the 1950s, the incidence of rheumatic fever following untreated exudative streptococcal pharyngitis in military recruits was 3%, but under usual conditions in the community was much lower, 0.3% or less. School-aged children are most frequently affected; the disorder is uncommon in infants under 3 years of age and exceedingly rare under the age of 18 months. Rheumatic fever is more common in the lower socioeconomic groups. Certain families seem to be at particular risk for the development of rheumatic fever, and patients who have had one bout of the disease are at great risk for another.

The exact pathogenesis of rheumatic fever remains uncertain, but persistence of streptococci appears to be necessary. Eradication of the organism (as with penicillin therapy) greatly reduces the incidence.

Rheumatic fever generally presents in one of three ways: with the insidious development of carditis; with an acute, explosive onset of polyarthritis; or, least commonly, with chorea. The clinical findings may suggest a number of alternative diagnoses, including juvenile rheumatoid arthritis, systemic lupus erythematosus, serum sickness, sickle cell disease, viral pericarditis or myocarditis, leukemia, Henoch-Schönlein syndrome, or bacterial endocarditis.

There is no laboratory test specific for acute rheumatic fever; the diagnosis is still based on guidelines proposed by T. Duckett Jones more than 50 years ago and periodically revised. The current Jones criteria require evidence of a preceding streptococcal infection, together with the presence either of two major criteria or of one major criterion and two minor criteria. The five major criteria are carditis, polyarthritis, erythema marginatum, subcutaneous nodules, and chorea. *Carditis* is almost always associated with a mitral regurgitation murmur; in the absence of such a murmur (even when myocarditis or pericarditis is present), the diagnosis of acute rheumatic fever is questionable. Echocardiography may reveal evidence of carditis and valvular insufficiency even in the absence of clinical signs such as murmur. It is advised not to base a diagnosis of acute rheumatic fever on such findings in the absence of a murmur, however, since the technique may be too sensitive; some normal children can be demonstrated to have mitral regurgitation by echocardiography. Prolongation of the PR interval on the electrocardiogram (ECG) is common but by itself is not sufficient evidence of rheumatic carditis and is considered a minor criterion. The *polyarthritis* of acute rheumatic fever is nearly always migratory and is objective arthr*itis*; arthr*algia* is not a major criterion. Joint pain is generally severe but responds dramatically to aspirin; failure of articular symptoms to improve promptly with aspirin brings the diagnosis of acute rheumatic fever into question. *Erythema marginatum* is an evanescent, pink rash with round margins and clear centers, without pruritus or induration; it is said not to occur on the face. *Subcutaneous nodules* develop on extensor surfaces of the limbs and in the occipital region; they are nontender and freely movable and do not elicit a reaction in the overlying skin. Erythema marginatum and subcutaneous nodules are not specific for rheumatic fever, and nodules in particular usually are not present unless the patient has carditis. *Chorea* is a feature of rheumatic fever that may occur up to 6 months after the initiating streptococcal infection and in the absence of other major manifestations of the disease.

The minor criteria are of two types, clinical and laboratory. The clinical criteria include arthralgia and fever. Laboratory criteria are elevation of acute-phase reactants (increased erythrocyte sedimentation rate and the presence of C-reactive protein) and prolongation of the PR interval on the ECG.

Documentation of the preceding streptococcal infection is usually accomplished serologically, since most cases of rheumatic fever occur 2–4 weeks after acute infection, by which time the throat culture is negative in 75% of patients. Antibody titers against an extracellular product of the streptococcus (e.g., antistreptolysin O) are elevated in 80–85% of patients; measurement of antibodies against two additional extracellular products (e.g., antihyaluronidase, anti-DNAase) permits identification of 95% of patients who have had a previous streptococcal infection.

Treatment is empiric and consists of the following: rest, to decrease demands on the myocardium and relieve joint pain; pharmacologic agents, to control inflammation; and antibiotics, to prevent the recurrence of streptococcal infections. Bed rest has not been studied scientifically but is recommended for children with severe carditis; children with arthritis limit their activity themselves, according to the degree of joint inflammation. The anti-inflammatory agent used most frequently is aspirin, with steroids reserved for patients with acute severe carditis. Treatment with penicillin should begin with the diagnosis and should be continued in a prophylactic regimen of injections of benzathine penicillin every 3 or 4 weeks; alternatively, if compliance can be ensured, penicillin may be given twice daily by mouth. Prophylaxis is a particularly important aspect of therapy because rheumatic fever can recur, often more severely.

It is said that rheumatic fever either “bites the heart and licks the joints” or the reverse. The prognosis for future heart disease is worse in patients with carditis during the initial episode, those with a family history of rheumatic heart disease, and those with repeated attacks, particularly in the first year after the acute disease. Chronic arthritis is not a sequela of rheumatic fever.

Prevention of rheumatic fever by antibiotic treatment of streptococcal pharyngitis is a limited approach because in only one third of patients in whom rheumatic fever develops is the preceding sore throat of sufficient symptomatic magnitude to cause the parents or the patient to seek medical attention. More specific strategies do not appear possible at present, however, since the pathogenesis of rheumatic fever remains obscure. Efforts to develop an effective streptococcal vaccine (that will not itself cause rheumatic fever) continue.

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97. KAWASAKI SYNDROME AND TOXIC SHOCK SYNDROME

Kenneth B. Roberts

Both Kawasaki syndrome (KS) and toxic shock syndrome (TSS) were identified and described in the past few decades. In both, the diagnosis is based on meeting a set of criteria rather than on results of a specific laboratory test. Some of the clinical features overlap, such as fever, rash, dilatation of conjunctival vessels, and injected oral mucosa with strawberry tongue. Occasionally, a child will have an illness that meets the diagnostic criteria for both disorders, and the clinician must exercise knowledge of details of the individual features and considerable judgment to sort out the two and select a course of treatment. The cause of TSS is known; the cause of KS is not.

In the early 1960s, Dr. Tomisaku Kawasaki in Japan recognized what he considered to be a new syndrome, characterized by six clinical features: (1) high, persistent fever; (2) prominence of conjunctival vessels; (3) changes in oropharyngeal mucous membranes; (4) changes of the hands and feet; (5) rash; and (6) cervical lymphadenopathy. The syndrome was designated “mucocutaneous lymph node syndrome” and was soon accepted as being of epidemic proportions in Japan, where 6,000 children are affected annually, a rate exceeding 1 per 1,000 children. Though the attack rate is highest in Japan, the disorder is found worldwide.

On the basis of clinical features, results of laboratory tests, and histologic examination of selected tissues, KS appears to be a triphasic disease. Phase I is dramatic clinically, marked by high fever, irritability, and the constellation of findings listed above. Attention to clinical detail is critical in establishing the diagnosis: (1) The fever begins high and remains high for 5 or more days; antipyretics may reduce the temperature, but they usually do not bring it all the way down to normal. (2) The conjunctival vessels are prominent, but there is no exudate or “pink eye.” (3) The lips, mouth, and pharynx are injected; a strawberry tongue is present in 75%. (4) The hands and feet are edematous and indurated; erythema extends to the wrists and ankles. (5) The rash generally occurs on the trunk. It may be morbilliform, scarlatiniform, or erythema multiforme; it is not vesiculobullous, however, and does not form crusts. (6) Lymphadenopathy is the least frequent of the six clinical features and generally affects a single cervical node rather than being generalized. Additional features include extreme irritability, a desquamative perineal rash, arthralgia or arthritis in 30–50%, diarrhea, aseptic meningitis, uveitis, and, less commonly, hydrops of the gallbladder. Laboratory findings are nonspecific: a leukocytosis with “shift to the left,” normal platelet count, elevated sedimentation rate, and pyuria (with sterile urine culture). During this phase of the illness, carditis and arrhythmia may be present, though they are generally asymptomatic.

After 5–10 or more days, the fever subsides, and desquamation of the fingertips begins, ushering in phase II. Although the patients appear to have recovered clinically, this is the period of greatest risk, as coronary aneurysms develop, the platelet count rises, and coronary thrombosis becomes a threat. Virtually all children who develop aneurysms do so within 1 month after onset of disease. The platelet count and sedimentation rate usually return to normal by 6–8 weeks, and convalescence ensues (phase III).

The diagnosis is made on clinical grounds both by inclusion and by exclusion; that is, the characteristic features of KS must be present (fever plus four of the other five features), and other conditions that might provide an explanation for the illness should be excluded (by clinical or laboratory findings). Disorders that need to be considered include scarlet fever, TSS, measles, leptospirosis, Rocky Mountain spotted fever, juvenile rheumatoid arthritis, enteroviral infection, and systemic lupus erythematosus. Occasionally, patients do not “fit the criteria” precisely, but a better alternative diagnosis is not readily apparent. At present, it seems prudent to manage these children during the first several weeks after onset of illness as though they had KS, because cardiac complications can occur in this group.

Before the introduction of intravenous g-globulin (IVGG) treatment, approximately half of the children with KS had echocardiographic evidence of coronary artery abnormalities, with a peak incidence occurring approximately 2–3 weeks after onset. The majority had simple dilatation or fusiform swelling that regressed, but some had saccular aneurysms; aneurysms larger than 8 mm in diameter proved to be of particular concern. At 4–6 weeks, between 20% and 25% still had abnormal echocardiograms (now 2.4% after IVGG treatment); the rate declined to approximately 1% by 1 year.

Initial fatality rates approached 2.0%; more recent surveys document a rate of less than 0.5%. Death is most common in the first 2 months, but late “sudden deaths” are well described. Long-term sequelae include coronary stenosis and ischemic heart disease.

The cause of KS has not been determined. No infectious agent has been incriminated directly, and many favor the possibility of a toxin from a bacterium such as *Staphylococcus aureus*. Other hypotheses include KS representing a hypersensitivity reaction to an unidentified agent.

Since KS is histologically indistinguishable from infantile polyarteritis nodosa, treatment with corticosteroids appeared logical. Early studies suggested that steroid therapy resulted in an increased number of aneurysms when compared with aspirin, however. Aspirin rapidly became the drug of choice, but in the absence of data from controlled clinical trials, there has been disagreement about the optimal dosage. During the acute inflammatory stage, “moderate” (30–60 mg/kg/d) dosage was favored in Japan, but “high” dosage (100 mg/kg/d, or whatever was required to achieve a serum level of 20–30 mg/dL) was generally recommended in the United States. The high dose is particularly useful in children with complaints involving the joints. The controversy has been rendered largely irrelevant by the use of IVGG, which controls phase I signs and symptoms much more effectively than aspirin, generally within a few days. During phase II, the dosage is reduced, commonly to 3–5 mg/kg/d or, simply, one “baby” aspirin (82 mg) per day. Dipyridamole was formerly used as a second drug if large aneurysms are present, but there is no evidence that dipyridamole provides additional benefit to aspirin alone; currently, warfarin is used, if a second drug is considered necessary.

The mainstay of treatment is IVGG, which is infused as early in the course as is feasible (generally between 5 and 10 days after onset of illness) as a single, large dose (2 gm/kg) infusion. It shortens the duration of fever and laboratory evidence of inflammation; more important, it also reduces the incidence of coronary artery abnormalities at 2 and 7 weeks into the illness. Because IVGG accelerates the sedimentation rate directly, this test should not be monitored after IVGG has been infused.

Supportive care of the family is of great importance, particularly because multiple factors tend to make KS such a difficult illness with which to cope: exotic, unfamiliar diagnosis, often made only after other, more common diseases have been proposed; unresponsive, persistent high fever; profound irritability; protracted, apparently progressive course with the development of new signs and symptoms; and the invisible threat of cardiac involvement, “heart attack,” and sudden death.

The designation *toxic shock syndrome* was first used in 1978, when Todd and coworkers reported on a series of seven children between the ages of 8 and 17. The children had a multitude of signs and symptoms, including fever, headache, confusion, prominent conjunctival vessels, rash, watery diarrhea, and oliguria. All had fine desquamation of the areas in which the rash was prominent and peeling of the palms and soles during convalescence. One child died. The investigators studied five of the children prospectively and isolated exotoxin-producing *S. aureus.* Thus, in the original paper, the authors not only identified a new syndrome, but also named it, described its major features and clinical course, and established the cause. Their observations have held up well.

The number of recognized cases in the United States increased dramatically between 1978 and 1980, the vast majority in menstruating women. Once the epidemiologic link to superabsorbent tampons was recognized, control measures were instituted: removal of the incriminated form of superabsorbent tampons from the market and education of menstruating women, including warnings in tampon boxes of remaining brands. The number of cases of menstruation-associated TSS fell; the incidence of cases not associated with menstruation did not, however.

The Centers for Disease Control and Prevention (CDC) case definition for epidemiologic purposes is based on clinical and laboratory findings: (1) fever (temperature

higher than 38.9°C [102°F]); (2) rash (diffuse macular erythroderma); (3) desquamation after 1–2 weeks of illness (especially of palms and soles); (4) hypotension (static or orthostatic); (5) involvement of three or more organ systems (gastrointestinal; musculoskeletal; mucous membranes, including the conjunctivae; renal; hepatic; platelets; and CNS); and (6) no other obvious cause such as sepsis, Rocky Mountain spotted fever, leptospirosis, or measles.

The fever in TSS is not only high but also frequently accompanied by chills. The rash is a blanching, erythematous “glow,” similar to that produced by endotoxin in gram-negative sepsis. Hypotension is not always documented, but many patients note confusion and orthostatic dizziness early in their course; the CDC case definition was revised to accept this history as sufficient to establish hypotension. Of the organ systems involved, as detailed in the case definition, the most prominent are the musculoskeletal (myalgia and arthralgia) and gastrointestinal (vomiting and diarrhea). The muscles generally are tender to touch, and muscle enzyme levels may be elevated in serum. Headache and sore throat are common complaints, with pharyngitis and a strawberry tongue present on physical examination. The prominence of conjunctival vessels is indistinguishable from that seen in KS.

Laboratory findings are nonspecific, such as a leukocytosis with “shift to the left,” or may reflect involvement of multiple organs. Platelet counts frequently are reduced, and azotemia is common.

Toxic shock syndrome is caused by a toxin (or more than one) produced by *S. aureus,* currently designated TSS toxin-1 (TSST-1). The vasodilatation caused by the toxin requires the clinician managing a patient with TSS to provide three or more times the normal fluid requirement to maintain adequate perfusion. An antibiotic effective against staphylococci, generally a semisynthetic penicillin, is administered; the antibiotic does not shorten the clinical course but appears to reduce the incidence of recurrences. Clindamycin may reduce toxin production

Toxic shock syndrome is no longer of epidemic proportions, but sporadic cases continue to occur and require awareness of the diagnosis. Currently, TSS is most likely to occur after operative procedures and childbirth.

In the 1980s, another form of TSS was recognized, due to group A, b-hemolytic streptococcal infection and the elaboration of scarlet fever toxin A. The disease resembles not only TSS, but also what Trousseau described as severe scarlatina a century ago. The basis for the temporal association of rheumatic fever outbreaks, the apparent increase in invasive group A streptococcal infections, and the return of scarlet fever toxin A disease is not clear.

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Kawasaki Syndrome: Reviews

2. Melish, M. Kawasaki syndrome. *Pediatr. Rev.* 17:153–162, 1996.
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3. Rowley, A., and Shulman, S. Kawasaki syndrome. *Pediatr. Clin. North Am.* 46: 313–329, 1999.
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4. Rowley, A. Controversies in Kawasaki syndrome. *Adv. Pediatr. Infect. Dis.* 13: 127–141, 1997.
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5. American Heart Association Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. Diagnostic guidelines for Kawasaki disease. *Am. J. Dis. Child.* 144:1218–1219, 1990.
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98. ANEMIA

Chon Lee

Anemia is a pathologic reduction in the red blood cell mass compared with age-matched normal values, and is reflected by decreases in the hemoglobin concentration, hematocrit, and red blood cell number. Hematologic indices in childhood vary with age. Term newborns have a red cell mass that is higher than at any other time of life, an appropriate condition for the low oxygen environment of intrauterine life. A physiologic nadir is expected by the second or third month of life, exaggerated in infants of low birthweight and with a history of perinatal blood loss or hemolysis. Hemoglobin concentration should exceed 11.0 g/dL by 1 year of age and rise to more than 11.9 g/dL by 8 years. Boys have higher levels at all ages, and African-American children have slightly lower levels offset by higher levels of 2,3 diphosphoglycerate. Higher levels are expected in conditions of relative hypoxia (high altitude, cyanotic heart disease, chronic pulmonary disease).

The discovery of anemia in childhood is usually the result of a screening program or an incidental laboratory finding during evaluation of another condition. Occasionally, the parent or child will complain specifically about symptoms of anemia, although these are generally insidious. Clinical features are more likely evident with rapid onset and greater severity of anemia. Parents may note pallor, irritability, anorexia, and pica. During exercise the child may experience fatigue, shortness of breath, and palpitations. With severe anemia, headache, dizziness, and syncope may be complaints. History taking should focus on identifying the etiology or etiologies of anemia. The perinatal history, dietary history, use of medications, and presence of concurrent illness are all important factors. Family history, including ethnic background, is also important. Children of African, Southeast Asian, and Mediterranean descent are more likely to have heritable anemias. A history of jaundice, splenectomy, early cholelithiasis, or cholecystectomy in the patient or family suggests hemolytic disorders.

The physical examination may reveal or identify signs of anemia. Pallor may be evident when hemoglobin levels fall below 9 g/dL and is best appreciated in the conjunctivae, gums, and nailbeds. With levels less than 7 g/dL, the color of palmar creases matches the surrounding skin. In addition to pallor, with severe anemia there may be findings of a hyperdynamic state, including tachycardia, a systolic flow murmur, bounding pulses, and ultimately, congestive failure. There also may be evidence for an underlying pathologic process, including jaundice, splenomegaly, bony anomalies, or signs of nutritional deficiency.

A capillary microhematocrit is a useful screening tool for anemia in an office setting. It has high reliability in detecting anemia and is simple to perform. Many pediatricians screen children for anemia between 9 and 18 months of age. Confirmation of anemia with a second sample is indicated when using this method. For diagnosis of the cause of anemia, a complete blood cell (CBC) count will provide most of the information necessary. The automated CBC includes the red cell indices, white blood cell count with differential, and platelet count. It is important to determine whether anemia occurs in isolation or with involvement of other cell lines. The red cell indices directly measured are the hemoglobin (HGB), mean corpuscular volume (MCV), and red blood cell count (RBC). Calculated indices include the hematocrit (HCT), red cell distribution width (RDW), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). The RDW is a measure of the variability of red cell size, higher values correlating with greater anisocytosis. A manual blood film is necessary to identify abnormalities of red cell morphology including size, shape, and color. Identification of red cell inclusions and a reticulocyte count also require manual reading of the smear. Reticulocytes are immature red cells that contain RNA, synthesize hemoglobin, and require special staining

The MCV and RDW are the most useful indices in categorizing anemias. Categorization of anemia is traditionally by size and morphology of the red cells. Other classifications are by pathophysiology and/or age of the child. The following overview of anemias is organized by pathophysiology with subcategorization by morphology. The two major mechanisms for anemia are (1) inadequate production and (2) premature loss. Inadequate production can be further subdivided into microcytic, macrocytic, and aplastic categories.

Microcytic anemias are the most commonly encountered in childhood. Insufficient heme or globin synthesis will inhibit effective production of hemoglobin and delay cytoplasmic maturation. The MCV is low, the reticulocyte count is low, and the smear is abnormal. Microcytic anemias include iron deficiency, anemia of chronic disease, thalassemias, and lead poisoning.

Historically, iron deficiency has been the most common cause of nutritional deficiency and anemia in childhood. Through the early 1970s the prevalence of iron deficiency anemia in infants was 20–24%. Following the introduction of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) in 1974, and with the availability of iron fortified foods, there has been a marked decline with a current prevalence of 3–5%. Suspicion for iron deficiency as the cause of anemia should be raised by a history of prematurity, inappropriate dietary intake, blood loss (previously or chronically), or rapid growth. Most commonly now, iron deficiency anemia is found in young toddlers and in adolescent females who are athletic, pregnant, or lactating. Iron stores in full-term newborns are sufficient until 4–6 months of age, when a dietary source of iron becomes necessary to increase the hemoglobin mass in proportion to somatic growth. Early introduction of whole cow's milk before 12 months of age and consumption greater than 24 ounces a day is associated with iron deficiency anemia in infants and toddlers. Cow's milk is a poor source of iron, replaces foods with higher iron content, and inhibits iron absorption, and cow's milk protein will induce occult gastrointestinal blood loss in some young children. Although human milk has a lower content of iron than cow's milk, the iron has greater bioavailability. Infant formulas are iron fortified and have modified cow's milk protein or soy protein, which are less likely to cause gastrointestinal bleeding. For older children, the best sources of iron are meats, especially liver, and fish. These heme irons are well absorbed and the absorption is enhanced by anemia. The absorption of nonheme iron is favored with iron deficiency, pregnancy, increased erythropoiesis, and by ingestion of acids (vitamin C) and animal proteins.

Most body iron is contained in hemoglobin, with smaller amounts bound to ferritin and hemosiderin in the reticuloendothelial system, myoglobin in muscle, circulating transferrin, and iron-containing enzymes. Deficiency of iron progresses in stages. In the first stage, tissue iron stores are depleted. Under normal conditions, this correlates directly with a decrease in the ferritin level. At this stage, widening of the RDW to greater than 14.5% develops and the reticulocyte percentage decreases. The second stage is loss of circulating iron. This is evident by a low serum iron level less than 30 µg/dL, low transferrin saturation and/or elevated total iron binding capacity (TIBC). The TIBC reflects the availability of iron-binding sites on transferrin. Overt microcytic anemia is the last stage of iron deficiency following depletion of both marrow stores and circulating iron. There is an association of iron deficiency anemia with developmental delay and behavioral disturbances, including decreased motor activity, social interaction, and attention to tasks, but causality is not proved.

With the recognition of anemia and an appropriate history in a young toddler, it is acceptable to begin an empiric trial of iron as a diagnostic and therapeutic measure. Treatment is 3–6 mg/kg/d of elemental iron. A reticulocytosis can be seen in a few days (4–7) after initiation of treatment. Red cell mass should recover, with an increase in hemoglobin level of 1 g/dL or more following a month of treatment and can be considered confirmatory of iron deficiency. Treatment continues for 2–3 months to replete iron stores. If the anemia fails to respond after a month of iron therapy or if the child is older, it is necessary to entertain other etiologies for anemia. This diagnostic evaluation begins with a CBC to determine if the pattern is different from that of typical iron deficiency. Abnormal indices expected in iron deficiency include a low MCV, MCH, and MCHC, and elevated RDW (i.e., a microcytic, hypochromic anemia with increased variability of red cell size and shape) and an intermediate or low reticulocyte count. Iron studies show a low serum iron, low transferrin saturation, and high TIBC. However, iron studies are subject to diurnal variation and alteration by inflammation. The ferritin level is low even in latent iron deficiency, but during inflammation it has limited utility, since it is elevated as an acute phase reactant. Rarely is it necessary to confirm the absence of iron in the marrow by biopsy.

The second most common cause of anemia in childhood is anemia of chronic disease, more properly described as anemia of inflammation from either acute or chronic disease. Fairly trivial events, including fever, immunizations, and mild viral illness, will induce anemia, as will serious chronic illness. Cytokines mediate the acute phase response. They play an active role during inflammation by decreasing available iron through multiple mechanisms. Red cell survival is shortened by premature removal in the reticuloendothelial system, release of circulating iron is suppressed, and the erythropoietin response is blunted. The anemia is generally mild to moderate, with hemoglobin levels 1–2 g/dL below the lower limit of normal for age. Red cell indices show a microcytic or normocytic anemia with low or normal reticulocyte count. Iron studies will show results similar to those seen in iron deficiency, with low serum iron and low transferrin saturation; however, the TIBC is

generally low as well. The serum iron level is inversely proportional to the erythrocyte sedimentation rate and the serum ferritin is elevated, indicating inflammation and/or iron repletion. The best course of action with suspected anemia of inflammation is to defer an evaluation of the anemia for 1 to 3 months following resolution of the underlying condition.

A third cause of microcytic anemia is thalassemia, which is actually a group of inherited disorders of insufficient globin chain synthesis. Major homozygous forms are relatively rare, but milder forms are fairly common in children of Southeast Asian, African, and Mediterranean descent. The two most common forms of thalassemia are a-thalassemia trait and b-thalassemia trait. The overall prevalence of a-thalassemia trait in the Southeast Asian population ranges from 5% to 15%, and in the African-American population is 3%. Clinically, affected children manifest a hypochromic microcytosis with mild anemia that can be mistaken for iron deficiency. A useful measure is the discriminate index (MCV/RBC) that is usually high in iron deficiency but low in thalassemia. Also in contrast to iron deficiency, the red cells are more uniformly small in size as evident by a normal RDW. Target cells are usually present in the blood film, but they occur in other microcytic disorders as well. Electrophoresis, as in the silent carrier state, is not helpful except in the neonatal period when Bart's hemoglobin is 3–10%. If a CBC is done in the neonate, a microcytosis can be demonstrated. Techniques are available to establish the diagnosis by determining the rates of chain synthesis and, more recently, by direct molecular probe analysis of the genes themselves.

b-Thalassemia trait has a prevalence of 3–4% in Mediterranean and Southeast Asian populations. Except for the presence of a mild hypochromic, microcytic anemia with basophilic stippling and target cells, affected children are clinically normal. On electrophoresis, increased percentages of hemoglobins A2 and F are present as gamma- and delta-chains associate with surplus alpha-chains. Hemoglobin A2 is in excess of 3.5%, establishing the diagnosis.

