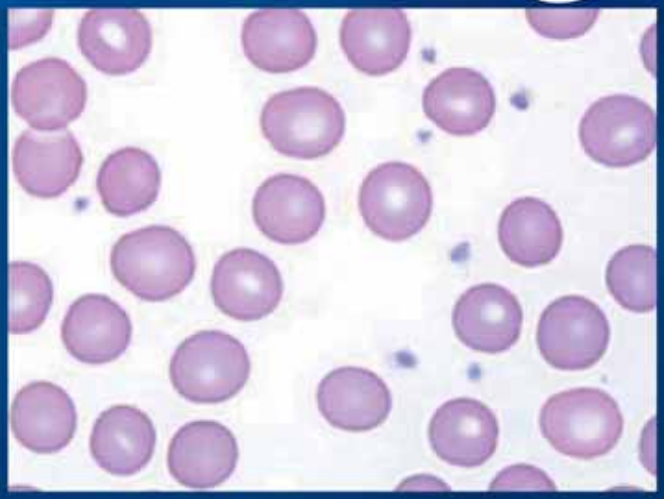
DEBORAH TOMLINSON
NANCY E. KLINE
Editors

Pediatric Oncology Nursing

PEDIATRIC ONCOLOGY



ADVANCED
CLINICAL HANDBOOK

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Deborah Tomlinson
Nancy E. Kline
(Eds.)

Pediatric Oncology Nursing

Advanced Clinical Handbook

With 43 Figures and 203 Tables

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Dedication

To the nurses, and others,
who use the information in this book,
and to the children they serve,
we dedicate this work.

To my husband Chris and our children,
Vivian, Sam and Suzanne –
to the moon and back.
Deborah Tomlinson

To my parents, and Michael.
I am forever grateful for your love and support.
Nancy E. Kline

Preface

"Pediatric Oncology Nursing: Advanced Clinical Handbook" is a joint effort between nurses in Canada, the UK, and the USA. This is a first-time collaboration between pediatric hematology and oncology nurses from two continents and represents a blending of knowledge from these experts. The book is designed to be a comprehensive clinical handbook for nurses in advanced practice working with pediatric hematology / oncology patients. Specific issues related to young children and adolescents with cancer and hematologic disorders are discussed.

Twenty-two contributors and two editors participated in the writing of this text. Nurses in advanced practice and academic roles – nurse practitioners, clinical nurse specialists, clinical instructors, lecturers, and educators – were involved. One of the most appealing features of this text is the varied experience represented by nurses from different countries and different educational backgrounds.

The book is divided into five sections: pediatric cancers, hematologic disorders, treatment of childhood cancer, side effects of treatment and disease, and supportive and palliative care. Many tables and illustrations are included for quick reference in the clinical setting. Future perspectives and opportunities for new treatment options and research are discussed.

Part One focuses on pediatric cancers: the leukemias and solid tumors. The most common pediatric tumors, as well as some rare tumors, are discussed with regard to epidemiology, etiology, molecular genetics, symptoms and clinical signs, diagnostic and laboratory testing, staging and classification, treatment, prognosis, and follow-up care.

Part Two focuses on pediatric hematology. The anemias, bleeding disorders, neutropenia, and thrombocytopenia are discussed in detail. Epidemiology, etiology, symptoms and clinical signs, diagnostic and laboratory procedures, treatment, prognosis, and follow up care are included for each of the disorders.

Part Three covers cancer treatment, including chemotherapy, radiation therapy, peripheral stem cell transplantation, surgery, gene therapy, and complementary and alternative medicine. The principles and description of treatment, method of treatment delivery, potential side effects, and special considerations for each type of treatment are discussed.

Part Four focuses on the side effects of cancer treatment in relation to metabolic processes and the gastrointestinal, hematologic, respiratory, urinary, cardiovascular, neurologic, musculoskeletal, integumentary, and endocrine systems. The incidence, etiology, treatment, prevention, and prognosis are included for each side effect reviewed.

Part Five includes essential information regarding supportive and palliative care of pediatric cancer patients. Nutrition, hydration, pain, transfusion therapy, growth factors, and care of the dying child are covered. The principles of treatment for these conditions, method of delivery, and special considerations for certain conditions are included.

As the editors of "Pediatric Oncology Nursing: Advanced Clinical Handbook" we want to recognize and thank everyone who participated in the development of this text. We are profoundly aware of the personal time and commitment that was devoted to make this an outstanding resource, and we are grateful. It is our hope that nurses in advanced clinical practice will find this publication useful and that it will enrich knowledge and improve care for young people with cancer and hematologic disorders.

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PART I

Leukemia

Deborah Tomlinson

Contents

Leukemia is the most common malignancy that affects children, accounting for approximately a third of cancer diagnoses. It may be defined as a neoplastic disease that involves the blood-forming tissues of the bone marrow, lymph nodes, and spleen.

Normal hematopoiesis occurs in these blood-forming tissues; the development of blood cells is shown in Fig. 1.1. A range of extracellular protein factors regulates the growth and differentiation of pathways of developing cells. This ensures that the mature blood cell types are produced in appropriate proportions. Leukemia is a clonal disease that is due to genetic mutations and transformation of a single early progenitor myeloid or lymphoid cell during hematopoiesis. The type of leukemia that results is therefore dependent on the cell lineage that is affected by the mutation. Table 1.1 shows the blood cells that can be affected from either stem cell lineage. In leukemia, there is an overproduction of immature white blood cells that cannot function effectively. These immature white blood cells, such as the myeloblasts, lymphoblasts, and monoblasts, are commonly called "blasts." An abnormal population of immature white blood cells decreases the space available