Lead poisoning has decreased in prevalence as environmental sources of contamination have been controlled by reducing and eliminating lead from paint and gasoline (see Chap. 15). Anemia, when present, is generally due to a coexisting iron deficiency, which also enhances lead absorption. As with any sideroblastic anemia, lead at moderate levels interferes with the synthesis of protoporphyrin. Iron accumulation results in an abnormal erythroid precursor in the marrow, the ringed sideroblast. At a lead level of 40 µg/dL hemoglobin synthesis is inhibited, and with levels greater than 75 µg/dL frank anemia is seen. Microcytosis is present with the basophilic stippling of denatured RNA.

The next subcategory of inadequate erythrocyte production is macrocytic anemia. Macrocytosis is a normal finding in neonates because of the large size of cells containing fetal hemoglobin and is otherwise uncommon in childhood. Macrocytic anemia is a consequence of defective DNA synthesis in the red cell, which delays maturation of the nucleus relative to the cytoplasm. The MCV is high and reticulocyte count is low or intermediate. Inhibition of DNA synthesis can result from many different mechanisms. In 35% of childhood macrocytosis, a drug can be implicated. The classes of drugs that are most commonly involved are anticonvulsants, zidovudine, immunosuppressive agents, and chemotherapeutic agents. Other causes of macrocytosis in decreasing order of frequency are congenital heart disease, Down syndrome, reticulocytosis, marrow failure/myelodysplasia, hypothyroidism, and liver dysfunction.

True megaloblastic anemia as the result of either vitamin B_{12} or folate deficiency is rare in childhood. Adequate B_{12} requires sufficient dietary intake, intact gastric parietal cells, and a functioning ileum. Children at risk of deficiency include those with pure vegan diets (lacking eggs, fish, meat, and dairy products), inflammatory bowel disease, and pernicious anemia from either absence of intrinsic factor or antibodies to parietal cells. In addition to anemia, severe B_{12} deficiency can manifest with spinal cord degeneration characterized by diminished vibratory and position sensation. Folate deficiency may be the result of severe malnutrition, malabsorption, or excessive utilization from prematurity, pregnancy, lactation, or hemolytic disease. In addition to macro-ovalocytes, leukopenia with hypersegmented polymorphonuclear cells and thrombocytopenia are present in megaloblastic anemia.

The last subcategory of inadequate erythrocyte production is red cell aplasia. Hypoplastic anemias or red cell aplasias are an uncommon group of normocytic/macrocytic anemias characterized by a low or absent reticulocyte count. The inadequate erythroid activity may be a pure aplasia or part of a generalized bone marrow failure with associated granulocytopenia and thromobocytopenia.

Transient erythroblastopenia of childhood (TEC) is an uncommon disorder, but there is increasing recognition of this condition. Children with this disorder are generally 12 months to 2 years of age and present with a moderate-to-severe normocytic anemia, reticulocytopenia, and often neutropenia. The course is insidious and at the time pallor is recognized, aplasia has been present for at least 2 months. There appears to be an autoimmune pathogenesis with antibody inhibition of erythroid progenitors (erythroid colony-forming unit [CFU-E] or erythroid blast-forming unit). Recovery is spontaneous and may be mistaken for a hemolytic state as reticulocytosis begins.

Parvovirus B19, the cause of erythema infectiosum or fifth disease, can induce aplastic crisis in children with hemolytic anemias. The parvovirus directly infects CFU-E, damaging the cells and causing cessation of erythrocyte production. The inhibition is for 1 to 2 weeks and well tolerated in a normal person. However, in children with hemolytic anemia in which erythrocyte lifespan is reduced significantly, 1–2 weeks of aplasia will result in profound anemia. Reticulocytopenia is present instead of the expected reticulocytosis of hemolytic disease and is often accompanied by thrombocytopenia. Treatment is supportive, with blood transfusions for profound anemia and severe symptoms.

Other conditions causing aplasia are rarely seen in practice. Congenital hypoplastic anemia or Diamond-Blackfan syndrome is a rare condition that is generally sporadic and occasionally familial. Most affected children have anemia by 6 months of age and nearly all by 1 year of age. The anemia is profound with a hemoglobin level of 2–5 g/dL and the bone marrow shows an absence of erythroid precursors. Renal failure is also a cause for normocytic anemia from lack of adequate amounts of erythropoietin. Aplastic anemia or pancytopenia is also rare. Bone marrow aplasia can be acquired from destruction or dysfunction of the pluripotential stem cell by drugs, infection, environmental factors, radiation, and chemicals. Drugs are associated either in a predictable dose-related response (antineoplastic agents, benzene, chloramphenicol, inorganic arsenicals) or as an idiosyncratic reaction to a variety of agents. Pancytopenia can also be the result of marrow infiltration by malignancy.

The other major category for anemia is premature loss of red blood cells, subcategorized as either acute hemorrhage or increased destruction. Acute hemorrhage is evident by history, hemodynamic instability and impaired oxygenation. Premature destruction of red cells occurs by two general mechanisms. The more common mechanism is red blood cell uptake by the macrophages of the spleen and liver, where they are destroyed and digested (extravascular hemolysis). The mononuclear-phagocytic system removes cells from the circulation under conditions in which there is an intrinsic abnormality of the red blood cell or antibody is bound to the red cell membrane. Less commonly, red cells are hemolyzed in the circulation with release of contents directly into the peripheral blood. Intravascular hemolysis may be caused by trauma to the red blood cells, fixation of complement to the red blood cells, or exogenous toxins.

For hemolysis to result in anemia, the destruction of red blood cells must exceed compensatory reticulocytosis. The normal life span of a red cell is 100–120 days, so in steady state approximately 1% of cells are senescent and replaced by reticulocytes. The reticulocyte count is the single most useful test for hemolysis. Often reported as a percentage, normally 0.5–2.0%, it is more useful with significant anemia to determine the effective percentage of reticulocytes by multiplying the observed percentage with the ratio of the observed hematocrit over the expected hematocrit. Alternatively, determining the absolute number of reticulocytes can be done by multiplying the observed percentage and the red blood cell count. The usual range is 25–75 × 10^{9}/L. In severe anemia, reticulocytosis can increase four- to six-fold and be misinterpreted as macrocytosis in automated cell counters due to a relatively large size.

In addition to an elevated reticulocyte count and smear with abnormal morphology, hemolysis can be inferred by increased levels of the metabolic products of hemolysis. The catabolism of hemoglobin in the reticuloendothelial system produces bilirubin. In hemolytic disease, 1–3 mg/dL of indirect bilirubin is typically seen. Increased excretion of bilirubin can be a cause of pigment gallstones in early childhood. With brisk hemolysis, free hemoglobin is released directly into plasma. Other products of hemolysis include lactate dehydrogenase and uric acid. Low levels of haptoglobin are characteristic of hemolysis. Free haptoglobin in the plasma irreversibly binds two hemoglobin molecules and the complex is removed in the liver and spleen. However, haptoglobin is an acute phase reactant and can be spuriously elevated with inflammation. When the amount of free hemoglobin exceeds the binding capacity of free haptoglobin, it is catabolized in the kidney and it appears in urine as hemosiderinuria. When the level of free hemoglobin exceeds 100–150 mg/dL, the renal threshold is exceeded and hemoglobinuria is present as well.

Causes of hemolysis include intrinisic red cell abnormalities involving the cell membrane, enzymes, or hemoglobin. The most common disorder of the red cell membrane is hereditary spherocytosis, the prevalence of which is highest in individuals of northern European descent. Spectrin deficiency impairs flexibility of the red cell membrane, and cells that are initially biconcave become spherocytic as they traverse the spleen. Anemia presents at any age accompanied by fluctuating pallor, jaundice, splenomegaly, and pigment gallstones. The characteristic erythrocyte abnormality is the spherocyte with reticulocytosis varying from 5% to 20%. The condition is usually inherited as an autosomal dominant condition and the family history is helpful. The disorder ranges in severity from being asymptomatic to a severe hemolytic anemia. There is no definitive diagnostic test, but an increased osmotic fragility is supportive evidence. Treatment varies, and in severe cases

splenectomy is necessary and curative. Other disorders of the erythrocyte membrane include hereditary elliptocytosis and stomatocytosis.

Red cells contain two major enzymatic pathways for glucose metabolism. Deficiences of enzymes occur in both pathways and are inherited as recessive disorders. The most common defect is glucose-6-phosphate dehydrogenase (G6PD) deficiency which is a major enzyme of the hexose monophosphate shunt. The G6PD gene is located on the X chromosome and inherited in an X-linked fashion. The most common enzyme variant seen in the African-American population is present in 13% of males and 2% of females. Enzyme activity is 5–15% of normal. Affected individuals of Mediterranean, Arabic, and Asian ethnicity have a variant in which the males and homozygous females have less than 5% of normal enzyme activity. In general, hemolysis occurs only with ingestion of oxidant agents, such as antipyretics, sulfonamides, antimalarials, and naphthaquinolones, or the fava bean. The definitive diagnostic test is a G6PD assay. Enzyme deficiencies of the primary glycolytic pathway are rare, the most common of which is pyruvate kinase deficiency resulting in depletion of adenosine triphosphate and shortened erythrocyte survival.

The most important of the hemoglobinopathies is sickle cell hemoglobin (Hb S). Sickle trait is found in 8% of African-Americans, and up to 2% of individuals with ethnic backgrounds from Italy, Greece, the Middle East, and India (see Chap. 99).

Hemolysis as a result of extrinsic problems to the red cell include antibody-mediated hemolysis and microangiopathic hemolysis. Antibodies are of two general categories, either alloimmune or autoimmune. Alloimmune reactions are common in the newborn period from fetal and maternal blood group incompatibility. With maternal sensitization against fetal red cells, maternally derived immunoglobulin G (IgG) antibodies are transferred transplacentally to the fetus, resulting in neonatal jaundice. Similarly, hemolytic reactions will result from incompatible blood component transfusion

Autoimmune antibodies may be of either the IgG, “warm” type, or immunoglobulin M (IgM), “cold” type. The autoantibodies may be idiopathic or related to an underlying chronic disorder, viral syndrome, or drug. Mechanisms by which drugs produce hemolysis include induction of autoantibodies to erythrocytes, adsorption of antidrug antibodies to the red cell membrane, or formation of a complex with plasma proteins and IgM, which settles onto erythrocytes. Cold antibodies form classically as a consequence of infectious mononucleosis or mycoplasmal disease. Less commonly, they are a complication of a lymphoproliferative disorder. The hemolysis may be inapparent or cause profound anemia. The blood smear is normocytic but with a large number of spherocytes. The single most useful test is the direct antibody test (Coombs' test), which, when positive, indicates the presence of antibody or complement on the RBC surface. No treatment is needed for mild anemia. Discontinuing the offending drug and supportive care for viral illness are generally sufficient. Autoimmune hemolysis that is idiopathic or secondary to an underlying chronic disease may benefit from other treatments. Transfusion may be required, but is only transiently beneficial because transfused red cells are coated nonspecifically and hemolyzed. Most patients respond promptly to prednisone at 2 mg/kg/d with a decrease in hemolysis. This dose is continued until the hemoglobin and hematocrit approach normal levels, then is tapered. Some patients will persist with chronic hemolysis and other treatments may be necessary, including splenectomy, cytotoxic agents, and intravenous immunoglobulin.

Intravascular destruction or microangiopathic hemolysis is the result of mechanical injury to red cells as they traverse an abnormal vascular bed. Acquired problems of the vasculature include disseminated intravascular coagulation, hemolytic-uremic syndrome, hemangioma, vasculitis, and mechanical valves. The anemia is normocytic, but bizarre red cell shapes are present. The characteristic fragmented cell is the schistocyte. Treatment should be directed at the underlying condition. Transfused red cells are subject to the same intravascular injury so the effect of transfusion is limited.

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99. SICKLE CELL DISEASE

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Sickle hemoglobin differs from normal hemoglobin by a single amino acid substitution (valine for glutamic acid) in the number 6 position of the b-chain. It can be distinguished from normal hemoglobin by electrophoresis and solubility testing and less reliably by its morphologic effect on the red blood cell when exposed to low oxygen tension ("sickling"). Sickle cell (hemoglobin [Hb]SS) disease is caused by the replacement of both normal hemoglobin (A) genes by genes for hemoglobin S (homozygous HbSS). It is a common inherited disorder in African-Americans in the United States (1 of 375 African-American newborns) and causes both morbidity and mortality. Combinations of other abnormal hemoglobins with hemoglobin S (such as SC, S-b-thalassemia, S-hereditary persistence of fetal hemoglobin) are distinguished by electrophoresis and often by clinical characteristics. For example, patients with HbSS do not have a palpable spleen after about age 6 years, but splenomegaly may persist in patients with SC or S-b-thalassemia; patients with S-hereditary persistence of fetal hemoglobin have particularly mild disease, due to the influence of increased amounts of fetal hemoglobin in each red blood cell.

When hemoglobin S is combined with normal hemoglobin A (AS), the result is sickle trait, found in approximately 8% of African-Americans, in 3% of the Hispanic population in the eastern United States, and in less than 1% of other racial/ethnic groups in the United States. It is important not to confuse sickle trait with sickle cell *disease;* it is only the latter that is associated with profound hemolytic anemia, serious illness, and decreased life expectancy. However, individuals with AS will have positive sickle screening tests.

The clinical course of patients with sickle cell disease is punctuated by the occurrence of episodic events called *crises,* which are of three major types: aplastic, sequestration, and vaso-occlusive (painful). *Aplastic* crises may occur in any type of chronic hemolytic anemia; they are usually triggered by infection, particularly parvovirus B19 infection, and last up to 7–10 days. Since survival of the red cell in sickle cell disease is 15–25 days (rather than the normal 120 days), markedly increased production by the bone marrow is required to maintain even the modest hemoglobin level of 5.5–9.5 g/dL in steady state. The consequences of aplastic crises may therefore be profound; with the reticulocyte count less than 1%, severe anemia may result, sometimes necessitating transfusion. The delicate balance between increased production and premature destruction in sickle cell disease can also be upset by accelerated hemolysis *(hyperhemolysis).* Infection may be the precipitating event, leading to increased icterus, increased reticulocytosis (which helps distinguish hyperhemolysis from aplastic crisis), and a fall of hemoglobin. A frequent cause is G6PD deficiency. Testing for G6PD activity should be done *after* recovery from accelerated hemolysis; this inherited disorder is relatively common in the American black population, especially males (approximately 11%).

Sequestration crises are uncommon but dramatic events in infants and small children with sickle cell disease; the spleen rapidly enlarges and traps most of the circulating red blood cells, leading to shock and death in some children. Recurrent infarctions and fibrosis of the spleen appear to protect against sequestration crises after the age of 5 or 6 years, but elective splenectomy to prevent recurrence is frequently considered in infants following a first or second sequestration event.

By far the most common crises are the *vaso-occlusive,* or *painful,* type. These are most frequently skeletal or abdominal. Painful symmetric swelling of the hands and feet due to dactylitis (the "hand-foot syndrome") may be the earliest sign of sickle cell disease in an infant. In older children, skeletal pain more commonly is located in the long bones. Children with sickle cell disease have an increased incidence of osteomyelitis (particularly with *Salmonella*), and differentiating between infarction (vaso-occlusive crisis) and infection is often difficult. Joint pain and effusion occasionally occur. Avascular necrosis of the hip is also a skeletal complication; it occurs more frequently in individuals with SC than with HbSS disease. Newer techniques of noninvasive diagnostic imaging, especially magnetic resonance imaging, have improved our ability to evaluate skeletal complications.

Any intraabdominal organ may be affected by ischemic necrosis resulting from occlusion of capillaries by sickled cells. Patients may have recurrent abdominal crises, but in any given episode the distinction between a vaso-occlusive crisis and an acute surgical abdomen, such as appendicitis or cholecystitis, may be difficult. Sickle cell disease also affects other organ systems, including the nervous system. Cerebrovascular events, although uncommon in infants, do occur in children; they may present with hemiplegia or seizures. A program of regular transfusion is often instituted after a cerebrovascular accident to prevent recurrence. It is currently recommended that all children be screened for abnormal internal carotid and middle cerebral artery blood flow at age 5 to identify those at high risk and institute a transfusion program to prevent stroke.

The lungs are commonly subjected to infarction and infection—again, the differentiation in a given episode may not be possible. Organisms that generally produce a clinically mild pneumonia, such as *Mycoplasma pneumoniae*, may cause a more dramatic picture in individuals with sickle cell disease, with pleural effusion and progression to "white out" of the lung on x-ray. Hypoxemia from lower respiratory tract infarction or infection is common and particularly hazardous, since it may promote further sickling and a vicious cycle ("acute chest syndrome" [ACS]). This syndrome appears to have increased in frequency and has become a leading cause of death in sickle cell disease after the age of 10 years. Of children who develop ACS, approximately 70% have signs on admission and the remaining 30% develop ACS during the course of treatment for painful vaso-occlusive crisis. Complications include severe hypoxemia, pulmonary vasoconstriction, oxygenation failure, acute respiratory distress syndrome, pulmonary sequestration, stroke, and death. Because pulmonary infiltrates may progress rapidly, often accompanied by falling hematocrit, hypoxia, and oxygenation failure, children with sickle cell disease who have pneumonia need to be monitored closely. Principles of management of ACS include oxygen; antibiotics; maintenance of adequate hemoglobin delivery; pain and fluid management; nebulized bronchodilator; incentive spirometry; control of fever; and close monitoring of respiratory rate, signs of respiratory distress, and oxygenation.

Cardiomegaly and left ventricular hypertrophy, resulting from chronic anemia and increased cardiac output, are common and eventually contribute to diminished life expectancy in sickle cell disease. Infarction of renal tissue, particularly in the medullary area, leads to inability to concentrate the urine (hyposthenuria), papillary necrosis, and hematuria; hyposthenuria and hematuria occur both in individuals with sickle cell disease and in those with sickle trait. Priapism may occur in boys but is more common following puberty (median onset 21 years in a study of Jamaican males). If prolonged, priapism can result in impotence. Leg ulcers are not usually a problem until adolescence or early adulthood but then become a source of continued morbidity.

The greatest threat to life is serious overwhelming infection, which is a common complication in the first 5 years of life. Prior to the current era of penicillin prophylaxis and bacterial vaccines, the incidence of septicemia and/or meningitis was 10–15%. Pneumococcus is the usual organism, but there is also a marked increase in the incidence of serious infections with other encapsulated organisms. The major determinant of inadequate host protection appears to be dysfunction of the spleen. Beginning at several months of age, long before anatomic infarction and fibrosis of the spleen have taken place, a state of "functional asplenia" can be demonstrated. During this time, presumably both the antibody-producing and the mechanical-filtering functions of the spleen are compromised. After the age of 5 or 6 years, serious infections become less frequent, possibly because of accumulated antigenic experience, and the hospitalization rate for fever and infection in children with sickle cell disease decreases.

The repeated crises, time lost from school, limited tolerance for strenuous physical activity, and delayed growth and maturation combine to make sickle cell disease not only a physically painful disorder but a potentially emotionally difficult one as well. Children require reassurance that they will not be allowed to suffer and that appropriate analgesia will be prescribed. Parents should always have a supply of acetaminophen, ibuprofen, or other nonsteroidal antiinflammatory drug, and codeine or other oral narcotic so that most painful crises can be managed at home instead of in the emergency department or hospital.

Although the molecular basis of sickle cell disease has been known for decades, there is still no cure or even satisfactory palliation. Prevention of pneumococcal infections with daily prophylactic penicillin should be initiated early in infancy (by 3 months) and continued until at least age 5 years, in addition to pneumococcal and *Haemophilus influenzae* type B vaccination. Despite these prophylactic measures, severe infections may still occur; children with sickle cell disease should be

evaluated when they have significant fever (>38.5°C) or look ill and should be treated with antibiotics parenterally.

Transfusions may be lifesaving, for example, during a sequestration crisis, and are indicated in the treatment for severe chest syndrome, prolonged aplastic crisis, and as preparation for major surgery. In some circumstances simple transfusion may be appropriate, while in others exchange transfusion may be preferable, such as in ACS. The aim of exchange transfusion is to reduce hemoglobin S percentage without raising the hematocrit above 35. Because of the likelihood of transfusion in sickle cell disease, hepatitis B vaccination, now recommended for administration to all infants, is particularly important.

Therapy for vaso-occlusive crises consists primarily of sufficient analgesia and adequate hydration. Infections (known or suspected) require prompt antibiotic treatment; hypoxemia is treated with oxygen. Current research focuses on agents that can increase the hemoglobin F percentage in red cells, which decreases the likelihood that hemoglobin S will polymerize. Clinical benefit has been demonstrated in adults; trials are now being conducted in children and evaluated. Preliminary results appear promising. Bone marrow transplantation can be curative but is rarely performed. Research into gene transfer techniques also provides a possible curative approach for the future.

Prenatal determination of sickle cell disease is possible. State-administered mandatory neonatal screening programs have become more numerous, in large part due to the demonstration of benefit from early penicillin prophylaxis. Counseling and education need to be provided to parents with the results of screening.

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A useful resource that describes epidemiology, laboratory screening methods, medical management of newborns and infants, and recommendations for educating and counseling parents of newborns with sickle cell disease and trait. Can be ordered (FREE) by calling 800-358-9295. For cost-effectiveness analysis of neonatal screening, see Arch. Pediatr. Adolesc. Med. *148:461–468, 1994, and* J. Pediatr. *136:201–208, 2000, and accompanying commentary, pp. 145–146.*

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*In children with HbSC, growth was comparable to those with HbAA, but children with HbSS disease had progressive deficits in both weight and height, even before 2 years of age. Children with HbSS also have delayed puberty (*Arch. Dis. Child *71:404–408, 1994). Growth delay is due to chronic malnutrition and zinc deficiency. Nutritional supplementation (*Lancet *1:903–906, 1985) and zinc supplementation improved growth (*Ann. Intern. Med. *100:367–371, 1984).*

100. IDIOPATHIC THROMBOCYTOPENIC PURPURA

Kenneth B. Roberts and Conrad J Clemens

The three cardinal features of childhood idiopathic thrombocytopenic purpura (ITP) (also known as immune thrombocytopenic purpura) are (1) thrombocytopenia, with a platelet count of less than 100,000/µL (usually much less); (2) the presence of normal or increased number of megakaryocytes in the bone marrow; and (3) the absence of other disorders capable of causing thrombocytopenic purpura, such as leukemia or systemic lupus erythematosus (SLE). Some authors also include absence of splenomegaly as a characteristic of ITP, but up to 10% of affected children have a palpable spleen tip.

The normal platelet count in the peripheral blood is between 150,000 and 400,000/µL, platelet survival time is 9.9 days, and there is a turnover of 35,000/µL/d. In severe ITP, the half-life of the platelets may be less than 9 minutes. The problem is one of destruction and removal by the reticuloendothelial system rather than lack of production; indeed, platelet production is 2–8 times normal.

On the basis of age, sex, and outcome, it is clear that ITP is not a single, homogeneous disorder. In younger children (peak age 3–4 years), the sexes are equally affected, and the clinical course is usually benign. In adults and adolescents in their late teens, girls outnumber boys by 2–3:1, and the course is likely to be protracted and complicated. The initial clinical picture is the same in both groups, however; petechiae, purpura, and bruises are present in virtually all affected children. Gastrointestinal, genitourinary, and mucous membrane bleeding occurs in one fourth to one third of patients. The most serious complication is intracranial hemorrhage, but this occurs in less than 1% of children, usually—but not always—in the first month of illness.

Approximately 50% of the children with ITP have a history of an infectious illness in the prior 6 weeks, usually an upper respiratory tract infection. Chickenpox, rubella, infectious mononucleosis, hepatitis, mumps, measles, and pertussis have also been associated. These children with postinfectious ITP have the shortest, most benign course; 90% recover, one half within 4–8 weeks. Mechanisms proposed to explain the development of ITP following viral infection include adsorption of viral antigens onto the platelet surface followed by antibody binding, and binding of preformed immune complexes to the platelet surface via platelet Fc receptors. An immunoglobulin G (IgG) antiplatelet antibody can be demonstrated in as many as 85% of patients.

Laboratory evaluation of the child with a history suggesting ITP begins (and often ends) with a complete blood count. The platelet count is reduced and the individual platelets are often large, but the other elements are present in normal quantities and with normal morphologic features. If there has been blood loss, a mild anemia may be present, but if the anemia is striking, the white blood cell or neutrophil count is reduced, or blasts are seen in the peripheral blood smear, leukemia or aplastic anemia should be considered and a specimen of bone marrow examined. Previous dogma was that a bone marrow aspirate should also be obtained if corticosteroids are to be administered because of the concern of “partial treatment” of a leukemia that has not yet fully declared itself; this appears not to be necessary, however. Systemic lupus erythematosus infrequently presents in young children with thrombocytopenic purpura alone; antinuclear antibodies should be measured if other signs of SLE are present or develop. Approximately 2–3% of children thought to have ITP demonstrate evidence of SLE within 10 years after the acute episode. If the ITP is chronic and splenectomy is required, however, the incidence of SLE is approximately 30%. Isolated thrombocytopenia can be the initial manifestation of human immunodeficiency virus (HIV) infection. The patient's history should include an exploration for possible HIV risk factors and, in the appropriate clinical setting, serologic testing for HIV. Common variable immunodeficiency can also present with thrombocytopenia.

Treatment of ITP remains controversial. Consideration is probably necessary only if the platelet count is less than 20,000/µL or there is active bleeding. Corticosteroids increase platelet counts primarily by increasing platelet production. Long-term use of corticosteroids should be avoided because of potential toxicity. Intravenous immunoglobulin (IVIG) appears preferable to corticosteroids because it results in faster elevation in the platelet count. However, IVIG is more expensive and inconvenient to administer. Unfortunately, while both steroids and IVIG appear to increase platelet count faster than no treatment, it is not clear whether they offer any clinical significance in terms of decreasing active bleeding. In the past few years, preparation of anti-D immunoglobulin for intravenous administration has become available. Studies are reporting that it is as effective as IVIG at a fraction of the cost, except in the 12–15% of the population who are Rh-negative. Other treatments that are currently in clinical trials include interleukin-11 and thrombopoietin.

In chronic ITP that hampers the patient, additional treatment options include splenectomy (best avoided in children younger than 5 years old because of the important role of the spleen in protecting against sepsis with encapsulated organisms such as *Streptococcus pneumoniae*), anti-D (in Rh-positive children who have not had a splenectomy), danazol, or combination chemotherapy. Platelet transfusions are only beneficial for approximately 1 hour but, together with splenectomy, can be administered as an emergency procedure in the setting of intracranial hemorrhage.

Mortality during the acute episode of ITP is very rare, and most patients recover without recognized sequelae. Clinical relapses are unusual and suggest the presence of an underlying disorder such as SLE. “Cure” may be more apparent than real, however; platelet kinetic studies in many patients demonstrate continued peripheral destruction of platelets, although at a rate that can be matched by increased bone marrow production. During intercurrent illness, marrow activity slows, and thrombocytopenia may again be manifested. Newborns of mothers with a history of ITP may be thrombocytopenic, reflecting persistent maternal antiplatelet IgG.

Reviews

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2. Yu-Waye, C., Korb, J., and Sakamoto, K. Idiopathic thrombocytopenic purpura. *Pediatr. Rev.* 21:95–103, 2000.
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Series

3. Lusher, J., and Zuelzer, W. Idiopathic thrombocytopenic purpura in childhood. *J. Pediatr.* 68:971–979, 1966.
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4. Choi, S., and McClure, P. Idiopathic thrombocytopenic purpura in childhood. *Can. Med. Assoc. J.* 97:562–568, 1967.
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10. Dubansky, A., et al. Isolated thrombocytopenia in children with acute lymphoblastic leukemia: A rare event in a Pediatric Oncology Group study. *Pediatrics* 84: 1068–1071, 1989.

A retrospective review of 2,239 children enrolled in acute lymphoblastic leukemia (ALL) protocols showed that none of these children had significant thrombocytopenia without other hematologic or physical manifestations of ALL when they were first seen by the hematologist. The results suggest that routine bone marrow aspiration in the child with isolated thrombocytopenia may be unnecessary to rule out ALL.

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    Infectious thrombocytopenia in infectious mononucleosis mimicked leukemia.
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    Infection with human immunodeficiency virus can mimic ITP.

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    The authors found that 17% of children had a major hemorrhage (although only 2 of the 332 children had an intracranial bleed). Response to therapy in these children was unimpressive.
16. Lilleyman, J. Intracranial hemorrhage in idiopathic thrombocytopenic purpura. *Arch. Dis. Child*. 71:251–253, 1994.
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    This entire supplement (pp. 1–51) reviews recent treatment modalities, especially anti-D immunoglobulin.
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    Reversal of clinically important thrombocytopenia assessed by the number of days taken to achieve platelet count >50×10^9/L was significantly faster in children randomly assigned to receive intravenous immunoglobulin (IVIG) (median, 2 days; range, 1–34 days) than in those receiving prednisone (median, 4 days; range, 2–13 days; p < 0.001) or no therapy (median, 16 days; range, 2–132 days; p < 0.001). Also see Lancet *344:703–707, 1994.*
21. Buchanan, G. Childhood acute idiopathic thrombocytopenic purpura: How many tests and how much treatment required? *J. Pediatr.* 106:928–930, 1985.
    The author offers his opinion regarding diagnostic tests, hospitalization, prednisone, and IVIG.
22. Imbach, P., et al. Intravenous immunoglobulin versus oral corticosteroids in acute immune thrombocytopenic purpura in childhood. *Lancet* 2:464–468, 1985.
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    Single-dose therapy (rather than 5-day course) was effective both in untreated and in steroid-treated children with acute disease.
24. Kattamis, A., Shankar, S., and Cohen, A. Neurologic complications of treatment of childhood acute immune thrombocytopenic purpura with intravenously administered immunoglobulin G. *J. Pediatr.* 130:281–283, 1997.
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Chronic Idiopathic Thrombocytopenic Purpura

26. Beardsley, D. Oral dexamethasone therapy for chronic immune thrombocytopenic purpura: Home run or base hit? *J. Pediatr.* 130:1–2, 1997.
    A thoughtful editorial commenting on two small studies in the same volume (pp. 13–16, and 17–24), showing potential, but needing confirmation from larger studies.
27. Reid, M. Chronic idiopathic thrombocytopenic purpura: Incidence, treatment and outcome. *Arch. Dis. Child*. 72:125–128, 1994.
    This large British series suggests that bad clinical outcomes in chronic ITP are exceedingly rare. Close follow-up but little intervention may be the best plan.
28. McMillan, R. Chronic idiopathic thrombocytopenic purpura. *N. Engl. J. Med.* 304: 1135–1147, 1981.
    A thorough (12-page) review as of 1981. See also Arch. Dis. Child. *65:502–506, 1990.*
29. Warrier, I., et al. Intravenous gammaglobulin (Gamimune) for treatment of chronic idiopathic thrombocytopenic purpura (ITP): A two-year follow-up. *Am. J. Hematol.* 23:323–328, 1986.
    Of 13 children, 2 of whom had already undergone splenectomy, 6 had a "good" or "excellent" initial response to a 5-day course of g-globulin, and 1 had a "fair" response; 6 of these 7 required booster doses. By 1 year, g-globulin was no longer effective in 3 of the 7 initial responders.
30. Figueroa, M., et al. Combination chemotherapy in refractory immune thrombocytopenic purpura. *N. Engl. J. Med.* 328:1226–1229, 1993.
    Combination chemotherapy is beneficial in some patients in whom immune thrombocytopenia is refractory to corticosteroids and splenectomy.

101. LEUKEMIA

Brent W. Weston

The most common malignancy diagnosed during childhood is acute leukemia, which accounts for about 35% of pediatric cancers. Remission is now achieved for more than 95% of children with acute lymphoblastic leukemia (ALL), and most of these patients become long-term, disease-free survivors (about 75%). In acute myelogenous leukemia (AML), remission is now achieved in almost 80% of patients, and long-term survival has improved with intensive chemotherapy and bone marrow transplantation (BMT). Current childhood leukemia treatment studies focus on reducing the toxicities of treatment in favorable patient subgroups and developing innovative therapies for poor-risk subgroups.

Each year, approximately 2,500–3,000 new cases of childhood leukemia are diagnosed in the United States. Of these, 75% are ALL, 20% are AML, and the remaining few are mixed lineage, undifferentiated, or chronic forms of leukemia (e.g., chronic myelogenous leukemia [CML]). Despite extensive molecular and epidemiologic investigations, causes for most forms of childhood leukemia have been elusive. Because acute leukemia is much more common during childhood, this section focuses on ALL and AML.

The most common signs and symptoms of leukemia at the time of diagnosis are pallor, bruising, and fever. Splenomegaly and lymphadenopathy occur in a sizable minority of patients. Bone or joint pain is occasionally due to leukemia rather than infectious or rheumatologic disorders. Most patients with leukemia are anemic and thrombocytopenic. The white blood cell count may be either high or low. Inadequate production of neutrophils, platelets, and red blood cells is due to infiltration of the bone marrow in ALL, where a monotonous sheet of lymphoblasts is usually seen replacing normal elements. In AML, a more varied bone marrow blast count can be found (with studies using 20–30% blasts as a minimum for diagnosis). Myeloblasts are larger, and nuclear folding or cytoplasmic granules are sometimes seen. The diagnosis is confirmed by flow cytometric analysis of markers on the surface of the blasts (e.g., B cell, T cell, and lymphoid precursor markers for ALL) and by special stains (e.g., terminal deoxynucleotidyl transferase for most cases of ALL; myeloperoxidase for most cases of AML).

Clinical and biological markers for ALL and AML have become increasingly sophisticated and allow better design of therapy. In ALL, disease-free survival is possible for 80% of those in the best clinical risk group: children aged 2 through 9 years with initial white blood cell (WBC) count of less than 50,000/µL with B-lineage (“pre-B cell”) ALL. Approximately 85% of ALL arises from B-lineage lymphoblasts, and 90% of these express a common acute lymphoblastic leukemia antigen (CALLA, or CD10). Patients with T cell ALL, approximately 15% of cases, and those with WBC greater than 50,000/µL or central nervous system (CNS) involvement require more intensive treatment. T cell ALL characteristically occurs in older children, frequently in association with an anterior mediastinal mass. “Mature” B cell leukemia is rare, accounting for less than 1% of cases; it is not responsive to standard ALL therapy and was rapidly fatal before B cell lymphoma protocols were employed. In AML, the M3 subtype is now treated with the differentiating agent trans-retinoic acid combined with chemotherapy, rather than standard induction therapy and BMT.

Cytogenetic and molecular studies of leukemic blasts have become increasingly important in the diagnosis, treatment, and prognosis of both ALL and AML, and are now considered standard care. These studies and treatment plans necessitate referral of children with oncologic diseases to experienced pediatric oncology groups rather than community medical oncologists. For example, infants and children with ALL and specific translocations (9,22 and 4,11) have a dismal prognosis unless allogeneic BMT is performed in first remission; such therapy is not indicated in “standard-risk” ALL. In AML, t(15,17) identifies the M3 subtype when morphology is indeterminate, drastically altering therapy (above). As more precise risk groups are defined by molecular markers, more appropriate treatments plans (combining maximum effectiveness with limited toxicity) will continue to be developed.

Over 25 years' worth of multi-institutional pediatric oncology trials have demonstrated that initial intensive treatment and subsequent consolidation combined with effective CNS prophylaxis afford the greatest opportunity for curing acute leukemia. Therapy for ALL has progressed to the present multidrug protocols with (1) induction of remission, (2) CNS prophylaxis/treatment, (3) intensification or consolidation, and (4) “maintenance” or continuation for 2–3 years. In AML, consolidation is achieved with either BMT or high-dose chemotherapy, with no maintenance or continuation therapy.

During the induction phase of ALL treatment, most protocols combine vincristine and a corticosteroid (prednisone or dexamethasone [Decadron]) with two or three additional drugs (typically methotrexate, L-asparaginase, and sometimes doxorubicin). In AML, induction is much more myelosuppressive, with combined cytosine arabinoside and anthracycline infusions forming the mainstay. These differences lead to generally shorter but more intensive inpatient treatment plans for AML, while most ALL therapy (especially maintenance) is given in the outpatient setting. In both ALL and AML, the rapidity of remission induction (i.e., clearance of leukemic blasts from the peripheral blood, bone marrow, and cerebrospinal fluid) is a critical prognostic factor that affects further treatment. Patients with slower responses often receive alternative agents and more intensive therapy.

Leukemic cells in “sanctuaries” such as the CNS may escape the effects of some systemic drugs. Central nervous system “prophylaxis” with intrathecal methotrexate and/or cytosine arabinoside or intermediate-dose intravenous methotrexate has dramatically reduced the incidence of CNS relapse (now 2–6%) and improved the probability of disease-free survival. Cranial irradiation, once a mainstay of CNS prophylaxis, is now reserved for high-risk patient groups. The testis may also act as a sanctuary, although more intense chemotherapy has reduced the likelihood of testicular relapse. Continuation regimens for ALL vary in the number of agents used and duration (2–3 years). Some successful ALL protocols include intermittent (“delayed”) periods of intensification designed to eliminate subclinical leukemia (“minimal residual disease,” or MRD).

Relapses are sometimes treated with the same induction therapy or with agents not previously used to overcome drug resistance. Once a second remission is achieved, intensive treatment with allogeneic bone marrow transplantation may follow in selected patients. The likelihood of long-term second remission correlates with factors such as duration of first remission, time off therapy, and presence or absence of MRD by polymerase chain reaction.

Acute metabolic, hematologic, and infectious complications may occur due to the disease and its therapy. Uric acid nephropathy results from the deposition of the breakdown products of leukemic cells in the kidneys; alkalinization, hydration, and allopurinol are used to prevent this complication. Tumor lysis syndrome with hyperkalemia, hypocalcemia, hyperphosphatemia, and renal compromise is most likely when the initial WBC count is high and there is massive organ infiltration (hepatosplenomegaly and/or mediastinal mass). A high serum lactic dehydrogenase reflects a heavy leukemia burden and may correlate with the severity of tumor lysis. If acute renal failure develops, dialysis may be required.

Hemorrhage can be a significant risk. Prophylactic platelet concentrates are usually given when the platelet count drops below 10,000/µL in otherwise healthy patients and below 20,000–50,000/µL in patients at high risk for bleeding due to invasive procedures (e.g., lumbar puncture), coagulopathy, or concurrent infection. Red blood cell transfusions may also be required, especially during induction. Families usually have concerns about the safety of transfusions that must be addressed during initial and subsequent discussions.

The major cause of death during treatment of acute leukemia is infection. The usual organisms are bacteria (enteric gram-negative bacilli, such as *Pseudomonas* and *Escherichia coli*, and gram-positive organisms, such as coagulase negative *Staphylococcus* and *Streptococcus viridans*). The risk of serious infection is related to the presence of indwelling catheters and to the degree and duration of neutropenia. Fever in the neutropenic patient must initially be considered as indicative of sepsis; prompt acquisition of specimens for culture, institution of antibiotic therapy, and close observation for signs of impending shock are required. With cumulative immunosuppression, viruses (especially varicella-zoster and other herpesviruses), fungi (especially *Candida* and *Aspergillus* species), and protozoa become organisms of concern. *Pneumocystis carini*, a cause of diffuse, interstitial pneumonitis, was formerly the most frequent cause of death in patients in remission; as with human immunodeficiency virus patients, prophylactic trimethoprim-sulfamethoxazole has greatly reduced its incidence and severity. Because treatment plans have become increasingly myelosuppressive, granulocyte colony-stimulating factor is often used in supportive care.

Psychosocial support is an important part of comprehensive care and again requires referral to a pediatric center. This team approach is accomplished with the

involvement of a variety of health care professionals: child life specialists, social workers, child psychologists, pediatric nurses, primary care physicians, and pediatric oncologists. While new treatment plans are being developed and introduced, enthusiasm for the technical aspects of leukemia therapy should not prevent members of the health care team from recognizing the needs of the child and the family for open communication and a supportive relationship throughout the illness.

With increasing numbers of long-term survivors, there is now a focus on recognition and prevention of late effects. Three major areas of concern are growth and development, neuropsychological sequelae, and the possibility of developing a second neoplasm. Long-term follow-up thus also requires a comprehensive approach. Continued efforts at reducing toxicities (e.g., decreased use of cranial irradiation in lower risk ALL subgroups) are obviously warranted as more pediatric leukemia patients reach adulthood.

Reviews and Collections

1. Margolin, J., and Poplack, D. Acute lymphoblastic leukemia. In: Pizzo, P., and Poplack D. (eds.). *Principles and Practice of Pediatric Oncology* (3rd ed.). Philadelphia: Lippincott, 1997.
   This is a comprehensive review chapter in a standard subspecialty text, with sections on epidemiology, pathogenesis, pathobiology, clinical features, and prognostic factors (847 references). See also the detailed chapters on acute myelogenous leukemia, bone marrow transplantation, and late effects. Separate chapters are devoted to all important aspects of supportive care in pediatric oncology.
2. Grier, H., and Civin, C. Myeloid leukemias, myelodysplasia, and myeloproliferative diseases in children. In: Nathan, D., and Orkin, S. (eds.). *Nathan and Oski's Hematology of Infancy and Childhood* (5th ed.). Philadelphia: Saunders, 1998.
   Also from a standard text, this chapter provides a useful overview of the clonal myeloid disorders, including less common diagnoses and their clinical characteristics (399 references).
3. Pui, C., and Evans, W. Acute lymphoblastic leukemia. *N. Engl. J. Med.* 339:605–615, 1998.
   A succinct review of childhood acute lymphoblastic leukemia (ALL), with summaries of biologic and treatment information (105 references).

Biology and Prognostic Markers

4. Linet, M., et al. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. *N. Engl. J. Med.* 337:1–7, 1997.
   The subject of exposures frequently arises when parents ask "why." The results of this study argue persuasively against a significant association of power lines with development of ALL. The accompanying editorial (pp. 44–46) reviews the lack of reliable data. More likely etiologic associations are reviewed in the texts cited above.
5. Uckun, F. Biology and treatment of childhood T-lineage acute lymphoblastic leukemia. *Blood* 91:735–746, 1998.
   The importance of immunophenotyping lymphoblasts is emphasized in this review article detailing the differences in the T cell subgroup of ALL patients, who frequently have "bulky disease" (high white blood cell count, mediastinal mass, lymphadenopathy, and/or hepatosplenomegaly) and a higher risk of overt central nervous system (CNS) leukemia at presentation. These patients require therapy that markedly differs from standard-risk "pre-B cell" ALL ("common ALL").
6. Beyermann, B., et al. Clinical features and outcome of children with first marrow relapse of acute lymphoblastic leukemia expressing BCR-ABL fusion transcripts. *Blood* 87:1532–1538, 1996.
   The importance of cytogenetic and molecular studies in the current diagnosis, treatment, and prognosis of ALL is underscored by this study showing that about 12% of patients with bone marrow relapse have this abnormality detectable by reverse transcription polymerase chain reaction (PCR), and a 2-year event-free survival of only 8%.
7. Cave, H., et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia. *N. Engl. J. Med.* 339:591–598, 1998.
   Detection of residual disease in the bone marrow by PCR during the first few months of remission identifies patients at risk for relapse. The clinical utility of these assays remains to be determined. See also N. Engl. J. Med. *336:317–323, 1997, for results later in therapy.*

Treatment

8. Nachman, J., et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. *N. Engl. J. Med.* 338:1663–1671, 1998.
   Patients with ALL who respond slowly to induction chemotherapy end up requiring more intensive therapy. This trial provides a good overview of patient selection for pediatric ALL protocols, and underscores the necessity of tailoring therapy to clinical and biological risk factors. The efficacy and toxicity of augmented therapy are succinctly reviewed.
9. Pui, C., et al. Early intensification of intrathecal chemotherapy virtually eliminates central nervous system relapse in children with acute lymphoblastic leukemia. *Blood* 92:411–415, 1998.
   With aggressive chemotherapeutic treatment plans for high-risk ALL patients, cranial irradiation is now reserved for a small subgroup. This approach is being extended to other subgroups in the hopes of eliminating CNS leukemia in pediatric patients while avoiding serious late complications ascribed to cranial radiation (neurodevelopmental effects and secondary brain tumors).
10. Welte, K., et al. A randomized phase-III study of the efficacy of granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia. *Blood* 87:3143–3150, 1996.
    As treatment plans become more intensive for high-risk ALL patients, supportive care issues become more important. This study showed reduced rates of infection and antibiotic use with granulocyte CSF support; cytokines are also useful in acute myelogenous leukemia (AML) protocols (see below).
11. Woods, W., et al. Timed-sequential induction therapy improves postremission outcome in acute myeloid leukemia: A report from the Children's Cancer Group. *Blood* 87:4979–4989, 1996.
    This study of 589 pediatric patients with AML illustrates how intensive the chemotherapy has become for this disease and the effect of dose-intensification on long-term survival. See also N. Engl. J. Med. *334:1428, 1996, for the role of brief but intensive consolidation therapy in AML.*
12. Tallman, M., et al. All-trans–retinoic acid in acute promyelocytic leukemia. *N. Engl. J. Med.* 337:1021–1028, 1997.
    This randomized trial with 346 patients (46 of whom were less than 15 years old) showed that all-trans–retinoic acid significantly improved disease-free survival in acute promyelocytic leukemia (AML subtype M3) when combined with conventional chemotherapy. Also, see the accompanying editorial (p. 1074) for the significance of this finding.

102. SOLID TUMORS

Julie Blatt, Kristen B. Geib, and Stuart H. Gold

Books and Reviews

Compared to the more than 1 million new cancer diagnoses in adults each year in the United States, fewer than 10,000 cases are diagnosed in children under 15 years of age. More than 70% of these children will be cured, yet cancer remains the second leading cause of death in this age group, two facts that underscore the importance of diagnosis and treatment.

Leukemia is the single largest pediatric cancer diagnostic category, but the solid tumors as a group are more common and comprise 70% of all patients. The overall distribution is brain tumors (19%), lymphomas (13%), neuroblastoma (10%), soft tissue sarcomas (7%), Wilms tumor (6%), bone tumors (5%), retinoblastoma (3%), and liver tumors (1%). Other rare tumor types make up the remaining 6%.

As noted above, *brain tumors* are the most frequent group of solid tumors in childhood. The peak incidence is between 5 and 10 years of age, with a close to equal male-to-female ratio. There are many different types of brain tumors, and the semantics can be confusing. There is a mix of benign and malignant tumors, though the word “benign” may not be the best terminology as these tumors are life-threatening due to their location if growth cannot be arrested. In contrast to the frequent supratentorial location of tumors in adults, tumors of the posterior fossa are common in childhood. The most common brain tumor categories are primitive neuroectodermal tumors (PNETs), which are either supratentorial or infratentorial (medulloblastoma); high-grade gliomas; low-grade gliomas; brainstem gliomas; germ cell tumors; atypical teratorhabdoid tumors; and craniopharyngioma.

The clinical presentations of these diverse tumor types are fairly uniform. In the infant, irritability, a bulging fontanelle, enlarging head circumference, lack or loss of developmental milestones, and strabismus may be among the most common of symptoms. Older children exhibit signs of increased intracranial pressure, with morning nausea and vomiting, visual disturbances, ataxia if the posterior fossa is involved, cranial nerve palsies, headaches, or seizures. If the motor strip is involved, limb weakness may be evident. Patients who present with stigmata of neurofibromatosis, including axillary freckling and café-au-lait spots, even if asymptomatic, should be followed very carefully for brain tumors, especially low-grade optic chiasm gliomas. Other situations that should clue the clinician in to looking for a brain tumor include the diencephalic syndrome (failure to thrive with a good appetite, and emaciation) and endocrine abnormalities (precocious puberty, diabetes insipidus, or short stature).

The evaluation first includes a careful neurological exam—with special attention paid to papilledema, cranial nerves, and any localizing findings. When a brain tumor is suspected, magnetic resonance imaging (MRI) of the head with gadolinium is the preferred imaging technique. If not available, contrasted computed tomography (CT) scan will suffice. Once a biopsy has been performed, if it is a lesion that is known to spread in the spinal fluid (PNET, high-grade astrocytoma, germ cell tumor) a spinal MRI with gadolinium is needed along with spinal fluid for cytology. Ventricular fluid for cytological evaluation is not sufficient. Few brain tumors (PNET) may spread outside of the central nervous system (CNS) axis, and bone marrow aspiration and bone scans may be needed.

The treatment and prognosis for these tumors is very dependent upon the histology of the tumor. The treatment planning and implementation necessitate a multidisciplinary clinic. Involvement is essential from a pediatric oncologist, skilled pediatric neurosurgeon, radiation oncologist, neurologist, and physical and occupational therapists. Participation in cooperative group studies is equally important. The mainstay of treatment for the vast majority of these tumors is neurosurgical. A complete excision is curative in the low-grade gliomas and improves survival in many of the malignant lesions. Most of these tumors are radiosensitive. However, radiation to the brain and possibly to the spinal cord is fraught with many difficulties. Local radiation therapy is used for tumors that do not disseminate (such as low-grade gliomas), whereas whole brain and spinal irradiation is used for tumors that tend to seed the craniospinal axis (medulloblastoma, PNET). The younger the child, the higher is the probability of major long-term side effects, which include cognitive impairment, growth failure, endocrine abnormalities, small head, short spine, and secondary tumors later in life. The role of chemotherapy in these tumors is still being investigated. For high-risk medulloblastomas, chemotherapy given in conjunction with radiation therapy improves long-term prognosis. For the very small child, chemotherapy may delay or obviate the need for radiation therapy. Even the low-grade gliomas that are not resectable may respond to chemotherapy. Some tumors, such as brainstem gliomas, respond very poorly to all available treatments, and most children will not survive for even a year.

There are currently many clinical trials in the pediatric cooperative groups. A concerted effort and systematic evaluation, diagnosis, and treatment will be the only way to improve our understanding and long-term outcomes. Therapeutic trials are now looking at the role of chemotherapy, newer modalities of radiation therapy to lessen long-term toxicity, and long-term neuropsychiatric outcomes. With combined modality approaches, upwards of 60% of children diagnosed with brain tumors will be alive 5 years after diagnosis. Most children with medulloblastoma will be survivors, average-risk children (minimal residual tumor after resection and no spread of tumor) have approximately an 80% chance of cure. On the opposite end of the spectrum, most children with brainstem gliomas and atypical teratorhabdoid tumors will die of their disease, with survival rates less than 20%. Improving cure rates and lessening long-term morbidity will be the goals for the future. Newer modalities of therapy will be employed to help accomplish these goals. Myeloablative therapy with bone marrow transplant and sequential intensive chemotherapy with peripheral stem cell rescue are being tried at many institutions. Directed therapy with monoclonal antibodies or gene therapy will hopefully be the future for the treatment of this diverse group of tumors.

The *lymphomas*—non-Hodgkins lymphoma (NHL) and Hodgkins disease or Hodgkins lymphoma—comprise the third most common group of childhood cancers. These two broad categories of lymphoma overlap histopathologically, epidemiologically, and by clinical presentation. Males are affected almost three times as frequently as females. Patients with primary or secondary immunodeficiency (such as those with human immunodeficiency virus [HIV], or following solid organ or bone marrow transplantation) are at heightened risk. Both Hodgkins disease and some types of NHL, notably Burkitt lymphoma, have been linked to Epstein-Barr virus.

In contrast to what is seen in adults with NHL, in the pediatric age group high-grade aggressive lesions are the rule. The two major subtypes of NHL are lymphoblastic lymphomas, which are mostly T cell in origin, and nonlymphoblastic lymphomas such as Burkitt lymphoma, which are mostly of B cell origin. The clinical presentation of NHL corresponds to cell type. Patients with lymphoblastic lymphoma present with intrathoracic disease, notably mediastinal masses and pleural effusions. Adenopathy occurs above the diaphragm, in the neck or axillae. Bone marrow involvement is common, and lymphoblastic lymphoma is considered to be part of a spectrum of T cell diseases, on the other end of which is acute lymphoblastic leukemia (ALL). The distinction between the two is arbitrarily defined by the percentage of blasts in the bone marrow. The complications due to metabolic derangements and mass effects are identical in these two overlapping entities (see Chap. 101). Such complications also are seen in children with nonlymphoblastic lymphoma, 90% of whom have extranodal abdominal tumors that result in pain, distention, nausea, and vomiting often indistinguishable from appendicitis, or intussusception with tumor as the lead point. Less common presentations of NHL include skin nodules or the signs and symptoms of a primary bone tumor.

Hodgkins disease almost always presents with cervical adenopathy with or without a mediastinal mass. Patients may be asymptomatic and are said to have “A” stage disease, in contrast to the 30% of patients with “B” symptoms (fever, weight loss, or night sweats). Despite the presence of even large masses, patients with Hodgkins disease are less likely than those with NHL to experience airway or metabolic disturbances.

In the patient with adenopathy, subsequent evaluation is identical if either leukemia or lymphoma is suspected. As discussed above, this should include a complete blood count, serum chemistries, and a chest radiograph. Bone marrow aspirate with biopsy for routine histology, flow, and cytogenetics (looking for the typical translocations involving chromosome 8 in patients with Burkitt lymphoma or the t[2;5] seen in other of the nonlymphoblastic lymphomas) may identify tumor. Where this is not diagnostic, fine needle aspiration of suspect lymph nodes may be sufficient in patients with lymphoblastic lymphoma. However, most other lymphomas will require biopsy. For Hodgkins disease, excisional biopsy is desirable so as to enable examination of architecture of the entire lymph node with definition of histologic subtype (nodular sclerosis, lymphocyte predominant, lymphocyte depleted, mixed cellularity). In all cases, airway should be assessed before anesthesia or conscious sedation. There is no role for extensive surgical procedures, except in children with limited intra-abdominal disease whose tumors can be resected completely.

Staging is clinical and, in addition to physical examination, is based on documentation of tumor by abdominal ultrasound; contrasted and uncontrasted CT; or MRI scans of the neck, chest, abdomen, pelvis, and brain (for patients with immunodeficiencies). Radionuclide scans such as with gallium may be helpful in delineating

areas of tumor involvement. Pathologic staging with laparotomy for pediatric patients with Hodgkins disease, once necessary for tailoring radiation ports, rarely is done with the current emphasis on systemic chemotherapy. Staging classification systems for NHL are similar to those for Hodgkins disease, are based on extent and location of tumor masses more than on degree of resection, and rate tumors from stage I (one lymph node region or extranodal region on one side of the diaphragm) through stage IV (metastatic).

Treatment of NHL is subtype specific such that patients with lymphoblastic lymphoma receive leukemia-based multiagent chemotherapy with cure rates of 70–80%. Patients with mature B cell lymphomas are treated with shorter, more intense courses, and overall cure rates are close to 90%. The presence of CNS lymphoma with or without bone marrow disease remains an obstacle to cure in this latter group of patients. There is no clear role for radiation in front-line curative treatment of NHL. Varied treatment regimens for Hodgkins disease rely on combination chemotherapy commonly with COPP (cyclophosphamide, vincristine [Oncovin], prednisone, and procarbazine) an/or ABV (adriamycin, bleomycin, and vinblastine), with or without radiation therapy. Specific protocols may be age and gender specific, with a view toward minimizing late effects of treatment (below) in a disease for which outcome is excellent.

Neuroblastoma is one end of a spectrum of tumors that includes ganglioneuroblastoma and the benign ganglioneuroma. Neuroblastoma is the most common cancer diagnosis of the newborn period and has been detected with increasing frequency on prenatal ultrasound. Ninety percent of cases are diagnosed in the first 4 years of life, and it is rare after the first decade. Although neuroblastoma usually is a sporadic disease, children with hemihypertrophy or Hirschsprung disease are at increased risk. The distribution of neuroblastoma reflects its derivation from neural crest cells, so primary tumors are most common in the adrenal medulla, and other abdominal, pelvic, and thoracic paraspinal locations, including the posterior mediastinum. Common sites of distant spread (metastasis) include bone, bone marrow, liver, lymph nodes, and skin, where bluish subcutaneous nodules are said to look like blueberry muffins. Parenchymal CNS and pulmonary metastases are rare at diagnosis. Presenting signs and symptoms may be due to mass effects of the primary or metastatic tumor, sometimes relating to their tendency to form dumbbell lesions through the spinal cord. These include abdominal distention with a palpable mass, or hepatosplenomegaly, constipation, difficulty voiding, or leg weakness from abdominal or pelvic lesions. Horner syndrome or a neck mass is commonly seen in cervical lesions. Racoon eyes are periorbital ecchymoses attributable to retro-orbital tumor and are seen in children with widespread disease. Pallor, purpura, and fever are nonspecific findings but may represent bone marrow replacement by tumor. Patients also may present with nonspecific systemic symptoms due to metastatic disease, such as fever, weight loss or failure to thrive, bone pain, or limp. Paraneoplastic syndromes due to factors such as the catecholamine metabolites (vanillylmandelic acid and homovanillic acid) or vasointestinal peptide include hypertension and diarrhea. Opsoclonus-myoclonus (“dancing eyes, dancing feet”), often associated with cerebellar ataxia is uncommon, but, of pediatric patients presenting with this syndrome, 50% have been estimated to have neuroblastoma, which often can be detected only after careful radiographic evaluation.

Initial evaluation of children with suspected neuroblastoma is location specific but most commonly will include abdominal ultrasound, and contrasted CT or MRI scans of chest, abdomen, and pelvis. Chest radiographs may identify a tumor primary in the posterior mediastinum or a paraspinal mass. Further evaluation is intended to determine the extent of disease (stage) and its resectability for patients with locoregional tumor, and should be performed at a tertiary care center with pediatric oncology expertise. This should include technetium bone scan and skeletal survey, bone marrow aspirates, and biopsies. Radiolabeled metaiodobenzylguanidine (MIBG) scans are used in many centers to localize areas involved by tumor, and rely on the selective uptake of tracer by catecholaminergic cells. Other laboratory abnormalities that may be present in neuroblastoma include thrombocytosis, elevated serum ferritin and lactate dehydrogenase (LDH), and anemia (even without bone marrow involvement). Abnormal liver function tests may suggest liver involvement. Definitive diagnosis of neuroblastoma requires biopsy documentation, or a bone marrow involved by tumor cells consistent with neuroblastoma in combination with elevated VMA and/or HVA levels as measured on random or 24-hour urine collections.

Staging by the International Staging Study criteria (INSS) is most universally accepted and rates tumors according to extent of surgical and pathologic resection, and the presence of disease on one or both sides of midline from stage I (localized tumor confined to the area of origin, complete gross excision with negative ipsilateral and contralateral lymph nodes) through stage IV (metastatic). A subset of infants less than 1 year of age with small (stage I or II) primary tumors and a specific constellation of metastatic disease (skin, liver, bone marrow but not bone)—stage IV-S—is remarkable for a high incidence of spontaneous resolution.

Screening for neuroblastoma using VMA and HVA measurements on random urine samples has been studied in newborns and young infants. While this approach has been successful in identifying increased numbers of low-stage tumors in very young patients, it has not changed the incidence of metastatic lesions and has not had an impact on morbidity and mortality. It is not recommended as standard of care.

Nonspecific management of patients with neuroblastoma includes prevention or treatment of oncologic emergencies, which may arise even before a specific tissue diagnosis is made. Although metabolic emergencies are more likely to occur in leukemia or lymphoma, children with neuroblastoma may require emergency treatment for cord compression. Infants with stage IVS disease commonly require treatment for respiratory embarrassment or renal failure due to massive hepatomegaly. These problems may require chemotherapy (corticosteroids or cyclophosphamide), but may respond to low-dose local radiation or surgery (e.g., laminectomy for cord compression). The specific treatment of neuroblastoma varies with stage and prognostic category, and ranges from surgery (biopsy and/or resection) for low stage tumors with favorable prognosis to protocol-based multidisciplinary therapy including bone marrow transplantation for more aggressive lesions.

Patients are assigned to low-, intermediate-, or high-risk categories with low stage (I, II, IVS), age under a year, favorable histology according to the Shimada classification, and lack of amplification of the oncogene MYCN being the major determinants of low risk. Other favorable prognostic risk factors include tumor DNA aneuploidy, absence of deletions of chromosome 1p, and normal serum ferritin levels for children with advanced stage. Prognosis ranges from >90% likelihood of cure for patients with low-risk disease to <40% 2-year disease-free survival for high-risk patients. Recent preliminary data suggest that sequential myeloablative doses of chemotherapy with stem cell rescue may bump this last figure to as high as 60%.

Wilms tumor, also called nephroblastoma, is the most common renal cancer of childhood. The peak incidence occurs at 2–3 years of age and 75% of diagnoses are made before age 5. Boys and girls are affected equally, and there is a higher incidence in African-American children than in Asians or Caucasians. While most cases are sporadic, about 1% are familial, thought to be austosomal dominant with variable penetrance. Children with isolated congenital anomalies (such as hemihypertrophy, aniridia, or genitourinary malformations) or syndromes (such as Beckwith-Wiedemann syndrome, WAGR [Wilms tumor, aniridia, genitourinary tract abnormalities, mental retardation], or Denys-Drash syndrome [pseudohermaphroditism, glomerulopathy]) are at increased risk. Abnormalities of two maternally imprinted tumor suppressor genes, WT1 on chromosome 11p13 and WT2 on chromosome 11p15, have been implicated in the pathogenesis of Wilms tumor.

More than 90% of patients have local or regional disease at diagnosis. The most common site of distant disease is the lung. Children with Wilms tumor are most commonly asymptomatic and present with abdominal distention or a palpable flank mass, which is detected by an observant parent at bath time or during a routine physical examination. Other signs and symptoms, each found in about 25% of cases, include hypertension, hematuria, fever, or abdominal pain, and anemia (due to hematuria or intratumoral hemorrhage). Polycythemia and a reversible tumor-related bleeding diathesis with the laboratory findings of von Willebrand disease have been described. The physical findings of the above-noted syndromes should be looked for in patients with suspected Wilms tumor.

Screening for Wilms tumor in children with Beckwith-Wiedemann syndrome or aniridia is controversial. However, the American Academy of Pediatrics has recommended abdominal ultrasounds every 3 months for the first 2 years of life, then yearly until age 6.

Initial radiographic evaluation in children with suspected Wilms tumor should include an abdominal ultrasound to confirm the presence of an intrarenal mass, patency of the inferior vena cava, and appearance of the contralateral kidney. A contrasted CT or MRI scan will further clarify tumor anatomy, allow definition of nodal or hepatic metastases, and document function of the second kidney. Although CT scan of the chest may identify nodules, for purposes of staging and treatment, the National Wilms' Tumor Study Group (NWTS) defines pulmonary metastases by the presence of nodules on chest radiograph. Other useful studies include a complete blood count and serum chemistries, especially creatinine, urea nitrogen, and liver function tests. The surgical approach should be via a transabdominal incision to allow visualization and palpation of both kidneys and nephrectomy with en bloc tumor resection. Biopsy alone is discouraged under most situations and may lead to upstaging of tumors (below). Pathologic examination distinguishes Wilms tumor from precursor lesions such as nephroblastomatosis or from cancers such as rhabdoid tumor of the kidney or clear cell sarcoma (which previously were classified as Wilms tumor variants), and documents the presence of favorable (FH) or unfavorable histology such as diffuse anaplasia.

Staging is based on a combination of radiographic studies (which rule out the presence of pulmonary or hepatic disease in about 90% of cases), and a surgicopathologic description of the procedure with confirmation of extent of resection (e.g., gross total resection without microscopic residual disease) and nodal involvement. As defined by the NWTS, involved kidneys are individually staged from I (limited to the kidney and completely excised) through III (regional nonhematogenous tumor confined to the abdomen). Patients with metastatic disease (metastases may need to be documented by biopsy) are said to have stage IV disease, and patients with bilateral tumors (each of which is staged from I to III) are considered to have stage V disease.

The treatment of Wilms tumor is frequently cited as a model for multidisciplinary cooperation. The roles of surgery, radiation, and chemotherapy (vincristine,

dactinomycin, with or without doxorubicin and cyclophosphamide) for all categories of disease have been well-defined through the NWTS, and should be protocol based. Data suggest that chemotherapy should begin within 5 days of surgery. Courses of treatment can be as brief as 4 months for children with stage I FH (vincristine, dactinomycin only) to more than a year for children with stage III or IV tumors who also receive radiation to the tumor bed and whole lung, in the case of pulmonary metastases. Attempts to treat low-stage tumors with surgery alone or with shorter courses of chemotherapy have been disappointing.

Prognosis is inversely proportional to stage for children with stages I–IV. Children with bilateral disease appear to have a prognosis that is determined by the stage of the most involved kidney. Unfavorable histology, which is found in fewer than 10% of patients, also adversely affects prognosis for patients with at least stage II disease and conveys 50–60% mortality. By stage, 2-year disease-free survival and presumed cure for Wilms tumor patients with FH is stage I, >90%; stage II, 90%; stage III, 80%; and stage IV, 70–80%.

Malignant bone tumors are rare in pediatric patients overall, and cancer involving bone usually is due to metastasis from nonbone primaries. However, among adolescents primary malignant bone tumors are the third most common cancer category, exceeded only by leukemias and lymphomas. Osteogenic sarcoma is the most common of the bone cancers and, with Ewing sarcoma family of tumors (often referred to as peripheral primitive neuroectodermal tumor/Ewing sarcoma or PNET/Ewing), makes up more than 90% of malignant bone tumors. Osteosarcoma is less likely than Ewing sarcoma to be seen in the first decade; like Ewing sarcoma it affects males more than females, and it does not discriminate by race. In contrast, Ewing sarcoma is rarely seen in African Americans. The etiology of malignant bone tumors usually is not known, but there may be a genetic component. Patients with mutations of the RG tumor suppressor gene (such as those with bilateral retinoblastoma) or with mutations of p53 (such as those with the Li-Fraumeni family cancer syndrome) are at increased risk. Exposure to radiation and alkylating agents also predisposes to osteosarcoma as a second malignancy in patients with a prior childhood cancer.

The most common clinical presentation of malignant bone tumors is intermittent severe pain with or without warmth or swelling of the involved bone. Long bones, especially the tibia and femur, are common primary sites in osteosarcoma whereas PNET/ Ewings are equally likely to occur in the long bones or central axis. Fever is more common in Ewing sarcoma patients. About 20% of these bone cancers will be metastatic at presentation, with lung and other bones being the usual sites. Pulmonary symptoms are not common even with lung metastases. Median time from onset of symptoms to diagnosis is more than 6 months.

Evaluation of patients with severe or persistent bone pain should include plain radiographs, which, however, often are normal or show only subtle abnormalities. Nonetheless, these may show the characteristic metaphyseal lytic or sclerotic lesions of osteosarcoma with periosteal new bone formation or the lytic diaphyseal lesions of Ewing sarcoma, often with associated soft tissue. Increased uptake on bone scan and an MRI will demonstrate the extent of bony, intramedullary, and soft tissue involvement. Sedimentation rates are not always elevated and a normal value should not dissuade further work-up. Although fine needle aspiration has been used for tissue diagnosis, biopsy remains the standard of care. The presence of the characteristic t(11;22) on tumor cell cytogenetics is confirmatory for PNET/Ewing sarcoma.

Once a tumor diagnosis is confirmed, metastatic work-up should include chest radiograph, CT scan, and bone marrow aspirate and biopsy (for Ewing sarcoma). For both tumor types, prognosis is favorable (about 70% cure) for patients without metastases who have small primary tumors (<5 cm) of long bones. Patients with large or central axis bony lesions do less well, and patients with metastatic disease have a <20% cure rate. Other favorable prognostic features include normal serum alkaline phosphatase and LDH.

Treatment for osteosarcoma commonly relies on postbiopsy neoadjuvant chemotherapy, with combinations of cisplatin, doxorubicin, and methotrexate. Ifosfamide and etoposide have been included in many current regimens. Excellent response, demonstrated pathologically at the time of surgical resection of residual mass, conveys a favorable prognosis. In many cases, limb salvage techniques avoid the need for amputation. Chemotherapy is continued following definitive surgery, and immune modulators such as muramyl tripeptide phosphatidylethanolamine may have a front-line role in the management of osteosarcoma. Surgery also may be curative and frequently is palliative for patients with pulmonary lesions. For Ewing sarcoma, multiagent chemotherapy also is used prior to “local control” with high doses of radiation therapy or surgery. A role for myeloablative therapy with stem cell “rescue” in newly diagnosed Ewing sarcoma has been proposed. Because these tumors have a prolonged natural history, cure cannot be presumed for more than 5 years after diagnosis.

Late effects of treatment must be considered, since, over the next decade, as many as 1:250 young adults will be survivors of childhood cancer. About 40% of these survivors will have treatment-related medical or psychosocial problems, most of which can be predicted and even screened for, based on individual treatment histories. Major issues include growth and development (especially related to cranial radiation), fertility (in pubertal patients treated with high doses of alkylating agents or with gonadal radiation), learning disorders (cranial radiation or methotrexate), cardiotoxicity (best described following anthracyclines or radiation to the chest), and second malignancies (due to alkylating agents, epipodophyllotoxins, or radiation).

Books and Reviews

1. Arndt, C., and Crist, W. Common musculoskeletal tumors of childhood and adolescence. *N. Engl. J. Med.* 341:342–352, 1999.
   Up-to-the-minute medical and molecular progress on rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma, leaving out the still more rare pediatric sarcomas that encumber most textbook presentations. Wonderful color figures (that do not photocopy well, unfortunately), including light micrographs and radiographs, together with a comprehensive bibliography.
2. Lanzkowsky, P. (ed.). *Manual of Pediatric Hematology and Oncology* (2nd ed.). New York: Churchill Livingstone, 1995:696.
   Good overview of childhood cancers, with tables that lend themselves to quick reference. Excellent text for 2- to 4-week oncology rotations, where students should be able to read 10–20 pages a day and get through the whole thing.
3. Link, M. (ed.). Pediatric oncology. *Pediatr. Clin. North Am.* 44:791–1064, 1997.
   Includes reviews on the biology and treatment of neuroblastoma (pp. 919–937); the Ewing family of tumors, Ewing sarcoma, and primitive neuroectodermal tumor (pp. 991–1004); Hodgkin disease (pp. 891–906); brain tumors (pp. 907–918); osteosarcoma (pp. 973–989); Wilms tumor (pp. 939–952); and non-Hodgkin lymphoma (pp. 863–890). This volume is easy to read through in its entirety during the course of rotations on pediatric or hematology-oncology services.
4. Malatack, J., Blatt, J., and Penchansky, L. Hematology and oncology. In: Zitelli, B., and Davis, H. (eds.). *Picture Atlas of Pediatric Physical Diagnosis* (3rd ed.). St. Louis: Mosby-Wolfe, 1997:305–341.
   A photographic guide to physical findings in children with oncologic disease.
5. Pizzo, P., and Poplack, D. (eds.). *Principles and Practice of Pediatric Oncology* (3rd ed.). Philadelphia: Lippincott-Raven, 1997:1522.
   The definitive pediatric oncology text, with extensively referenced chapters on individual diseases, oncologic emergencies, treatment modalities, late effects of therapy, molecular oncology, and epidemiology. The comprehensive index is an excellent starting place for just about any aspect of pediatric oncology.
6. Pollack, I. Pediatric brain tumors. *Semin. Surg. Oncol.* 16:73–90, 1999.
   A state-of the-art review of general principles in the clinical presentation, diagnosis, and treatment of childhood brain tumors, with ample discussion as to how these differ from their more common adult counterparts.
7. Sandlund, J., Downing, J., and Crist, W. Non-Hodgkin's lymphoma in childhood. *N. Engl. J. Med.* 334:1238–1248, 1995.
   While maybe not quite as up-to-date with respect to therapy and prognosis as several of the more recent reviews, this is a particularly clear encapsulation of a complicated group of heterogeneous tumors. The color plates of histomicrographs are quite nice in this medical progress report.
8. Schwartz, C., et al. (eds.). *Survivors of Childhood Cancer. Assessment and Management.* St. Louis: Mosby, 1994:413.
   Chapter by chapter review of organ system–specific late effects of childhood cancer therapy written for the generalist, medical student, and even lay audience. Algorithms define schemes for monitoring patients based on what treatment they have received.
9. 1-800-4CANCER.
   A National Institutes of Health–funded telephone resource in English and Spanish. Personnel available to provide information about clinical trials, patient resources, anything you might need to know as a practitioner or a patient.

103. IMMUNITY AND PRIMARY IMMUNE DEFICIENCY

Lawrence K. Jung

Great strides in basic immunology, originally fueled by clinical studies of immunodeficiencies, have provided significant insights into the pathogenesis and therapy of these diseases. This underscores the relevance of understanding the immune defense mechanisms in clinical practice.

Immunity may be nonspecific or specific and may be mediated by cellular or humoral factors. The cellular components include lymphocytes, polymorphonuclear granulocytes (PMN) and macrophages; the humoral components include cytokines, immunoglobulins, and complement proteins.

An important nonspecific component of immunity is the protection provided by physical barrier at skin and mucosal surfaces, a breach of which can result in local and systemic infections. In such an event, the endothelial cells at these sites respond by producing vasoactive compounds (e.g., prostacyclin, nitric oxide) and cytokines (e.g., interleukin-8 and platelet activating factors). Along with a family of adhesion molecules (selectins) that appear on the endothelial and leukocyte cell surfaces to enhance cell-to-cell contact, these factors attract PMNs and macrophages to the site of injury (chemotaxis). These cells help to clear the site of foreign matter by ingesting and digesting the substance (phagocytosis) and by attracting other cells involved in specific immune response.

Humoral factors are also involved in nonspecific immunity. Upon activation, the components of the complement cascade activate each other and in so doing produce chemotactic, opsonic, and other factors that aid in the control of infection. In addition to the classic sequence of complement activation (Cl-C4-C2-C3, etc.) an “alternative pathway” (properdin pathway) is recognized in which the first few steps of the classic pathway are bypassed. Studies of patients with sickle cell disease and with C3b inactivator deficiency indicate an important clinical role of the alternative complement pathway.

Antigen-specific immunity is mediated by T and B lymphocytes and their products. From a common lymphoid progenitor in the fetal liver, these two cell types develop into their respective phenotypes in different organs: thymus for T cells, and bone marrow for B cells. During these processes, the lymphocytes acquire specific surface molecules to recognize antigens: T cell receptors for T cells, and surface immunoglobulin for B cells.

Of the circulating lymphocytes, approximately 70–80% are T cells and identifiable by the surface molecules, CD2 and CD3; 60–70% of these are characterized as CD4+ (helper/inducer T cells); 30–40% are CD8+ (cytotoxic/suppressor T cells). In addition to their usefulness in identifying these T cell subsets, these cell-surface molecules play crucial roles in cell function and HLA-associated antigen recognition. Activated T cells may serve as memory cells, secrete lymphokines or interleukins, or directly produce specific cytotoxic effects. They play a major role in host defense against viral, fungal, protozoal, and some bacterial pathogens; are responsible for delayed hypersensitivity; and appear to be important in immune surveillance against cancer.

B cells, representing 8–20% of the circulating mononuclear leukocytes, are identified by presence of surface immunoglobulins and B cell–specific molecules, CD19, CD20, and CD21, the function of which is under much scientific scrutiny. Upon stimulation by specific agents, B cells differentiate into plasma cells which produce specific antibodies. These antibodies, found in the g-globulin fraction of plasma, are differentiated on the basis of molecular weight, structure, and function into various classes (immunoglobulin G [IgG], immunoglobulin M [IgM], immunoglobulin A [IgA], immunoglobulin D, and immunoglobulin E). Immunoglobulin G antibodies are relatively small, are associated with protection against infectious agents, and constitute the commercially available human immunoglobulin (Ig) for intramuscular injection and intravenous g-globulin (IVIG) for infusion. Antibodies of this class are actively transported across the placenta, providing the full-term newborn with normal adult levels of IgG and full passive protection. (Because this transfer occurs primarily during the third trimester of pregnancy, the prematurely born infant has less IgG, and the very prematurely born infant, less than 34 weeks' gestation, may have virtually none.) Not much IgG is produced by the normal infant in the first month of life, and because the half-life of IgG is approximately 21 days, serum levels may drop as low as 200 mg/dL. (The lower limit of normal for an adult is 600 mg/dL.) Four subclasses of IgG are recognized; of them IgG2 has attracted the most interest in pediatrics because of its importance in immunity against the capsular polysaccharides of bacteria such as *Haemophilus influenza*. Immunoglobulin M antibodies are larger than IgG, are produced earlier than IgG in infections, and seem to be of particular importance against gram-negative bacteria. They do not cross the placenta and so are normally absent or present in low amounts in cord sera; their presence at birth suggests prenatal infection. Immunoglobulin A is of two types, circulating and secretory. The importance of circulating IgA is unclear; secretory IgA may well have an important role in the local immunity of mucosal surfaces, at least those of the gastrointestinal and respiratory tracts. Like IgM, IgA is normally absent at birth, and its presence implies prenatal infection.

Recurrent infections can result when any of the above immune mechanisms become abnormal. For example, bacterial infections often result when the skin in a child with eczema is broken down, or when the normal mucus clearance mechanism is impaired as in cystic fibrosis or in immotile cilia syndrome.

Abnormalities of phagocytic function often result in skin or deep-seated infections. An important example is chronic granulomatous disease (CGD), which is due to an abnormality of cytochrome b of the NADPH-oxidase complex in the phagocytes. As a result, the patient's PMNs ingest bacteria normally, but fail to generate hydrogen peroxide and superoxide (O_2–) to kill them. Defects in adhesion and/or chemotaxis due to a defect in the expression of the b- subunit of CD11 adhesion molecule results in leukocyte adhesion deficiency (LAD), characterized by recurrent infections of the skin, mucosa, and respiratory tract. Other locomotion defects due to actin assembly and disassembly have also been described.

Congenital complement deficiencies have a variety of clinical manifestations. Abnormalities involving the earlier components often result in the development of autoimmune diseases such as systemic lupus erythematosus, while the abnormalities of the terminal components are associated with recurrent meningococcal or gonococcal infections (the terminal component complex is critically important in bacteriocidal function). These primary disorders must be distinguished from secondary complement deficiencies since infectious and autoimmune diseases can result in complement consumption and abnormal CH50 measurement.

Immunodeficiency is commonly due to abnormalities in B cell function. A delay in the maturation of the B cell system results in transient hypogammaglobulinemia of infancy, which will improve in time. In contrast, X-linked agammaglobulinemia (Bruton agammaglobulinemia) and common variable immunodeficiency (CVID) require IVIG to protect these patients from recurrent bacterial infections that otherwise can lead to bronchiectasis and chronic pulmonary insufficiency. X-linked agammaglobulinemia, recently shown to result from a genetic defect in an important intracellular protein tyrosine kinase, Bruton tyrosine kinase (Btk), is characterized by the absence of circulating B cells. On the other hand, CVID is a heterogeneous group of diseases and is characterized by normal numbers of B cells and hypogammaglobulinemia.

A significant number of children with recurrent infections is associated with IgG subclass deficiency. IgG2-IgG4 deficiency, IgG3 deficiency, IgG1deficiency, and IgG4 deficiency have all been reported in association with recurrent infections. Although undoubtedly IVIG has clinical benefit, there is much controversy for its use in IgG subclass deficiency, as the deficiency often improves with time. Appropriate use of antibiotics with careful clinical follow-up is the best approach.

Hyper-IgM syndrome is a rare congenital disorder characterized by recurrent infections, low IgG and IgA, but normal or elevated IgM levels. The most common form is an X-linked disorder resulting from the abnormality of the CD154 expression on activated T cells. CD154 normally triggers CD40 on B cells to switch immunoglobulin production from IgM to IgG; its absence results in the clinical manifestation of this syndrome. Intravenous g-globulin, *Pneumocystis carinii* pneumonia prophylaxis, and stem cell transplantation are therapeutic options.

Cellular immunodeficiencies are much less common but usually have significant viral and fungal infections. Since T cells regulate B cell functions as well, T cell

deficiency often is associated with B cell dysfunction, as in the case of severe combined immunodeficiency (SCID). Many etiologic factors lead to the development of the syndrome of SCID, including adenosine deaminase deficiency, abnormality of HLA antigen expression (bare lymphocyte syndrome) and in the case of X-linked SCID, abnormal assembly of the cytokine receptors due to an abnormal common subunit for these receptors. DiGeorge syndrome, characterized by neonatal tetany, congenital heart disease, and abnormal T cell function, is due to a malformation of the third and fourth pharyngeal pouch during embryogenesis, and is associated with the deletion of 22q11.2. The defect is variable in expression and the T cell deficiency may be mild or severe. Wiskott-Aldrich syndrome (WAS) is characterized by thrombocytopenia, eczema, and T and B cell dysfunction, and recent analysis of the X chromosome has localized the WAS gene defect at the Xp11.22-11.3 region.

The physician's awareness is critically important in the early diagnosis of immunodeficiency and in a favorable outcome. A careful history is of particular importance when the physician suspects that the child may have an undue susceptibility to infection. Concern is often expressed about the number of infections the child has contracted, but this is not as important as the nature and severity of the infections. A normal child may have 100 infections in the first 10 years, the majority of which are self-limited viral infections of the gastrointestinal and respiratory tracts. This is often due to exposure to older siblings, or other children in an enclosed daycare/school setting during winter months. A child with recurrent infections but with consistent, normal gains in linear growth is unlikely to have a severe long-standing immunodeficiency, as failure to thrive is a notable feature of immunodeficiency. Mechanical factors rather than immune factors are more likely to be a cause of a child with recurrent localized infections (e.g., urinary tract infections). The pattern of infections often suggests the nature of a possible immune deficiency: A disturbance in B cell function (antibody) should be suspected if a child has recurrent, complicated, or severe pyogenic infections, whereas chronic recurrent *Candida* infection of the scalp, nails, and mucous membranes (mucocutaneous candidiasis) would prompt consideration of faulty T cell function.

The physical examination helps to identify known syndromes with associated immunodeficiency; for example, the presence of eczema, and petechiae (thrombocytopenia) suggest WAS, while absence of lymphoid tissues (e.g., tonsils, lymph nodes) suggests SCID.

Evaluation of phagocytic activity includes a total and differential white blood cell count to determine the absolute number of neutrophils, normally exceeding 1,500 per µL. The nitroblue tetrazolium test can be used to detect CGD. The ability of cells to migrate appropriately is assessed by a Rebuck skin window: Minor injury to the skin is inflicted by scraping, and coverslips are applied at various intervals; these are removed and stained to detect cells entering the injured area. More sophisticated tests are performed in specialized laboratories.

The complement system can be assayed by measuring the serum's ability to hemolyze opsonized red blood cells (total hemolytic complement or CH50). Quantitative assays of C3 and C4 are now widely available; assays of other components of the complement cascade still require the services of research laboratories.

B cell function can be tested by quantitative determination of immunoglobulins, and functionally by measurement of antibody titers to isohemagglutinins (anti-A, anti-B), or to the toxins of diphtheria and tetanus if the child has completed his primary series of immunizations. Quantitation of peripheral B cells and specific responses to antigens can be performed when necessary in specialized laboratories.

Screening tests available for assessing T cell immunity include chest x-ray, peripheral lymphocyte count (normally greater than 2,000 per µL), and skin testing for delayed hypersensitivity. The absence of a thymic shadow on chest x-ray, in the absence of stress, is highly suggestive of SCID or DiGeorge syndrome. Lymphopenia usually indicates T cell dysfunction since the majority of circulating lymphocytes are T cells. Flow cytometric analysis of the circulating T cells is now readily available for the study of the T cell subset abnormalities. Skin testing in infants may be difficult and is supplanted by more sophisticated measurement of T cell function using mitogens such as phytohemagglutinin to activate T lymphocytes.

Between one half and three fourths of children recognized as immunodeficient have abnormalities of B cell function, and another one fourth have combined T cell and B cell abnormalities. Only about 5% have deficits limited to T cell function, and 1% each have complement or phagocytic disorders. As knowledge increases, so does the number of clinically identifiable abnormalities.

Advances in treatment generally have not kept up with increased knowledge of basic immunopathogenic mechanisms. Supportive therapy remains vital and includes the avoidance of live viral vaccines, such as poliomyelitis vaccine, and prompt recognition and treatment of infections. Children with antibody deficiency benefit from IVIG infusion every 3 to 4 weeks. The replacement of immunoregulatory cytokines such as g-interferon for CGD and interleukin-2 for CVID hold promise for some patients. Bone marrow transplantation has been used for severe immunodeficiencies, such as SCID and WAS, if a suitable donor is available. Finally, recent advances in genetic engineering have made gene therapy an attainable goal in many immunodeficiencies.

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104. HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

Laura L. Gibson and William Jerry Durbin

Enormous progress has been made in the care of people infected with human immunodeficiency virus (HIV) during the past decade. Advances in both clinical and laboratory research have provided a better understanding of the pathogenesis, natural history, and treatment of HIV disease. For example, clinicians now routinely use laboratory parameters such as CD4 T cell counts and plasma levels of HIV RNA to make decisions regarding disease management. New antiretroviral agents such as protease inhibitors have improved the variety and effectiveness of drug treatment regimens. Although the emergence of drug resistance has made therapy more challenging, methods to identify resistance mutations are helping to direct more appropriate treatment choices. In addition, the risk of acquiring perinatal HIV infection has significantly decreased with new prevention strategies. All this progress has resulted in a decrease in morbidity and mortality for people infected with HIV, who are now considered to have a chronic infection rather than an inevitably fatal disorder. Nonetheless, efforts directed at management and prevention of HIV disease need to continue, especially given the enormous burden of this disease in third world countries.

According to the Joint United Nations Programme on HIV/AIDS (acquired immunodeficiency syndrome), by 1999 more than 33 million people around the world were infected with HIV, including 13.8 million women and 1.2 million children. The proportion of HIV-infected women is increasing, with the obvious risk of vertical transmission to their children. In addition, almost 14 million people have died from AIDS, including 4.7 million women and 3.2 million children. More than 95% of people living with or dying from AIDS are in the developing world, where the rates of infection and death, and the proportion of infected women and children continue to rise. In contrast, the rates of new cases and death from AIDS have been decreasing in the United States. However, certain subgroups of HIV-infected people in this country have not benefited from such trends. Women, minorities, and those infected by heterosexual contact (women) and injection drug use (men) represent an increasing proportion of adults and adolescents living with AIDS.

Ongoing research has also identified many unique characteristics of HIV disease in children, including modes and timing of infection, pathogenesis, diagnosis, clinical manifestations, and management. In the United States, vertical transmission is the most common mode of acquisition, with more than 90% of children with HIV disease acquiring the infection from their mothers around the time of birth. Infection occurs either during gestation (in utero; 25–30% of patients), during delivery (intrapartum; 70–75% of patients), or through breast-feeding (uncommon). Both maternal and obstetric factors can affect the risk of mother-to-child transmission. Illicit drug use, smoking, and unprotected sexual intercourse with multiple partners have been shown to increase the likelihood of transmission, as does primary HIV infection or advanced disease during pregnancy. Similarly, prolonged rupture of membranes, preterm delivery, maternal hemorrhage or infection, invasive fetal procedures, and vaginal (versus cesarean) delivery have all been associated with higher risk of vertical transmission. However, various modes of intervention may significantly decrease this risk. Before the mid-1990s, transmission rates ranging from 14–33% were reported from industrialized countries, including 20–25% in the United States. In 1994, the results of AIDS Clinical Trials Group (ACTG) Protocol 076 were published, showing that vertical transmission of HIV could be dramatically reduced (by two thirds) with zidovudine administration to the mother before and during delivery and to the infant for a few weeks after birth. More recently, a far simpler and less expensive regimen with nevirapine has been shown to markedly lower vertical transmission rates. As a result, routine prenatal HIV testing is recommended for all women, with prophylactic therapy recommended for HIV-infected women to prevent neonatal acquisition. This practice, as well as efforts to prevent and optimally treat HIV infection in women, delivery by cesarean section, and discouragement from breast-feeding, have lowered perinatal transmission rates to under 5% in some industrialized countries. In contrast, in many developing areas of the world, inadequate access to prenatal care, lack of simple and inexpensive prophylactic drug regimens, and lack of safe alternatives to breast-feeding act as barriers to reduction in vertical transmission rates, which may still be as high as 30–40%. Efforts to eliminate these barriers for women around the world are ongoing.

Horizontal spread of HIV continues to occur. Most children with transfusion-associated HIV infection acquired the disease prior to 1985, when screening of blood products for HIV antibody became routine in the United States. This mode of infection is now exceedingly rare, with the estimate that only 1 or 2 out of a million units of blood are contaminated. On the other hand, HIV infection via sexual contact remains a significant risk during adolescence. The proportion of adolescents, especially women, with HIV disease who acquired the virus by heterosexual contact continues to increase. Sexual abuse also accounts for a small number of cases in younger children and adolescents.

Human immunodeficiency virus belongs to the family *Retroviridae* and subfamily lentivirus, which includes viruses associated with slow disease progression. During acute infection, rapid viral replication and dissemination occur, marked by high levels of HIV RNA in blood (viral load), and decreasing CD4 T cell count. Eventually, the immune response brings viral replication under control, and an equilibrium between viral production and elimination is established (the set point). In adults, viral load decreases exponentially after a few months, while in vertically infected infants a high viral load persists through the first 1–2 years of life and then declines over the next several years. A highly variable period of clinical latency follows acute infection, although continued loss of CD4 T cells during this period eventually leads to severe immune dysfunction, with the subsequent array of clinical features of HIV disease. Due to both virologic and host immunologic factors, clinical disease appears sooner in vertically infected children compared to adults. For example, the relatively large CD4 T cell reservoir and inefficient immune responses of the infant may contribute to more rapid disease progression.

HIV selectively infects CD4 T cells, the primary regulatory cell of the immune system, as well as long-lived cells such as tissue macrophages and dendritic cells. The virus particle includes a central protein core containing two copies of RNA, surrounded by a host-cell derived lipid envelope that expresses viral glycoproteins. The RNA genome contains several well-described genes essential to the HIV life cycle. The *gag* gene encodes for proteins of the viral core, the *pol* gene for several viral enzymes including protease and reverse transcriptase, the *env* gene for envelope glycoproteins, and regulatory genes for products controlling viral replication. In order for infection to occur, viral envelope glycoprotein must bind to CD4 and a coreceptor molecule on the target cell membrane. This interaction allows fusion of cell membranes and entrance of the virus particle into the host cell. Catalyzed by reverse transcriptase, HIV RNA is transcribed to DNA, which integrates into the host cell DNA genome. The machinery of host cell protein synthesis produces both HIV genomic RNA and messenger RNA, which is translated to HIV-specific as well as host proteins. New virus particles are assembled in the cytoplasm and released, resulting in CD4 T cell death and propagation of HIV. Because reverse transcriptase lacks a means of correcting errors, mutations occur frequently and may be selected for by the host immune response or drug therapy.

In adults and children over 18 months of age, the detection of HIV antibody by enzyme-linked immunosorbent assay suggests, and the Western blot assay confirms, the diagnosis of HIV infection. However, during the first 18 months of life, such positive results may reflect maternal antibody acquired transplacentally. Therefore, the diagnosis in younger infants must be established using virologic assays, such as DNA polymerase chain reaction or viral culture. In children born to HIV-infected mothers, these assays are routinely performed at birth, 1–2 months, 4 months, and 6 months of age. Infants testing positive at birth were likely infected in utero, while those testing negative initially but positive on subsequent studies were likely infected during delivery. If virologic testing is repeatedly negative through 6 months of age, HIV infection is ruled out. The Centers for Disease Control and Prevention classification system for HIV infection in children less than 13 years of age outlines three general categories, which take into account *infection*, and *immunologic* and *clinical* status. Thus, *infection* may be present, absent (seroreverter), or indeterminate (a child less than 18 months of age, HIV exposed due to birth from an HIV-infected mother, with HIV infection status unknown). The *immunologic* categories refer to degree of immune suppression (none, moderate, or severe) compared to age-specific parameters of normal CD4 T cell count and percentage (since normal absolute CD4 T cell counts are relatively high in young children and decline to adult levels by 6 years of age). Four *clinical* categories refer to absent symptoms, mild symptoms (e.g., lymphadenopathy), moderate symptoms (e.g., chronic diarrhea), and severe symptoms (e.g,. *Pneumocystis carinii* pneumonia).

The course and manifestations of untreated HIV disease in children are highly variable. Potent antiretroviral drug regimens administered early in the disease course markedly decrease morbidity and mortality. Two patterns of natural disease progression have been described. Untreated children infected in utero tend to progress rapidly, with symptoms in the first few months of life and death by age 3–4 years. In contrast, children infected during delivery or through breast-feeding are often healthy for years, with disease progression and death after about a decade. Early symptoms may include lymphadenopathy, hepatosplenomegaly, or hematologic abnormalities. Otitis media and sinusitis affect a similar proportion of HIV-infected children compared to HIV-uninfected children, but in HIV-infected children these

conditions tend to recur or persist. In addition, in such children viral respiratory infections are more often symptomatic, severe, and prolonged, especially with agents such as measles, adenovirus, respiratory syncytial virus, influenza, and parainfluenza. Other common viral pathogens, including herpes simplex virus, varicella-zoster virus, and cytomegalovirus, may cause severe local or disseminated disease. Similarly, children with HIV frequently develop invasive bacterial infections, including pneumonia, meningitis, and sepsis, at times complicated by neutropenia or lymphopenia. Other HIV-related conditions include cardiomyopathy, nephropathy, hepatitis, and parotitis.

As immune function wanes, advanced HIV disease develops, and conditions that meet the definition of AIDS may result. Wasting syndrome is characterized by abnormal growth (weight loss or failure to gain weight), which may be associated with diarrhea. Encephalopathy, seen especially often in children acquiring HIV in utero, is manifested by impaired brain growth, a delay or loss of developmental milestones, and progressive motor dysfunction. Imaging studies may show brain atrophy or calcifications in the basal ganglia and periventricular frontal white matter, findings unique to children with AIDS. Pulmonary manifestations include lymphoid interstitial pneumonitis (LIP), a chronic, often asymptomatic inflammatory condition possibly related to Epstein-Barr virus, and *Pneumocystis carinii* pneumonia, the most common opportunistic infection seen in children with HIV disease. Fungal disease may be local, such as esophageal candidiasis, or disseminated, as in coccidioidomycosis, histoplasmosis, or cryptococcosis. Similarly, *Mycobacterium tuberculosis* and nontuberculosis species such as *Mycobacterium avium* or *Mycobacterium kansasii* may lead to severe systemic disease. Diarrhea and poor growth caused by gastrointestinal pathogens such as *Salmonella* species and *Cryptosporidium* may affect children with advanced HIV disease. Cancers such as non-Hodgkins lymphoma, leiomyosarcoma, and Kaposi sarcoma may occur but are rare.

Management of HIV disease in children involves routine health care maintenance, the institution of highly active antiretroviral therapy, and measures to prevent opportunistic infections. These children should generally adhere to the normal vaccination schedule, including the use of inactivated polio vaccine. Children without severe immunosuppression should receive measles-mumps-rubella and varicella vaccines. In addition, pneumococcal vaccine should be given and influenza vaccine is recommended yearly after 6 months of age.

Ongoing research to identify the most effective antiretroviral therapy for HIV-infected children continues to modify specific treatment guidelines. Frequent evaluation of clinical status, CD4 T cell counts, and viral load are used routinely to monitor disease progression and response to therapy. However, illness or vaccination may transiently decrease CD4 T cell count or elevate viral load, so that these values should be measured during clinical wellness or repeated if results are unexpected. While recommendations regarding specific drug regimens continue to change, it is clear that combination chemotherapy, using multiple potent agents, active at different points in the HIV life cycle, produce the best outcome in both adults and children. Nucleoside reverse transcriptase inhibitors (e.g., zidovudine), non–nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and protease inhibitors (e.g., nelfinavir) are currently available, and many new agents and combinations are under development. In addition, HIV-infected children with significant immunosuppression should receive prophylaxis against opportunistic infections. For example, trimethoprim-sulfamethoxazole or dapsone to prevent *P. carinii* pneumonia should be given to perinatally exposed infants aged 4–6 weeks (until HIV is ruled out or indefinitely if HIV positive) and to children with low CD4 T cell counts. Other agents to prevent disease from *Mycobacterium avium*, toxoplasmosis, and certain bacterial, fungal, and viral pathogens are also available.

HIV disease, like any other chronic illness, affects not only the child, but also his or her family and community. The child may be the first in the family diagnosed with HIV, prompting evaluation of parents and siblings. Several individuals and generations may be simultaneously infected, resulting in variable degrees of functional ability in both children and caregivers. Consequently, regular follow-up and adherence to a complex treatment regimen may present a considerable challenge.

The primary care physician plays an important role, not only in providing community-based evaluation and management, but also in working with daycare centers, schools, and other local resources to help provide the optimal environment for HIV-infected children. Although a tertiary care referral center may provide medical expertise, community-based support systems remain vital in maintaining a high quality of life for these children.

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Baylor's website; an excellent scientific guide for parents, explaining HIV and therapies available. Also a video on pill-swallowing!

105. IMMUNIZATIONS AND VACCINE-PREVENTABLE DISEASES

Kenneth B. Roberts

The administration of immunizing agents exemplifies pediatricians' commitment to preventive medicine. The success of the immunizing agents is considered the greatest public health accomplishment of the twentieth century by the Centers for Disease Control and Prevention, and is reflected in the present rarity of such diseases as diphtheria, tetanus, and paralytic poliomyelitis. By midcentury, it was possible to create a vaccine to prevent disease despite ignorance of which component of the vaccine was responsible for immunity and which component was responsible for toxicity. As advances were made in immunology and molecular biology, it became possible to create “designer vaccines,” based on purified immunogenic components, free of major side effects.

To be used in an entire population, an immunizing agent should be effective and long lasting; safe (or at least much less harmful than the natural disease); and practical to administer in terms of cost, route, and number of doses required. Vaccines currently recommended for the entire population in the United States are hepatitis B vaccine, diphtheria toxoid, tetanus toxoid, pertussis vaccine, *Haemophilus influenzae* type b (Hib) vaccine, poliomyelitis vaccine, measles vaccine, mumps vaccine, rubella vaccine, varicella vaccine, and pneumococcal vaccine. Rotavirus vaccine was introduced but was withdrawn when episodes of intussusception were linked to the vaccine. Many other vaccines are available for specific at-risk populations, including influenza vaccine, hepatitis A vaccine, and meningococcal vaccine.

Hepatitis B vaccine is the agent given earliest in life; the first dose is administered before discharge from the newborn nursery. Overt clinically apparent hepatitis B is not a frequent problem in children, but the younger children are at the time of acquisition of infection, the more likely they are to become chronic carriers, subject to the long-term consequences of hepatitis B: chronic liver disease and hepatocellular carcinoma. Infection is generally spread at three times in childhood: intrapartum, from mother to infant; during early childhood, in households or group child care facilities; and in adolescence, by sexual transmission and intravenous drug use. The risk to a child of ever acquiring hepatitis B infection is estimated to be 5%. Previous strategies, attempting to identify mothers at high risk for hepatitis B, proved ineffective. Immunization of all newborns is not only more effective, but also has the advantage of being less expensive than vaccinating older individuals, since the dose of vaccine necessary is much less. Hepatitis B vaccine is safe, engineered by recombinant technology, and induces antibody to hepatitis B surface antigen. Currently, a three-dose series is recommended, with flexibility regarding the timing. Generally, as noted, the first dose is administered in the first days of life, though concern about the level of mercury contained in the preservative thimerosal delayed the first dose in mid-1999 until 2–6 months of age. The second dose is given 1–2 months after the first, and the third between 6 and 18 months after the first dose. If the baby's mother is infected with hepatitis B at the time of delivery, vaccine must be supplemented with hepatitis B immunoglobulin; both are given within 12 hours after delivery. Adolescents who have not already received vaccine should also be immunized.

Diphtheria is now a rare disease in the United States, with fewer than 10 cases reported annually since 1980. The disease is caused by a toxin elaborated by *Corynebacterium diphtheriae.* The case fatality rate in unimmunized persons is 10% (15% under age 5 years), despite the availability of antibiotics to which the organism is susceptible. Once symptoms have appeared, penicillin and erythromycin are adjuncts only, the primary therapy being antitoxin administration and supportive care. The usual site of disease is the upper respiratory tract, and the characteristic sign is the thick, tenacious membrane caused by the necrosing action of the diphtheria toxin. Toxin also reaches distant sites, such as the myocardium and the central nervous system.

The toxoid used for immunization is effective in preventing disease but does not affect carriage of the organism; thus, fully immunized persons may, if exposed, become infected with the agent and infect others. Because reactions to diphtheria toxoid appear to increase with the age of the host, the dose of toxoid is decreased after age 6. Immunity can be maintained throughout life by the administration of booster doses every 10 years.

Tetanus, like diphtheria, is a disease that results from the effect of a bacterial toxin. The bacterium, *Clostridium tetani,* is a spore-forming, anaerobic, gram-positive bacillus found in soil and feces. Fewer than 100 cases of tetanus are reported each year in the United States. The toxin causes sustained muscular contraction, leading to such clinical signs as rigidity, spasm, opisthotonos, laryngospasm, and trismus (thus the common name “lockjaw”). Once signs develop, the disease progresses to a fatal outcome in 60–70% of cases. Neonatal disease may occur if maternal immunity is lacking and infection is introduced at the time of delivery. The organism is sensitive to penicillin, but tetanus immunoglobulin (or tetanus antitoxin in countries in which the globulin is not available) is recommended once the disease is established.

Tetanus toxoid has an exceptional record as an immunizing agent for both effectiveness and safety. After a primary series, boosters are required only every 10 years, although many clinicians choose to administer toxoid 5 years or more following the last booster if a deep and dirty wound is sustained, particularly a puncture wound contaminated with soil.

Pertussis (whooping cough) is caused by *Bordetella pertussis.* The disease is highly contagious. Prior to the use of pertussis vaccine in the United States, whooping cough was a major cause of death in infants; 7 times as many babies died from pertussis as from meningitis, for example. At present, the annual number of cases in the United States appears to be increasing. The earliest clinical stage of pertussis is a 1- to 2-week period of coryza, indistinguishable from the common cold. The paroxysmal stage follows, during which the child has the characteristic series of coughs, commonly leading to suffusion of the face, conjunctival hemorrhages, cyanosis, and petechiae; a seizure may occur, presumably from anoxia, but perhaps in part due to small intracranial hemorrhages or encephalitis. During the series of coughs, the child is unable to draw air in; as the paroxysm abates, there is an inspiratory gasp, the classic “whoop.” The paroxysmal stage lasts 1–2 weeks and is followed by a several-week convalescence, during which time a milder cough is present.

The mortality rate is highest in the first months of life; death is rare beyond infancy. The diagnosis is suggested by the clinical course and by a marked increase in total circulating white cells, 70–80% of which may be small mature lymphocytes. The sedimentation rate is normal or decreased, and the chest roentgenogram may show a pattern of central involvement known as the “shaggy heart sign.” The organism is cultured on a special medium (Bordet-Gengou agar with antibiotic added) but may be recovered only during the catarrhal stage and early in the paroxysmal stage. The fluorescent antibody technique is more rapid than culture but is associated with an unacceptable rate of false-positive and false-negative results in many laboratories.

Antibiotics are not effective in ameliorating the clinical course once the paroxysmal stage is reached; erythromycin appears to be effective in shortening the period of contagiousness, however. The acellular vaccines now used are as effective as previously used whole-cell vaccine, which was associated with a high incidence of minor complications and some uncommon but more serious effects. The acellular vaccines are based on antigens associated with attachment of the organism to respiratory epithelium cells or on pertussis toxin, or both. The basic immunizing series consists of three doses with two booster doses.

Diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine are usually combined in a single product, DTaP. None of the components are live, so there need be no concern about causing the disease in an immunocompromised host. Reactions to DTaP immunization are generally minor (e.g., local tenderness) and occur within the first 24 hours. The immunization schedule presently recommended has been selected on the basis of optimal response to the antigens and practical considerations about the timing of visits for health supervision in the first year of life. The primary series of DTaP consists of three doses given 8 weeks apart beginning at 2 months of age. Booster doses are required between 15 and 18 months and prior to school entry.

Haemophilus influenzae type b was, until effective vaccination, the predominant cause of meningitis in infants and children, and a major cause of other invasive diseases as well, including septic arthritis, septicemia, epiglottitis, pericarditis, and pneumonia. Initial vaccines, based on the Hib carbohydrate (polyribose phosphate), were not immunogenic in infants, the peak age group for meningitis. Conjugate vaccines, in which polyribose phosphate is attached to a protein, were developed that are immunogenic in young infants. They were first licensed in 1990. Because of the young age at which infants became ill with Hib disease, it was expected that an impact would be apparent rapidly, and that proved to be the case, as the incidence of invasive Hib disease decreased dramatically, by 90–95%. Vaccination is begun at 2 months of age, along with DTaP. The recommended series consists of two or three doses, depending on the particular product, and is complete by 12–15 months of age.

Poliomyelitis affected thousands of infants and children annually, prior to vaccination; now, it has been eliminated from this hemisphere. Poliovirus is a neurotropic enterovirus that, once ingested, multiplies in the gastrointestinal tract. Its particular affinity for anterior horn cells in the spinal cord leads to weakness and paralysis, although the majority of infected persons do not have a clinically detectable neurologic deficit.

Killed virus vaccine administered by intramuscular injection was introduced in the 1950s and replaced early in the next decade by trivalent live attenuated oral vaccine. The oral vaccine had the theoretic advantage of inducing local secretory immunoglobulin A, and the route of administration simulated natural infection. However, the oral vaccine also had the potential to produce poliomyelitis in immunocompromised individuals who were given the vaccine directly or who were exposed to vaccinees. Vaccine-associated poliomyelitis occurred at a rate of approximately 1 case per 5 million doses. As poliovirus was contained, inactivated vaccine of “enhanced” potency became increasingly desirable. Effective January 1, 2000, inactivated poliomyelitis vaccine became the sole product recommended for general use.

Measles is commonly diagnosed by parents whenever any maculopapular rash erupts. In fact, the clinical syndrome of measles is distinctive and should not be confused with such disparate conditions as miliaria (prickly heat), enteroviral exanthem, drug rash, or rubella. Measles is ushered in by low-grade fever, followed by conjunctivitis, coryza, cough, and then the characteristic enanthem of bluish-white dots on an erythematous base located primarily on the buccal mucosa (Koplik spots). The rash appears initially on the face and upper trunk; at this time, the face is swollen, and the child is miserable. Fever and cough become more prominent, and the rash progresses caudad, becoming confluent over the face and upper trunk during the second and third days. In all, the rash lasts 5–7 days and the illness 7–10 days. Encephalitis complicates recovery in 1 of 1,000 children with measles, and death may occur from the encephalitis or from pneumonia. Subacute sclerosing panencephalitis (SSPE), the prototype of a slow virus infection, is a debilitating and ultimately fatal late complication of infection with measles virus.

The vaccine currently used is an attenuated live virus vaccine; virus multiplication occurs after subcutaneous administration. Fever appears in 5–15% of children 5–6 days after inoculation but is rarely present on the first day after vaccination. Encephalitis as a complication appears to be a thousand times less common after the vaccine than after natural disease; SSPE is also less frequent after vaccine than after natural disease. Transplacentally acquired maternal antibody interferes with the immunogenicity of the vaccine. The recommended age for immunization currently is 12 to 15 months, with a second dose after age 5 years, either at school entry (age 5–6) or at entry to middle/junior high school (age 11–12).

Mumps is commonly asymptomatic; only two thirds have clinical disease. Parotitis is the most familiar manifestation, but it is the complications of mumps that warrant the administration of vaccine, mainly encephalitis and deafness. Encephalitis complicates 3 cases in 1,000, more commonly in males than females and with a slightly higher incidence after adolescence. A complete, usually unilateral hearing loss may result from the neurologic involvement. The incidence of orchitis may be as high as 20% in postpubertal males but is rarely bilateral; thus, the risk of sterility is low. Pancreatitis is rare in children. The mumps vaccine in current use is live attenuated virus, and is usually combined with measles and rubella vaccines.

Rubella, or German measles, was considered a mild disease of relatively little importance until the epidemic of 1964–1965, when the previously recognized capacity of rubella virus to act as a teratogen was strikingly demonstrated: An estimated 20,000– 50,000 infants were born with congenital rubella syndrome. The manifestations—mild in some newborns but devastating in others—include the following: growth retardation; eye defects (cataracts, glaucoma, retinopathy, and microphthalmia); cardiac defects (patent ductus arteriosus; septal defects; pulmonary stenosis, especially of the peripheral pulmonary arteries); deafness; thrombocytopenic purpura; hepatitis; bone lesions; cerebral defects (retardation, microcephaly); organomegaly; and others. Rubella acquired in childhood, in contrast to congenital rubella, is a mild illness, characterized by a maculopapular eruption and posterior auricular adenopathy.

The main clinical feature that distinguishes rubella from enteroviral infections is the former's occurrence in winter and spring rather than in late summer and early autumn. A clinical diagnosis of rubella is unreliable; serologic documentation is mandatory. In adults, a mild prodrome may be recognized, and arthralgias may be associated with the clinical illness, particularly in adult women. Nevertheless, the diagnosis is still usually difficult, and serum should be tested if rubella infection is suspected.

Rubella vaccine is a live attenuated virus. The main side effects, arthralgias and peripheral neuritis, appear to increase in frequency with age, from less than 10% in young children to nearly 33% in adult women. In the United States, current recommendations are to vaccinate preschool children older than age 12 months and to provide a second dose with measles vaccine during adolescence. Susceptible adult women should be vaccinated in the immediate postpartum period. Because of the theoretic risk to the fetus, pregnancy is a contraindication to the administration of vaccine.

Varicella (chickenpox) is the result of primary infection with varicella-zoster virus. Although often considered a mild disease that all children are “supposed” to contract, complications are both common and potentially severe (bacterial superinfection, especially with group A streptococcus; Reye syndrome; thrombocytopenic purpura; en-cephalitis; arthritis; glomerulonephritis). Pneumonia is more common among adults with primary infection than among children. “Shingles,” or herpes zoster, is the result of reactivation of latent varicella-zoster virus following primary infection. Varicella during the first or early second trimester of pregnancy may result in an embryopathy if the mother is not immune. Humans are the only known source of virus, but the contagiousness of infection is very high, making exposure likely by adulthood. Individuals whose immune systems have been compromised are at particular risk of severe disease.

The incubation period is generally 14–16 days but may occasionally be as short as 10 days or as long as 21 days after contact. A hyperimmune globulin, varicella-zoster immunoglobulin, is available for exposed, susceptible individuals at high risk of severe disease. Oral acyclovir may also help, but it has marginal benefit in children with normal immune systems. Salicylates are specifically contraindicated during chickenpox, because of the association with Reye syndrome.

Varicella vaccine is a live, cell-free, attenuated immunogenic vaccine, with a seroconversion rate of 97% or more when given after the first year of life. The vaccine is highly effective, and duration of immunity appears to be good. The incidence of zoster following immunization appears to be lower than the rate after natural chickenpox. The vaccine was first recommended for universal use in 1995. Children older than age 1 year and younger than age 13 years should receive one dose of vaccine. After age 13, varicella is more severe, and susceptible individuals should be immunized, but two doses, at least 4–8 weeks apart, are required.

Influenza vaccine is one of the vaccines currently recommended for high-risk groups only. Clinically, influenza is characterized by fever, myalgia, and cough. It is a cause of considerable morbidity, but pneumonia is usually a serious complication only in children with underlying chronic disease. Influenza is also a cause of severe croup in infants, and Reye syndrome was related to outbreaks of influenza B.

Influenza virus has the capability to change its antigenic structure and does so frequently; therefore, vaccine composition changes each year in response to early predictions regarding the strain that is likely to be predominant. In children, influenza vaccine is recommended routinely only for those who are immunocompromised, or have heart, lung, or renal disease. Doses of whole influenza A virus vaccine that are sufficiently immunogenic to protect against disease may also be toxic; therefore, two fractional doses of purified (“split-product”) vaccine are utilized in children under age 12 years. Influenza vaccine does not contain live virus. Because the composition of the vaccine changes from year to year, children who are candidates for vaccination must receive doses annually. A new live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine is more widely effective than single-strain influenza vaccine. The intranasal route of administration may make mass vaccination more acceptable and feasible than has been the case with vaccine that requires an injection.

Pneumococcal vaccine has been recommended for high-risk groups (e.g., children with sickle cell disease) at 2 years of age. The new vaccine is a protein-conjugate vaccine, similar to Hib, and is recommended for all children younger than 5 years of age. The protein-conjugate vaccine contains the seven strains of pneumococci most frequently incriminated in invasive disease. The largest prelicensing trial of the vaccine suggested greater than 90% efficacy against invasive disease (bacteremia, meningitis) caused by the strains contained in the vaccine and a reduction in pneumonia with consolidation and otitis media as well.

Hepatitis A tends to occur in outbreaks and in daycare centers. A vaccine is available, recommended for use where the local rate of hepatitis A is twice the national

average, and for consideration when the local rate is between one and two times the national average. Proponents of universal hepatitis A vaccine point out that such a strategy does not prevent against outbreaks. Resistance to requiring another immunizing agent may well be overcome by a combination vaccine that combines hepatitis A with other agents.

Meningococcal disease occurs in epidemics and sporadically. Epidemics are more likely when susceptibles are crowded together, as in dormitories and barracks. Vaccine is available against meningococcal groups A, C, W-135, and Y—but not B, a major cause of disease in the United States. The vaccine is used during epidemics caused by the groups contained in the vaccine. There is controversy regarding the benefit of the vaccine to students entering college. Current recommendations advise *offering* the vaccine to students who will be living in dormitory conditions.

A vaccine against *rotavirus* was introduced for routine use in infants, but within months of licensure in 1999, cases were reported associating the vaccine with intussusception. Further investigation demonstrated sufficient reason for concern that use of the vaccine was suspended. This episode will undoubtedly serve as a timely reminder that trials sufficient in size to demonstrate efficacy are not always large enough to determine the safety of an agent when given to an entire population.

Currently, in the United States, the vaccines identified for universal immunization (i.e., given to all children) are effective, but a large number of children remain unimmunized and, therefore, unprotected. Reaching these children—and their families—remains a difficult and important problem in pediatrics and public health. The Childhood Immunization Initiative was begun in 1993 to increase vaccination coverage levels among children during the first 2 years of life to 90% or greater by 1996. In 1998, among children 19–35 months, those high levels had been reached for poliovirus vaccine, Hib, and measles, and nearly reached for DTaP and hepatitis B. Varicella immunization had been administered to only 43%.

General Reviews

1. American Academy of Pediatrics Committee on Infectious Diseases. *Report of the Committee on Infectious Diseases* (25th ed.). Elk Grove Village, IL: American Academy of Pediatrics, 2000.
   The "Red Book," a concise "cookbook" of information about immunization and diseases, updated periodically by Committee Statements published in Pediatrics. *Definitely start here.*
2. Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Immunization Practices Advisory Committee (ACIP). *M.M.W.R.* 43(RR-1):1–38, 1994.
   The other major source of information is the Centers for Disease Control and Prevention; the recommendations of the Immunization Practices Advisory Committee (ACIP) are published in M.M.W.R., *generally in summaries designated "RR" (Recommendations and Reports). Some are also published in* J.A.M.A. *(e.g., see following reference).*
3. Centers for Disease Control and Prevention. Impact of vaccines universally recommended for children—United States, 1900–1998. *M.M.W.R.* 48:243–248, 1999. (Also published in *J.A.M.A.* 281:1482–1483, 1999.)
   Cites the number of cases of diseases from the beginning of the century to point out the dramatic benefit of vaccines.
4. American Academy of Pediatrics Committee on Infectious Diseases. Recommended childhood immunization schedule. *Pediatrics* 105:148–151, 2000.
   The schedule is reviewed, revised, and issued in January of each year by the American Academy of Pediatrics (AAP), the Immunization Practices Advisory Committee (ACIP) of the Centers for Disease Control and Prevention, and the American Academy of Family Physicians.
5. American Academy of Pediatrics Committee on Infectious Diseases. Combination vaccines for childhood immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). *Pediatrics* 103:1064–1077, 1999. (Also published in *M.M.W.R.* 48[RR-5]:1–15, 1999.)
   The scoop regarding mixing immunizing agents together: What you can mix, what you can't mix, limitations, and prospects.

Hepatitis B

6. Centers for Disease Control and Prevention. Update: Recommendations to prevent hepatitis B virus transmission—United States. *M.M.W.R.* 48:33–34, 1999. (Also published in *J.A.M.A.* 281:790, 1999.)
   Highest priorities for immunization remain the same: All newborns and high-risk children, adolescents at high risk, and, third, all adolescents.
7. Losonsky, G., et al. Hepatitis B vaccination of premature infants: A reassessment of current recommendations for delayed immunization. *Pediatrics* 103:e14, 1999. (Available at: www.pediatrics.org/cgi/content/full/103/2/e14.)
   The first dose should be delayed for premies at low risk, particularly those <1,700 g at birth. In addition to low birth weight, poor weight gain in the first 6 months of life is another factor associated with a poor immune response.
8. Cassidy, W. School-based adolescent hepatitis B immunization programs in the United States: Strategies and successes. *Pediatr. Infect. Dis. J.* 17(Suppl. 7): S43– S46, 1998.
   A major obstacle to immunizing adolescents is getting to them. School-based programs are one strategy. (Also see ref 36.)

Diphtheria, Tetanus, and Pertussis

9. Centers for Disease Control and Prevention. Tetanus surveillance—United States, 1995–1997. *M.M.W.R..* 47(SS-2):1–13, 1997.
   Only 5% of cases were younger than 20 years, including 1 case of neonatal tetanus; no deaths occurred among individuals with 3 or more doses of vaccine.
10. Advisory Committee on Immunization Practices (ACIP). Pertussis vaccination: Use of acellular pertussis vaccines among infants and young children. *M.M.W.R.* 46(RR-7):1–25, 1997 [erratum: *M.M.W.R.* 46:706, 1997], and American Academy of Pediatrics Committee on Infectious Diseases. Acellular pertussis vaccine: Recommendations for use as the initial series in infants and children. *Pediatrics* 99:282–288, 1997.
    A review of the efficacy and adverse reactions from trials with the various vaccines, and recommendations for use.

Haemophilus influenzae Type b (Hib)

11. Centers for Disease Control and Prevention. Progress toward eliminating *Haemophilus influenzae* type b disease among infants and children—United States, 1987–1997. *M.M.W.R.* 47:993–998, 1998. (Also published in *J.A.M.A.* 281:409–410, 1999.)
    Demonstration of greater than 95% decline in invasive Haemophilus influenzae *type b (Hib) disease. (United States and Canada:* Pediatr. Infect. Dis. J. *17[Suppl. 9]: S132–S136, 1998.)*

Poliomyelitis

12. Centers for Disease Control and Prevention. Progress toward global poliomyelitis eradication—1997–1998. *M.M.W.R.* 48:416–421, 1999.
    The Americas have been polio-free since 1991; the Western Pacific Region has not detected poliovirus since March, 1997; and poliovirus transmission in the European region is confined to southeastern Turkey. The remaining trouble spots are Africa and southern Asia.
13. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of poliomyelitis: Recommendations for use of only inactivated poliovirus vaccine for routine immunization. *Pediatrics* 103:171–172, 1999.
    *The AAP beat its own target date of 2001 for an all–inactivated poliovirus vaccine regimen (*Pediatrics *103:171–172, 1999). These latest recommendations also include indications for use of live oral poliovirus vaccine.*

Measles, Mumps, and Rubella

14. Advisory Committee on Immunization Practices (ACIP). Measles, mumps, and rubella—Vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps. *M.M.W.R.* 47(RR-8):1–57, 1998.
    The AAP joined the ACIP in recommending the second dose of measles-mumps-rubella vaccine at age 4–6 years: Pediatrics *101:129–133, 1998.*
15. Centers for Disease Control and Prevention. Progress toward elimination of measles from the Americas. *M.M.W.R..* 47:189–193, 1998.
    Nearly half of the cases are "imported." The number of cases reported in 1997 was an increase over the number in 1996, but only one tenth the number reported in 1990. (For more on global measles control and elimination, see M.M.W.R. *47[RR-11]:1–23, 1998.)*
16. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Pediatric AIDS. Measles immunization in HIV-infected children. *Pediatrics* 103:1057–1060, 1999.
    The vaccine should be given unless the host is severely immunocompromised.
17. American Academy of Pediatrics Committee on Infectious Diseases. Recommended timing of routine measles immunization for children who have recently received immune globulin preparations. *Pediatrics* 93:682–685, 1994.
    Higher than "usual" doses of immunoglobulin (e.g., for children with Kawasaki disease) require a longer interval than the "usual" 3 months before resuming an immunization schedule with live vaccines. The guidelines are too complex to be summarized here. Be sure to look them up when the situation arises!
18. American Academy of Pediatrics Committee on Infectious Diseases. Personal and family history of seizures and measles immunization. *Pediatrics* 80:741–742, 1987.
    Seizures following measles vaccine usually are associated with fever and appear to be typical febrile seizures; they do not signal encephalopathy. (Encephalopathy does occur, though rarely, clustered on days 8 and 9 after immunization: Pediatrics *101:383–387, 1998.)*
19. Beeler, J., Varricchio, F., and Wise, R. Thrombocytopenia after immunization with measles vaccines: Review of the vaccine adverse events reporting system (1990 to 1994). *Pediatr. Infect. Dis. J.* 15:88–90, 1996.
    The thrombocytopenia can be severe.
20. Weber, D., Rutala, W., and Orenstein, W. Prevention of mumps, measles, and rubella among hospital personnel. *J. Pediatr.* 119:322–326, 1991.
    Nosocomial spread still occurs—say, you're immune, aren't you?

Immunocompromised Hosts

21. McFarland, E. Immunizations for the immunocompromised child. *Pediatr. Ann.* 28:487–496, 1999.
    More than the ACIP/AAP recommendations regarding what to give. Also includes what response to expect and brief comments about the various immunizing agents.

Varicella

22. American Academy of Pediatrics Committee on Infectious Diseases. Varicella vaccine update. *Pediatrics* 105:136–141, 2000.
Includes a summary of the burden caused by varicella, and new recommendations regarding postexposure vaccination and what to do with immunocompromised children. (The vaccine has proved to be highly effective. See Curr. Opin. Pediatr. *11:3–8, 1999, and* Pediatr. Ann. *28:516–529, 1999.)*

Influenza

23. Centers for Disease Control and Prevention. Prevention and control of influenza. Recommendations of the Immunization Practices Advisory Committee (ACIP). *M.M.W.R..* annually (generally May or June).
Includes recommendation for "this year's model" of vaccine, plus a discussion of antiviral medications.
24. White, T., Lavoie, S., and Nettleman, M. Potential cost savings due to influenza vaccination of school-aged children. *Pediatrics* 103:e73, 1999. (Available at: www.pediatrics.org/cgi/content/full/103/6/73.)
With a companion editorial (pp. 1280–1282), the case is made for routine vaccination of schoolchildren. The authors concede that there is likely to be resistance to "another shot," so is the answer the live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine that is effective against influenza A (H3N2) and B? (Safety, immunogenicity, and efficacy are demonstrated: N. Engl. J. Med. *338: 1405–1412, 1998, with editorial on pp. 1459–1461.)*

Pneumococcus

25. American Academy of Pediatrics Committee on Infectious Diseases. Policy statement: Recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. *Pediatrics* 106:362–366, 2000.
Everything promised in the title. (Technical report follows, pp. 367–376.)

Hepatitis A

26. Advisory Committee on Immunization Practices (ACIP). Prevention of hepatitis A through active or passive immunization. *M.M.W.R.* 48(RR-12):1–37, 1999.
*After a brief review of clinical features, the ACIP focuses on the epidemiology and indications for vaccine (and immunoglobulin). The author of a thorough review on hepatitis A (*Lancet *341:1643–1649, 1998), advocates routine hepatitis A vaccination in childhood, see* N. Engl. J. Med. *340:644–645, 1999.*

Meningococcus

27. Advisory Committee on Immunization Practices (ACIP). Prevention and control of meningococcal disease, and meningococcal disease and college students. *M.M.W.R.* 49(RR-7):1–20, 2000.
Two reports combined in one supplement.

Complications of Vaccines

28. Advisory Committee on Immunization Practices (ACIP). Update: Vaccine side effects, adverse reactions, contraindications, and precautions. *M.M.W.R.* 45(RR-12): 1–35, 1996. [erratum in *M.M.W.R.* 46:227, 1997].
Lists the serious reactions to each vaccine (e.g., hepatitis B: anaphylaxis; measles: thrombocytopenia, anaphylaxis, and disseminated disease in immunocompromised individuals; etc.).
29. Evans, G. National Childhood Vaccine Injury Act: Revision of the vaccine injury table. *Pediatrics* 98:1179–1181, 1996.
A brief review of the value of the act, with a helpful table that lists, for each vaccine, what conditions qualify for compensation (complete with "aids to interpretation").

National Issues

30. Centers for Disease Control and Prevention. National, state, and urban area vaccination coverage levels among children aged 19–35 months—United States, 1998. *M.M.W.R.* 48:829–830, 1999.
They have reached the goal of 90% immunization against diphtheria, tetanus, pertussis, Hib, polio, and measles, but not hepatitis B.
31. The National Vaccine Advisory Committee. Strategies to sustain success in childhood immunizations. *J.A.M.A.* 282:363–370, 1999.
A total of 15 recommendations related to vaccination financing, implementation of recall/reminder systems and office-based assessments, information systems, and resources for underserved children. (The Task Force on Community Preventive Services provides a systematic review of 17 interventions to raise vaccination coverage levels: M.M.W.R. *48[RR-8]:1–15, 1999.)*
32. Advisory Committee on Immunization Practices, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Medical Association. Immunization of adolescents. *Pediatrics* 99:479–488, 1997. (Also published in *M.M.W.R.* 45[RR-13]:1–16, 1996, and *J.A.M.A.* 277:202–207, 1997.)
A hard-to-reach group!

106. INFECTIONS OF BONES AND JOINTS

Kenneth B. Roberts

In the preantibiotic era, skeletal infections usually resulted in crippling or death. Today, despite improved techniques for early diagnosis and the availability of effective therapeutic regimens, many children still endure lasting sequelae because of failure to recognize and treat skeletal infections promptly.

Bones and joints can become infected by either of two mechanisms: by hematogenous “seeding” of organisms during bacteremia, or by direct inoculation (as by a penetrating wound or an adjacent focus of infection).

Osteomyelitis results when organisms circulating in the bloodstream enter the bone and lodge in the distal end of the metaphysis, where the circulation is sluggish. A self-perpetuating cycle is initiated, as inflammation further compromises blood supply, and an abscess is formed within the confines of the rigid bone. Pus, under pressure, spreads through the haversian and Volkmann canals, extending disease within the bone and outward between the bone and periosteum. At this stage, there is “point tenderness,” an important diagnostic sign reflecting disease that is well localized to the small area of deep soft-tissue swelling and underlying inflammation of the metaphysis (metaphysitis). By the third day of disease, pus has collected beneath the periosteum, and bone destruction is present; deep swelling has extended to the muscles.

It is not until the tenth to twelfth day of illness that bone destruction and periosteal new bone formation are evident on x-ray examination. Radionucleotide scanning may give evidence of inflammation from the first day of illness and may be useful when the disease is suspected and clinical signs are equivocal.

The child with osteomyelitis is usually febrile, with an elevated white blood cell count and acute phase reactants, such as C-reactive protein and fibrinogen (which causes an accelerated erythrocyte sedimentation rate). History of skeletal pain or—particularly in infants—unwillingness to move a limb or bear weight obligates the clinician to conduct a particularly thorough examination for bone tenderness. Once bone infection is established, it may serve as a continuing source of organisms and perpetuate the initial bacteremia; systemic signs of sepsis may dominate the clinical presentation. Under such circumstances, it is imperative to begin therapy for septicemia while considering possible foci of infection, including the bones.

Blood culture yields the organism in more than 50% of patients with osteomyelitis. *Staphylococcus aureus* is the most common organism in all age groups, and initial therapy therefore includes the intravenous administration of a penicillinase-resistant penicillin. *Salmonella* seldom causes osteomyelitis in the general population but is a leading cause in patients with sickle cell disease. Antibiotic therapy for osteomyelitis is prolonged (3 weeks or more) to achieve satisfactory results; treatment of relapses or of chronic osteomyelitis is often unsatisfactory, emphasizing the need for effective management of the acute infection.

If the child is seen early in the course, most physicians and orthopedic surgeons are content with a clinical diagnosis, perhaps supplemented by a positive nuclear scan or a roentgenogram that suggests deep soft-tissue swelling; some advocate needle aspiration of the suspected area of involvement, providing a diagnostic specimen for Gram stain and culture. However, once the infection has become well established or medical management fails to produce clinical improvement within 24–48 hours, surgical intervention is needed.

The diagnosis of secondary osteomyelitis, that associated with a contiguous focus of infection, is often difficult to establish and requires frequent reevaluation for signs of bone involvement as the superficial focus responds to antibiotic therapy. Penetrating wounds may cause indolent infections, particularly in the bones of the foot, where *Pseudomonas* is often the culprit.

When organisms from the bloodstream infect a joint and produce *septic arthritis*, they elicit an exuberant inflammatory response, with upward of 50,000 white cells/µL of synovial fluid; the majority of these cells are polymorphonuclear leukocytes. The concentration of glucose is decreased, and there is a poor mucin clot. There are two adverse consequences of this septic inflammation: enzymes that destroy articular cartilage are released, and intra-articular pressure increases, sufficient in the hip to compromise blood flow to the femoral head and cause an avascular necrosis. The clinical presentation may be similar to that described for osteomyelitis, except that the site of infection is more obviously involved. Erythema, swelling, and local warmth are characteristic, as is the posture assumed by the child to decrease motion and provide a maximal opportunity for distention of the affected joint. Thus, flexion and limitation are the rule, and the child with arthritis of the hip will have abduction and external rotation as well. Diagnostic aspiration of the joint is mandatory, both to provide a diagnostic specimen and to relieve pressure. If septic arthritis of the hip (or the shoulder, although this is much less common) is present, arthrotomy and lavage is an indicated operative procedure. If the joint is more readily accessible (e.g., a knee or an elbow), repeated needle arthrocenteses may be adequate.

As in osteomyelitis, *S. aureus* is the most common organism, but other bacteria must also be considered in patients in certain age groups: coliforms in neonates, *Haemophilus influenzae* type b in infants (particularly those not immunized), and *Neisseria gonorrhoeae* in adolescents. Antibiotic coverage for the more common organisms is generally effective against other pathogens, such as streptococci (both groups A and B) and penicillin-sensitive pneumococci. Direct instillation of antibiotics into the synovial fluid is unnecessary, since the drugs commonly used pass from the bloodstream into the synovial fluid in therapeutic concentrations. The duration of therapy is usually 2–3 weeks.

Septic arthritis can also be caused by a penetrating injury with inoculation of the joint or by spread from an adjacent focus of osteomyelitis. The latter rarely occurs, however, unless the hip or shoulder is involved or the patient is less than 18 months of age; this is because the site of infection, the metaphyseal portion of the bone, is extra-articular in all but the hip and shoulder joints, and vessels in the involved area do not penetrate the epiphyseal plate except in early infancy.

In one series, sequelae were discovered in one fourth of the patients. *S. aureus* and *H. influenzae* were associated with equal proportions of residua, and no particular age groups seemed to fare worse than others. The outcome was affected by a delay in treatment, and children whose hip or ankle was infected were more impaired than those with septic arthritis of the knee.

The outlook for normal skeletal development and function in children with untreated osteomyelitis or septic arthritis is not good. Current antibiotic therapy is effective, but delays in initiating appropriate treatment can seriously compromise the outcome. The clinician must therefore be alert to the possibility of these diseases, recognize skeletal infection prior to signs of bone or joint destruction, and initiate appropriate therapy promptly.

Traditionally, antibiotic therapy has been administered parenterally in the hospital, but in the past several years, the efficacy of alternatives, such as home antibiotic therapy or high-dose oral therapy, has been demonstrated. Because of the problems resulting from inadequate treatment, many clinicians are wary of oral therapy; present recommendations for its use include ensured patient compliance and the ability to monitor serum bactericidal activity and adjust dosage as needed.

General Reviews

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Osteomyelitis

3. Roy, D. Osteomyelitis. *Pediatr. Rev.* 16:380–384, 1995.

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Osteomyelitis—plus vertebral infections, transient synovitis, septic arthritis, Legg-Calvé-Perthes disease, lower extremity injuries, and osteoid osteoma. (For a review of the limping child with a table of diagnostic considerations by age of the child, see Curr. Probl. Pediatr. *7:88–94, 1995.)*
7. Roine, I., et al. Serial serum C-reactive protein to monitor recovery from acute hematogenous osteomyelitis in children. *Pediatr. Infect. Dis. J.* 14:40–44, 1995.
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Good outcome using sequential intravenous-oral therapy without serologic monitoring. (In a companion editorial, pp. 883–884, Nelson expresses his reservations.)
9. Jacobs, R. *Pseudomonas* osteochondritis complicating puncture wounds of the foot in children: *Semin. Pediatr. Infect. Dis.* 8:250–253, 1997.
Beware of the nail through the sneaker. (Where does the Pseudomonas *come from? One vote for the sneakers:* J. Pediatr. *106:607–609, 1985.)*
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11. Anand, A., and Glatt, A. Salmonella osteomyelitis and arthritis in sickle cell disease. *Semin. Arth. Rheum.* 24:211–221, 1994.
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13. Wong, M., et al. Clinical and diagnostic features of osteomyelitis occurring in the first three months of life. *Pediatr. Infect. Dis. J.* 14:1047–1053, 1995.
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14. Glazer, P., and Hu, S. Pediatric spinal infections. *Ortho. Clin. North Am.* 27: 111–123, 1996.
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Septic Arthritis

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C-reactive protein appears more useful than ESR, since it returns to normal more rapidly (by day 10). (C-reactive protein may help identify the "sequela-prone" patient with osteomyelitis: Clin. Infect. Dis. *24:849–853, 1997.)*
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Limp

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Osteomyelitis, septic arthritis—and some other diagnoses to consider.

107. INFECTIOUS MONONUCLEOSIS

Kenneth B. Roberts

The diagnosis of infectious mononucleosis is based on the presence of three characteristic findings: (1) a specific clinical syndrome, (2) atypical lymphocytes, and (3) heterophile antibodies. To this list, some clinicians have added the requirement of abnormal liver function test results. By far, the most common etiologic agent in infectious mononucleosis is the Epstein-Barr virus (EBV), a herpesvirus. Epstein-Barr virus can be recovered from throat washings of patients with infectious mononucleosis, lending scientific support to the designation of this illness as the "kissing disease." Patients probably shed virus intermittently for life, but secondary infection rates are low. Serologic demonstration of immunoglobulin M (IgM) antibodies, rather than viral isolation, serves to establish the diagnosis of acute EBV infection. However, acute EBV infection is not equivalent to infectious mononucleosis. Epstein-Barr virus infection produces different clinical expressions in addition to the infectious mononucleosis syndrome, and infectious mononucleosis can be caused by other agents. For example, young children infected with EBV are much more likely to develop mild upper respiratory illness or asymptomatic seroconversion than "mono," while previously uninfected adolescents and young adults may mount the immunologic response that is expressed as infectious mononucleosis. Therefore, the three original requirements maintain a position of central importance for the diagnosis of infectious mononucleosis, which appears to be an age-related, host immune response, usually to primary infection with EBV.

The *classic clinical syndrome* in adolescents and adults consists of fever, lymphadenopathy, exudative pharyngitis, and splenomegaly. The lymphadenopathy is generalized, with notable enlargement of the posterior cervical nodes. The tonsillopharyngitis may be confused with diphtheria or streptococcal infection; an aid in differential diagnosis is the longer prodrome present in infectious mononucleosis and the relatively later appearance of palatal lesions. Serum aminotransferase (transaminase) levels are almost universally elevated during clinical disease, but jaundice is much less common than aminotransferase abnormalities. Signs of hepatitis may dominate the clinical presentation in some patients, and the correct diagnosis may be delayed. Rash is an infrequent occurrence unless ampicillin is administered; under ordinary circumstances the antibiotic is associated with rash in 10% of patients, but those with infectious mononucleosis have nearly a ten-fold increase in the incidence of this complication. Periorbital edema occurs in one third of patients, and a multitude of other clinical problems, involving virtually every organ system, has been reported.

Not all patients have all of the clinical features of classic infectious mononucleosis; rather, their signs and symptoms tend to cluster to form particular subsyndromes, characterized as (1) pharyngeal or "anginose," (2) glandular, and (3) febrile or "typhoidal." The *pharyngeal* or *anginose* presentation is dominated by exudative tonsillitis with marked pharyngeal edema. The onset tends to be abrupt, fever is high, and the patient often appears toxic. Patients with this form of infectious mononucleosis tend to seek medical attention promptly, and the diagnosis therefore is usually made early in the course of the illness. Barring complications, the resolution of symptoms tends to be rapid, within 5–7 days. Upper airway obstruction due to massive lymphoid hyperplasia and pharyngeal edema may occur. The differential diagnosis of this clinical type of infectious mononucleosis includes streptococcal pharyngitis, which can frequently occur along with EBV, so the presence of one does not necessarily preclude the other. The *glandular* type of infectious mononucleosis is characterized by marked lymph node enlargement out of proportion to the pharyngeal involvement. Fever is present, more likely to be low grade and intermittent, and the patient does not look very ill but does have significant malaise. Medical attention is often delayed. The differential diagnosis of this clinical type includes other infections (e.g., toxoplasmosis) and conditions that are not as benign as infectious mononucleosis (e.g., lymphoma, leukemia, and human immunodeficiency virus [HIV] infection). The *febrile* or *typhoidal* subsyndrome is characterized by prolonged fever and malaise, without significant pharyngitis; lymphadenopathy is often delayed, appearing 2–3 weeks into the illness. Gastrointestinal symptoms may be pronounced, with anorexia, nausea, and vomiting. The onset is insidious, and as with the glandular form, the diagnosis may be missed initially or medical attention may be delayed. Similar clinical features are also seen in infections with cytomegalovirus (CMV), *Toxoplasma gondii*, rubella virus, adenovirus, human herpesvirus 6 (HHV-6), and HIV, as well as in the namesake, typhoid fever. Symptomatic CMV infection most closely resembles the typhoidal type of infectious mononucleosis, and accounts for half or more of heterophile antibody–negative mononucleosislike disease. Hematologic findings include an atypical lymphocytosis; mild hepatitis is also evident chemically, though not clinically apparent.

Atypical lymphocytes in infectious mononucleosis have been classified by Downey as monocytoid, plasmacytoid, or blastoid. All three cell types have abundant cytoplasm that may contain large vacuoles or appear "foamy." The cells are characteristically indented by neighboring erythrocytes. When a child has atypical lymphocytes, splenomegaly, and generalized lymphadenopathy, and particularly when thrombocytopenic purpura is also present (a not infrequent complication), the diagnosis of leukemia may be suspected; careful attention to the morphology of the lymphocytes may help establish the correct diagnosis, but examination of bone marrow may be required.

Heterophile antibodies form the third part of the triad of EBV infectious mononucleosis. Patients produce antibodies that agglutinate sheep red cells; this peculiar reactivity of human antibody against sheep protein is the basis for the term *heterophile* antibody. The antibody is predominantly of the IgM class and is absorbed by bovine red blood cells but not by guinea pig kidney cells, permitting a distinction from the heterophile antibody produced by patients with serum sickness. Although CMV and *T. gondii* may induce atypical lymphocytes and produce a clinical syndrome compatible with infectious mononucleosis, neither agent is associated with heterophile antibodies.

There is no specific therapy for infectious mononucleosis. Acyclovir does not appear to be helpful. Steroids may be useful in patients with severe odynophagia and impending upper airway obstruction, but they are required for only a few days.

The complications of greatest concern are upper airway obstruction during the acute phase of disease, and splenic rupture during the acute illness or the early convalescent period, the latter estimated to occur in 0.1–0.2% of patients. Other complications include neurologic involvement (e.g., meningoencephalitis, aseptic meningitis, Guillain-Barré syndrome, peripheral neuropathies, transverse myelitis) and thrombocytopenic purpura. In general, patients with acute onset recover more quickly than those with insidious onset, but convalescence may be quite prolonged. Chronic fatigue syndrome is NOT a sequela of EBV infectious mononucleosis, however.

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108. TUBERCULOSIS

Alan P. Picarillo and William Jerry Durbin

Tuberculosis remains a most serious worldwide disease, causing infection in one third of the world's population and 3–5 million deaths annually. In the United States, about 15 million people are infected. The decline in the number of reported cases of active tuberculosis disease in the United States, which began in the 1950s, ceased in the mid-1980s; by the late 1980s and the early 1990s the number of cases of tuberculosis reported to the Centers for Disease Control and Prevention (CDC), including cases among children less than 5 years old, increased annually. However, since 1993 the number of tuberculosis cases has again turned downward and is at an all-time low in the United States, with 18,000 new cases in 1998. This decline in the number probably reflects increased awareness of tuberculosis among health care practitioners and increased funding of public health care programs.

Tuberculosis is a disease of the underprivileged, the immunocompromised, the elderly, and the highly exposed. The highest risk to children comes from exposure to infected adults who have been residents of nursing homes or correctional institutions, foreign born, users of intravenous drugs, homeless or poor, infected with the human immunodeficiency virus (HIV), or health care workers. Coinfection with HIV has been a strong risk factor for tuberculosis disease in the United States. Although only small numbers of HIV-infected children have been reported to have tuberculosis, many healthy children have acquired tuberculosis from HIV-infected adults. Cases in children less than 15 years of age account for approximately 7% of total cases. In addition, the influx of foreign-born individuals from high-prevalence areas has added to the number of cases in the United States. As the numbers of tuberculosis cases declines, the proportion that is in the foreign born continues to increase, accounting for 36% of all cases in 1996.

The trend of increasing drug resistance of tuberculosis is very concerning. Reports from inner cities, hospitals, and prisons have documented that up to one third of *Mycobacterium tuberculosis* isolates may be resistant to the most commonly used primary drugs, isoniazid and rifampin. Overall resistance in the United States for *M. tuberculosis* isolates approaches 10% for isoniazid and 2% for both isoniazid and rifampin. Such isolates often develop in individuals treated with only single agents or who have had poor adherence to therapy. Treatment of patients with these multidrug-resistant organisms, even with the best second-line agents, is often unsatisfactory, with significant morbidity and mortality. Much of this drug-resistant tuberculosis has been seen in HIV-infected persons and in their close contacts, including health care workers and children.

Children acquire tuberculosis by inhalation of infected droplet nuclei. Although casual contacts may be the source of infection for children, the majority of cases are acquired from adults who are regular or household contacts of the infected child. Of note, children themselves, even with active pulmonary disease, are not usually contagious to others. The initial pulmonary lesion caused by *M. tuberculosis* is known as the primary complex and consists of (1) a small alveolar focus, (2) an associated lymphadenitis, and (3) enlarged regional lymph nodes. Often this process becomes radiographically detectable as a segmental infiltrate referred to as the collapse-consolidation lesion; it results from the primary pulmonary focus and atelectasis due to bronchial obstruction by the enlarged lymph nodes, with or without secondary bacterial infection. This lesion evolves over a several-month period following primary infection, with subsequent gradual calcification during the healing phase.

Several clinical outcomes may result following primary tuberculosis infection of the lung. Asymptomatic disease is most frequent: a child found to be tuberculin skin test–positive has no clinical symptoms, a normal physical examination, and a chest x-ray that either is normal or demonstrates a segmental lesion, possibly with hilar adenopathy. Another manifestation is endobronchial tuberculosis, in which bilateral large infiltrates are seen on chest x-ray; the child may have cough and fever or may be virtually asymptomatic. In older children, a third presentation, pleurisy with effusion, may be seen. These children develop fever, chest pain, and shortness of breath; on physical examination of the chest, there is dullness to percussion, and breath sounds are diminished. Thoracentesis reveals an exudative effusion with a high protein, low glucose, lymphocytic infiltration, and an absence of mesothelial cells. Tubercle bacilli may be present in small numbers in the fluid; the yield from culture of a pleural biopsy may be higher, and histologic study demonstrates granulomas. Another endothoracic complication, progressive primary pulmonary tuberculosis, is rarely seen in children. It results from a failure of host defenses to contain the primary lesion, which enlarges and liquefies, forming the so-called primary cavity. Affected patients are ill with cough and fever.

In addition to developing these initial intrathoracic complications, the majority of children with primary tuberculosis experience lymphohemogenous spread. Tubercle bacilli spread to any of a number of organs, including the meninges, bones, joints, kidneys, and lung apices. Most children do not develop symptoms from these dormant lesions, but the possibility of reactivation of disease in these sites remains through their lifetime. Miliary tuberculosis represents the most serious form of hematogenous spread and is thought to arise from discharge of a caseous focus directly into a blood vessel. It can occur in the early months after infection, especially in small infants, or at a later time, particularly in immunosuppressed individuals. Such individuals present with fever, chills, anorexia, weight loss, and pulmonary symptoms. Lesions may be found throughout the lungs, liver, spleen, and bone marrow. Tuberculous meningitis may be seen as part of miliary tuberculosis but more commonly occurs when a cerebral subcortical focus breaks down, inoculating the subarachnoid space.

Routine skin testing for tuberculosis is no longer recommended in the United States for all children. However, screening by history for children with risk factors (e.g., foreign-born children, children living in high-prevalence areas, or those with HIV infection or in a household with an HIV-infected individual) is recommended, with skin testing of those at risk. The simpler but less reliable multipuncture test has been replaced by the Mantoux test containing five tuberculin units (TU) of purified protein derivative (PPD). Guidelines for interpretation of PPDs have undergone modification in the past decade. Thus, individuals with small reactions (i.e., less than 5 mm induration) are not considered to have “positive” reactions (based on the fact that most such positive skin test reactions in fact represent cross-reaction due to infection with nontuberculous mycobacteria) unless (1) they are contacts of known cases; (2) they have abnormal chest x-rays; (3) they show clinical evidence of tuberculosis; or (4) they are HIV infected or otherwise immunosuppressed. A cutoff of 10 mm is used for children less than 4 years of age and for older children with medical risk factors (e.g., diabetes, lymphoma, malnutrition, renal failure) or with other risk factors for acquiring tuberculosis, such as contact with residents of prisons or nursing homes, the homeless or poor, users of intravenous drugs, health care workers, or foreign-born persons from high-prevalence countries. For children with no risk factors, 15 mm is the usual threshold for a true-positive, since reactions smaller than 15 mm in these individuals generally represent false-positive results.

Practitioners are often faced with the problem of interpretation of PPD skin testing of patients who have previously received bacille Calmette-Guérin (BCG) vaccination. Bacille Calmette-Guérin is prepared from live-attenuated strains of *Mycobacterium bovis* and currently given at birth or shortly thereafter in over 100 countries. Bacille Calmette-Guérin generally prevents disseminated or central nervous system disease caused by *M. tuberculosis* but does not necessarily prevent infection with *M. tuberculosis*. Purified protein derivative skin test reactivity may occur after BCG vaccination, but does not generally persist at a size greater than 10 mm for more than a few years after vaccination unless there has been exposure to *M. tuberculosis*. Thus, a positive PPD greater than 10 mm from BCG is unlikely more than 5 years after a single vaccination with BCG in infancy. Infection with *M. tuberculosis* should be assumed in such children, and evaluation and treatment or prophylaxis should be instituted.

The diagnosis of active tuberculosis in children often is difficult, in part because of the low numbers of tubercule bacilli found in tissues and secretions. Since children usually are unable to produce sputum, gastric aspiration may be necessary to obtain a proper specimen. Gastric secretions should be obtained early in the morning after an overnight fast and before the child arises. Newer radiometric culture methods combined with the use of DNA probes allow the identification of *M. tuberculosis* in 1 to 3 weeks rather than the 4 to 8 weeks required by traditional culture. New nonculture research techniques for detecting *M. tuberculosis* (e.g., by polymerase chain reaction, antigen assays, antibody responses, or biochemical markers) hold promise for becoming useful clinical tools. Newer technology that utilizes DNA probes for identification of *M. tuberculosis* directly in sputum or other clinical specimens is under study, with the possibility of rapid identification within hours instead of weeks.

Therapy for tuberculosis needs to take into account the increased incidence of resistance to the traditionally used agents isoniazid and rifampin. For children with active disease, a 6-month regimen of isoniazid, rifampin, and pyrazinamide is recommended for the first 2 months, and isoniazid and rifampin for the remaining 4 months, assuming a susceptible organism, with the goal of using at least two drugs active against the organism. If resistance is suspected, a drug by a nonfamily member (for example, ethambutol) is added until drug susceptibility testing is available. Directly observed therapy—observation of the administration of medication by a non-family member—is the gold standard, to assure compliance. In addition, information about the drug susceptibility of the isolates from the adult contact should always be obtained if possible. Infants, children, and adolescents with a positive skin test, but no evidence of active disease or previous exposure to antituberculosis drugs, should be given prophylactic isoniazid unless resistance is suspected or a specific contraindication exists, in which case an alternative regimen may be recommended. Duration of therapy is 6–9 months for these patients, with the exception being HIV-infected individuals, for whom 12 months of therapy is recommended. Fortunately, children tolerate antituberculous medication very well, and discontinuation because of side effects is rarely necessary.

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109. ROCKY MOUNTAIN SPOTTED FEVER AND LYME DISEASE

Kenneth B. Roberts

Rocky Mountain spotted fever (RMSF) and Lyme disease (LD) are both transmitted by ticks. In both, the diagnosis is clinical early on, when treatment is easiest and most effective; serologic confirmation is possible later, but early treatment may interfere with the expected rise in antibody levels. Both disorders present acutely with fever, headache, myalgia, and a characteristic rash, but there the similarity ends. The rashes and the clinical courses are quite different. Untreated, RMSF progresses to a fatal outcome, whereas LD is self-limited, only to return in a second and third phase. The agent of RMSF is a *Rickettsia*, and that of LD is a spirochete.

A century ago, Idaho physicians recognized a distinct febrile exanthem that was referred to as “Snake River measles.” The present name, *Rocky Mountain spotted fever,* stems from the work of Howard Taylor Ricketts in the Bitter Root Valley of Montana, and the subsequent establishment in that state of the Viral and Rickettsial Disease Center. The incidence of RMSF in the Rocky Mountain states 50 years ago was 100 times what it is there now, while the incidence in the Mid-Atlantic region remains essentially unchanged; thus, the incidence of the disease now is 10–20 times higher in the East than in the Rocky Mountain states.

The infecting organism, *Rickettsia rickettsii,* is about 1 µm in length and 0.2–0.3 µm in width. It is able to grow in both the nucleus and cytoplasm of infected cells of ticks and mammals. Ticks, generally wood ticks or dog ticks, become infected by either of two mechanisms: transovarially or by feeding on an infected host. Once infected, the tick carries the organism for several years and serves not only as a vector but also as a reservoir of the disease. In certain areas of the Mid-Atlantic seaboard, as many as 5% of ticks are infected.

Ticks require three different hosts in their life cycle. After the tick eggs hatch, the larvae migrate to vegetation and await the first host. If the larvae are successful in negotiating a host, they engorge themselves on its blood, fall off, and molt to a new stage. The nymphs engorge themselves on a second host, fall off, and molt again. The adults then find a final host for feeding (tick control is complicated by the adult tick's ability to survive up to 4 years without feeding). When the adults feed, attachment may last for 3–12 hours, but at least 1.5–2.0 hours are required before the tick injects any infected material from its stomach contents into the host. A rational, effective means of protection against RMSF for people living in areas where ticks are present is to inspect themselves (and their children) every few hours.

Rocky Mountain spotted fever is a true infectious vasculitis. The organism invades and multiplies in endothelial cells, resulting in damage that is clinically manifested by edema and petechiae; in severely ill patients, fluid balance and maintenance of adequate intravascular volume are difficult problems in management. Vascular lesions are most readily appreciated in the skin but also occur in other tissues, notably the myocardium and central nervous system (CNS).

The classic presentation is an ill patient with headache and fever. The headache is described as excruciating in severity and is generalized, although frequently more intense frontally. Fever is low grade in the morning but high (40.0–40.6°C, 104–105°F) during the day; the course of fever may be as short as 2 days in very mild disease or as long as 3 weeks in severe untreated disease. Myalgia may be prominent, with the abdominal muscles commonly affected; arthralgias may also be present. In addition to headache, about 50% of the patients have neurologic signs, such as lethargy, restlessness, and insomnia.

The rash of RMSF characteristically appears 2–6 days after the onset of fever. The initial lesions are pink macules (which may become papular) on the extremities, especially on the wrists, ankles, palms, and soles. After 6–12 hours, the rash extends centripetally to the trunk; only later do petechiae appear. If the rash progresses, hemorrhagic lesions coalesce and may lead to gangrene (purpura fulminans).

The diagnosis becomes clear as the disease progresses but may be difficult in the early stages, when treatment is most effective. The character and distribution of the rash may suggest atypical measles, but that disorder may be distinguished by its pulmonary manifestations and occurrence in the winter and spring months. Skin lesions caused by meningococcemia are often painful when stroked, and the organism may be seen if the lesion is aspirated and the specimen Gram stained. The rash of enteroviral infection is usually generalized, and fever is not as prominent as in RMSF. Serologic tests are not helpful early, since they are not positive until the second week; “acute” and “convalescent” titers are necessary to determine if infection has taken place. If therapy is begun early and is effective, however, there may be delay in a rise in antibody titers or no rise at all. Rickettsiae may be demonstrated in skin biopsy specimens by immunofluorescence; the technique takes only a few hours, but is not generally available.

Treatment with tetracycline, doxycycline, or chloramphenicol shortens the duration of fever and improves the survival rate. Duration of treatment is often based on the response of the patient, which correlates with the extent of illness at the time treatment is instituted: those who are treated early in the course generally require only a few days of treatment, whereas those who are not treated until vascular complications are evident are treated longer.

Prevention, as noted, is based on removal of ticks before they introduce infected material into the host. Crushing the tick in the process of removing it is to be avoided, since infected material may be squeezed from the tick into the “wound.” An abrasion is sufficient for inoculation; a penetrating bite is not required.

Rocky Mountain spotted fever is the most common of the rickettsioses in the United States. It is preventable and treatable, yet the case fatality rate remains 5–10%. It appears clear that earlier recognition is required, so that appropriate therapy may be administered.

Lyme disease has only been recognized as an entity since 1975, yet it is now considered the most frequent tick-transmitted disease in the United States. Its name derives from an outbreak in Lyme, Connecticut, of what was originally diagnosed as monoarticular juvenile rheumatoid arthritis (JRA); investigation of the cluster of cases led to the recognition of what was called Lyme arthritis. Subsequently, the *Ixodes* tick was found to be the vector of the infection, and the etiologic agent was identified as a spirochete, named *Borrelia burgdorferi* after Dr. Willy Burgdorfer, who isolated the organism from the midgut of an *Ixodes dammini* tick. As clinical experience with the disorder grew, it became clear that arthritis is but one feature, leading to the present designation, Lyme *disease.*

There are three stages of clinical illness separated by weeks or months: stage 1, with the typical skin lesion (erythema chronicum migrans [ECM]) and influenzalike illness; stage 2, with neurologic, cardiac, and eye involvement; and stage 3, with arthritis and CNS disturbances.

Erythema chronicum migrans begins at the site of tick attachment 3–32 days following the tick bite. It enlarges over a number of days to form an annular lesion several inches in diameter. In general, as the rash expands, the center clears. The borders are erythematous but not scaly (as in tinea corporis) or serpiginous (as in erythema marginatum). The lesion is not evanescent as is the rash of JRA; it tends to last for a few weeks. Because the location marks the site of tick attachment, the extremities are commonly involved, and lesions may be multiple.

The influenza-like illness of stage 1 Lyme disease is nonspecific, with low-grade fever, headache, myalgias, and arthralgias. It can be distinguished from influenza by the relative lack of respiratory symptoms and by the season; influenza is a wintertime malady, and Lyme disease occurs in warmer weather, when ticks are active.

After a month or so, stage 2 follows. Approximately 15% of patients experience neurologic symptoms and signs, such as aseptic meningitis or peripheral neuritis; facial palsy is common. The heart is affected in 8–10%, manifested by heart block or carditis. Conjunctivitis may be prominent during this stage of illness as well.

More than half the patients, if not treated, progress to stage 3 one to several months later, marked by the onset of monoarticular or pauciarticular arthritis affecting large joints, such as the knee. The arthritis may last only a week, especially in children, but it may be recurrent; it may also be chronic and, in approximately 10% of patients, erosive.

Central nervous system involvement in stage 3 may produce demyelination and result in a multiple sclerosis–like syndrome. Also reported are psychological disturbances and chronic fatigue.

Because the organism is a spirochete, concern has been expressed about congenital (transplacental) infection. Data currently available are limited but worrisome. In one study, one fourth of pregnancies of infected mothers had an adverse outcome, though no specific clinical “congenital Lyme disease syndrome” was suggested.

Diagnosis in early stages is clinical. Currently available serologic tests generally do not demonstrate positive results when ECM begins. Serologic confirmation is useful in later stages, particularly when there is no history of ECM. Most, but not all, patients develop immunoglobulin G antibodies, which can be detected by enzyme-linked immunosorbent assay (ELISA) or immunoblotting; attempts to develop tests with greater sensitivity and specificity continue.

Treatment during stage 1 and for mild symptoms in stage 2 is orally administered tetracycline, doxycycline, or amoxicillin for children 9 years and older; for children younger than 9 years, tetracycline and doxycyline are withheld because of their potential for dental staining, and amoxicillin or penicillin is prescribed. Children with more advanced Lyme disease who have persistent arthritis, severe carditis, meningitis, or encephalitis are treated with ceftriaxone or high-dose penicillin administered intravenously. Symptomatic treatment, such as antiinflammatory agents for the arthritis, is also important.

Prevention requires alertness to the presence of *Ixodes* ticks, most prevalent in the Northeast, northern Midwest (especially Wisconsin), and Northwest. This involves identification of their habitat (grassy areas that are home to mice and deer), application of tick repellent, covering legs and arms if one is to walk through the grass, and early tick removal. It appears that several hours of attachment are required before infection is likely to be transmitted, but the strategy of surveillance (“tick checks”) is more difficult than in the prevention of RMSF because *Ixodides* ticks are so much smaller (about the size of a pencil point) than the ticks that harbor *R. rickettsii.* At the end of 1998, the Food and Drug Administration licensed a recombinant outer-surface protein A Lyme disease vaccine for use in adults. A recent trial in children suggests that the vaccine is more immunogenic in children than in adults.

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110. SEXUALLY TRANSMITTED DISEASES

Olakunle B. Akintemi

According to the Centers for Disease Control and Prevention (CDC), 12 million Americans, including 3 million adolescents, are infected by sexually transmitted diseases (STDs) each year. The term “STD” is used to describe the 25 or so infectious organisms that are sexually transmitted and the associated diseases and syndromes these organisms cause. These organisms include *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum* (syphilis), hepatitis B virus, genital herpes simplex virus (HSV), human immunodeficiency virus (HIV), *Haemophilus ducreyi* (chancroid), human papilloma virus (HPV) (genital warts and cervical cancer), *Trichomonas vaginalis* (vaginitis), and *Gardnerella vaginalis* (bacterial vaginosis).

Other organisms that are transmitted sexually include: *Calymmatobacterium granulomatis* (granuloma inguinale); *Shigella*, *Campylobacter*, *Entamoeba histolytica*, *Giardia lamblia* (in homosexual men), *Candida albicans* (vulvovaginitis, balanitis), molluscum contagiosum virus (genital molluscum contagiosum), human T cell lymphotropic virus types I and II (human T cell leukemia or lymphoma), human herpes virus 8 (body cavity lymphoma, Kaposi sarcoma), *Phthirus pubis* (pubic lice), and *Sarcoptes scabiei* (scabies). Neonates may be infected vertically (i.e., from mother to baby) either during pregnancy (congenital syphilis), or during delivery (*N. gonorrhoeae*, *C. trachomatis*); some organisms, such as HIV, can infect at either time. In children, the presence of organisms that are uniquely transmitted by sexual contact implies sexual abuse. Adolescents, like adults, are infected through sexual activity; the rates of many STDs are highest among adolescents aged 15–19 years. The clinical manifestation provides a basis for classifying the diseases and clues to the infecting organism: genital ulcers (chancroid, HSV infection, lymphogranuloma venereum, syphilis, donovanosis); urethritis/cervicitis (gonorrhea, chlamydia, HSV infection); pelvic inflammatory disease (PID) (gonorrhea, chlamydia, *Mycoplasma hominis*); vaginal discharge/ vaginitis (*Trichomonas vaginalis*, bacterial vaginosis, *Candida albicans*); and genital warts (HPV infection). The most important organism in terms of mortality is HIV infection (see Chap. 104). In infants, children, and adolescents, the most common in terms of acute clinical disease are *C. trachomatis* and *N. gonorrhoeae*; the epidemiology and clinical manifestations of these two organisms are intertwined.

The gonococcus is an intracellular, gram-negative, nonmotile and nonspore forming diplococcus. *C. trachomatis* is an obligate intracellular parasite that cannot be cultured on artificial media and therefore requires tissue culture for growth in the laboratory. Because of the cost and difficulties of cell culture, rapid nonculture methods have been developed. These tests include direct fluorescent antibody (DFA), enzyme immunoassay (EIA), and nucleic acid probe (GenProbe), which can be used for cervical specimens. Ligase and polymerase chain reaction (LCR, PCR) methods are now available for testing cervical, urethral, and urine specimens.

Both organisms can be transmitted during vaginal delivery to the newborn and produce conjunctivitis. Studies have revealed that approximately 30–50% of infants born vaginally to chlamydia-positive mothers develop conjunctivitis. Gonococcal conjunctivitis, an acute purulent conjunctivitis, appears between days 2 and 5 after birth but may occur later than 5 days in some cases. Premature rupture of membranes and prematurity may increase the risk of *N. gonorrhoeae* in the newborn. *C. trachomatis* conjunctivitis usually begins 5 days after birth. The presentation may be mild with scant eye discharge or severe with copious purulent discharge and chemosis but generally without eyelid erythema or edema.

In contrast, gonococcal ophthalmia is a serious disease, with eyelid edema, and purulent, profuse exudate; untreated, it may lead to corneal ulceration. Until recently, the method of choice of ocular prophylaxis was the topical instillation of 1% silver nitrate. Because of the high incidence of chemical conjunctivitis with silver nitrate and its inactivity against chlamydia, either 1% tetracycline or 0.5% erythromycin is the preferred alternative. In cases of established conjunctivitis, treatment of choice is either parenteral ceftriaxone (gonococcus) or oral erythromycin (chlamydia). Other complications of neonatal gonococcal infection include arthritis, vaginitis, rhinitis, funisitis, scalp abscesses, and neonatal sepsis.

Of babies infected at birth with chlamydia, 10–30% develop a characteristic pneumonia between 4 and 12 weeks of age. The infants are afebrile, tachypneic with a repetitive staccato cough, and hypoxemic. On auscultation, crackles may be heard, but wheezes are uncommon. Hyperinfiltration and increased interstitial markings are seen on chest x-ray. The complete blood count reveals peripheral eosinophilia (>300 cells/mm ^{3}), which coupled with the cough, led to the old descriptive term for this infection, “pertussoid eosinophilic pneumonia.” The other significant laboratory finding is elevated serum levels of immunoglobulins. Erythromycin is considered the drug of choice.

The clinical manifestation of gonorrhea in prepubescent girls is vulvovaginitis; cervicitis and salpingitis are uncommon before puberty.

In sexually active women, most infections with *N. gonorrhoeae* or *C. trachomatis* are asymptomatic. Both organisms may infect the endocervical canal (cervicitis); urethra (urethritis); Bartholin's gland (bartholinitis); endometrium (endometritis); salpinx (salpingitis); peritoneum; liver capsule (Fitz-Hugh-Curtis syndrome or perihepatitis); and rectum (proctitis). When symptoms occur, they include mucopurulent vaginal discharge, dysuria, urinary frequency, intermenstrual vaginal bleeding, and menorrhagia. The most common complication of both gonococcal and chlamydial lower genital tract infection is PID. Pelvic inflammatory disease includes endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. The role of genital mycoplasma (mycoplasma hominis, ureaplasma urealyticum) in the pathogenesis of PID is unclear.

Acute PID may be asymptomatic; symptoms may be mild or severe, making clinical diagnosis difficult; and no symptom, sign, or laboratory test is pathognomonic. Given the difficulty in diagnosis and the long-term adverse effects of untreated or unrecognized PID (infertility, chronic pelvic pain, ectopic pregnancy), the CDC recommends that physicians should maintain a “low threshold for the diagnosis of PID.” Lower abdominal tenderness, adnexal tenderness, cervical motion tenderness, and absence of another diagnosis are the “minimum criteria” established for the diagnosis of PID. “Additional criteria” to support the diagnosis of PID include oral temperature >38.3°C, mucopurulent vaginal or cervical discharge, elevated C-reactive protein or erythrocyte sedimentation rate, and laboratory evidence of *N. gonorrhoeae* or *C. trachomatis*. Finally, the “definitive criteria” for diagnosis of PID are histopathologic evidence of endometritis on endometrial biopsy, thickened fluid-filled tubes with or without pelvic fluid or tubo-ovarian abscess on transvaginal sonography, and laparoscopic evidence of PID. Antibiotic therapy may be outpatient or inpatient and should be broad based to cover *N. gonorrhoeae* and *C. trachomatis*, anaerobes, gram-negative facultative bacteria, and streptococci. For hospitalized patients, recommended regimens are cefoxitin or cefotetan and doxycycline, or clindamycin and gentamicin followed by doxycycline. Alternative regimens include ofloxacin and metronidazole or ampicillin/sulbactam followed by doxycycline; or ciprofloxacin, doxycycline, and metronidazole. For outpatient treatment, recommended regimens are either oral ofloxacin and metronidazole; or ceftriaxone, cefotaxime, ceftizoxime, and doxycycline.

In males, gonococcal genital infection is manifested as urethritis with mucopurulent discharge and dysuria. Complications include epididymitis, prostatitis, posterior urethritis, seminal vesiculitis, and infections of Cowper glands.

The gonococcus may also infect other nongenital sites, notably the pharynx (exudative pharyngitis) and the rectum (proctitis). Disseminated disease also occurs with gonococcal disease (DGI), but there is no recognized counterpart caused by chlamydia. The two most common manifestations of DGI are arthritis and dermatitis, hence, the term “arthritis-dermatitis syndrome.” The “classic” skin lesions are tender, necrotic pustules on an erythematous base or papules, and maculopapular or haemorrohagic bullae. They are usually located on the distal portions of the extremities (palms and soles), and are uncommon on the scalp and oral mucosa. Gonococcal arthritis usually presents as migratory polyarthralgia; tenosynovitis in the fingers, wrists, toes, and ankles; polyarthritis; and monoarthritis (especially the knee). Gonococcal disease is more common in women than in men, and antibiotic treatment produces a diagnostic rapid clinical response.

For uncomplicated gonococcal infections of the cervix, urethra, and rectum, recommended treatment regimens are cefixime or ceftriaxone (or a fluoroquinolone for those older than 16 years) *plus* azithromycin or doxycycline. Alternative regimens include spectinomycin, single-dose cephalosporin (cefotaxime, ceftizoxime, cefotetan, cefoxitin, and probenecid) or single-dose quinolone (enoxacin, lomefloxacin, and norfloxacin) for those older than 16 years.

There are over 100 different HPV types, at least 35 of which infect the genital tract. Most HPV infections are asymptomatic and subclinical (without exophytic warts). Human papilloma virus causes genital warts (HPV types 6, 11) and cervical dysplasia (HPV types 16, 18, 31, 33, 35). There are four morphologic types of genital warts: condyloma accuminata, papular warts, keratotic warts, and flat-topped papules. They may be painful, friable, and pruritic. In most sexually active adolescents and young adults, the prevalence of HPV infection is very high. Because most HPV infections are asymptomatic and there is a high risk of cervical dysplasia associated with persistent infections, annual Pap smears are necessary for all sexually active adolescents. Human papillomavirus may be transmitted sexually (most common), nonsexually (formites), and vertically at delivery (laryngeal papillomatosis, and genital warts). Warts are treated to provide symptomatic and cosmetic improvement, but there is no evidence that available treatments eradicate or alter the natural history of HPV infection. Recommended treatment regimens are topical Podofilox solution/gel, Imiquimod cream, cryotherapy, podophyllin resin, trichloroacetic acid, bichloroacetic acid, intralesional interferon, and laser surgery.

Genital herpes simplex (HSV) infection is a recurrent, incurable disease with major public health implications. There are two serotypes of HSV: HSV-1 and HSV-2. Genital HSV infections may be primary or recurrent. Primary infections are associated with systemic symptoms (fever, headache, malaise, myalgia), prolonged viral shedding and dissemination, extragenital sites, and local symptoms. The local symptoms include pain, pruritus (from vesicles), dysuria, vaginal and urethral discharge, and tender inguinal adenopathy. Primary genital HSV infections are caused by both HSV-1 (5–30%) and HSV-2; however, most cases of recurrent genital herpes are caused by HSV-2. Following primary infection, the virus remains latent in dorsal root ganglia for life. Some individuals remain asymptomatic, but others have recurrent episodes; the flare-ups are generally milder than the primary infections. One of the most serious complications of genital HSV infection in pregnant women is the transmission of infection to the newborn. In the United States, the estimated incidence of neonatal HSV infection is about 1:2,000 to 1:5,000 (2,500–5,000 cases annually). Neonatal HSV can be acquired in utero (symptomatic congenital disease), intrapartum (80–90%), and postnatally. Factors that influence intrapartum transmission of HSV infection are type of maternal genital infection at the time of delivery (primary or recurrent), maternal primary disease late in pregnancy, and prolonged rupture of membranes (>6 h). Primary HSV infection is associated with high viral load and prolonged viral shedding (21 days), and when it occurs late in pregnancy, inadequate transplacental maternal neutralizing antibodies. Women with active genital HSV lesions at the time of onset of labor should be delivered by cesarean section. Acylovir, famciclovir, and valacylovir are of some benefit if begun early during the primary infection. They may also shorten duration of lesions in recurrent disease and “ameliorate or prevent recurrent outbreaks.”

In 1947, before penicillin was available widely, the incidence of syphilis was 66.4 cases per 100,000 population. Partly because of change in behavior, public health measures and discovery of penicillin, the rates declined to a low of 3.9 cases per 100,000. However, between 1988 and 1990, the prevalence increased from 16.43 to 20.10 cases per 100,000. The increase was associated with the AIDS epidemic. Since 1991, the prevalence has declined steadily; in 1998 the rate was an all-time low of 2.6 cases per 100,000 population. The modes of transmission of syphilis are by sexual contact and transplacental route. The stages of syphilis are divided into primary, secondary, latent, and tertiary. The usual presentation in the primary stage is of a single, painless, indurated genital ulcer (chancre) and regional lymphadenopathy. Secondary syphilis is characterized by rash, fever, malaise, regional lymphadenopathy, and mucocutaneous lesions (condyloma lata). Patients are usually asymptomatic during the latent period. Tertiary syphilis may take 15 years or longer to develop and is characterized by cardiac (aortic aneurysm, aortic regurgitation, coronary ostial stenosis) and neurologic (neurosyphilis, headaches, paresis, and tabes dorsalis) lesions, and “gummas.”

Serologic tests are of two types: nonspecific (e.g., Venereal Disease Research Laboratory [VDRL] and Rapid Plasma Reagin [RPR]) and specific tests for *T. palllidum* (e.g., fluorescent treponemal antibody absorbed, and microhemagglutination assay for antibody to *T. pallidum* [MHA-TP]). Nontreponemal tests quantitatively correlate with disease activity and can be used to assess the results of treatment; in 15–20% of individuals with primary syphilis, the VDRL or RPR may be negative in 2–3 years. Treponemal specific tests do not correlate with disease activity; patients remain reactive for life, and therefore should not be used to assess treatment. Darkfield microscopy and direct fluorescent-antibody for *T. pallidum* (DFA-TP) are useful in patients with primary syphilis or in tissues of those with advanced disease.

Untreated syphilis in pregnancy may result in spontaneous abortion, stillbirth, premature delivery, and congenital syphilis. Congenital syphilis may be asymptomatic or subtle, or involve multiple organs (early and late disease). Penicillin is the drug of choice in all stages of syphilis. The specific preparation, duration, dosage, and route depend on the stage of illness. For the nonpregnant penicillin-allergic patient, doxycycline and tetracycline are alternative drugs.

At present, there are no vaccines effective against the sexually transmitted pathogens other than hepatitis B. Since many factors influence the risk of sexually transmitted diseases, behavioral and biochemical interventions must be integrated at individual and population levels. The goals of prevention are to prevent exposure to STDs, prevent acquisition of infection once exposed, and prevent transmission of the infection to others. Personal measures, such as abstinence, careful selection of sexual partners, and use of latex condoms, are required to help protect individuals against infection. Adolescents in the United States can consent to confidential diagnostic and treatment services for STDs without parental consent or knowledge. Nevertheless, the high prevalence of asymptomatic infection, the usual mode of transmission, adolescents' predilection for risky behavior, and the lack of unlimited resources combine to make the prospect for control of STDs gloomy indeed. Secondary prevention following one bout of STD begins with effective treatment, and includes education and identification of sexual partners. In addition to promoting abstinence, current efforts to educate young people regarding “safe sex” and the use of condoms represent a dramatic societal shift, indicating a recognition of the magnitude of the problem of STDs in general, and of HIV in particular.

Reviews

1. American Academy of Pediatrics Committee on Infectious Diseases. *Report of the Committee on Infectious Diseases* (25th ed.). Elk Grove Village, IL: American Academy of Pediatrics, 2000.
   A valuable resource; contains guidelines for treatment of sexually transmitted diseases (STDs) in children and adolescents.
2. Centers for Disease Control and Prevention. 1998 Guidelines for treatment of sexually transmitted diseases. *M.M.W.R.* 47(RR-1):1–116, 1998.
   Practice guideline on the assessment and treatment of STDs.
3. St. Louis, M., and Workowski, K. 1998 Guidelines for the treatment of sexually transmitted diseases. *Clin. Infect. Dis*. 28(Suppl. l):S1–S90, 1999.
   Proceedings from a symposium organized by the Centers for Disease Control and Prevention (CDC) (Atlanta, Ga: February 10–12, 1997). It supplements ref. 2 and includes the following topics: new therapies and prevention strategies for genital herpes; treatment of chancroid; treatment of nonpregnant adults with syphilis; treatment of genital warts; nongonococcal urethritis; bacterial vaginosis; STDs in abused children and adolescents; and proctitis and proctocolitis.
4. Lappa, S., and Moscick, A. The pediatrician and sexually active adolescent. A primer for sexually transmitted disease. *Pediatr. Clin. North Am*. 44:1405–1445, 1997.
   An excellent review, but see ref. 1 and 2 for current treatment recommendations. For additional review, see Pediatr. Clin. North Am. *46:747–766, 1999, and* dolesc. Med. *11:315–326, 2000.*

Specific Pathogens

5. Recommendations for the prevention and management of *Chlamydia trachomatis* infections, 1993. *M.M.W.R.* 42(RR-12):1–39, 1993.
   Establishes guidelines for the prevention and management of Chlamydia trachomatis. *The CDC recommends testing all women with mucopurulent cervicitis; sexually active women younger than 20 years of age; women 20–24 years of age who have not consistently used barrier contraception, or have had a new sex partner or more than one sex partner during the past 90 days; and women younger than 30 years of age seen in family planning clinics. For cost-effectiveness analysis of three screening methods (CDC criteria, screening all women younger than 30 years, universal screening) using polymerase chain reaction, see* Ann. Intern. Med. *128: 277–284, 1998. Screening all sexually active women is most cost-effective. A prospective longitudinal study of 3,202 sexually active females 12–19 years of age found a staggering 29.1% incidence of* Chlamydia trachomatis. *The authors of this study in* J.A.M.A. *280:521–526, 1998, suggest screening all sexually active adolescent females every 6 months, “regardless of symptoms, prior infections, condom use, or multiple partner risks.” See editorial accompanying this article on pp. 564–565. For more on screening asymptomatic young women for chlamydia, see* Clin. Infect. Dis. *28:1002–1007, 1999;* N. Engl. J. Med. *339:739–744, 1998; and* Sex. Transm. Dis. *26:309–316, 1999.*
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   Briefly considers screening for each of the following: gonorrhea, chlamydia, trichomoniasis, candidiasis, bacterial vaginosis, herpes simplex virus, human papilloma virus, syphilis, chancroid, and lymphogranuloma venereum. This article is one of several in a two-part series on multiple aspects of STDs. These include epidemiology of STDs (p. 71); hepatitis (p. 77); gonorrhea (p. 4); pelvic inflammatory disease (PID) (p. 102); human immunodeficiency virus (p. 113); C. trachomatis *(p. 151); vulvovaginitis in prepubertal girls (p. 161); vulvovaginitis and cervicitis in adolescents (p. 167); urethritis and epididymitis (p. 177); and genital ulcers (p. 182). For screening asymptomatic males by testing first-void urine, see* J. Clin. Microbiol. *35:982–984, 1997.*
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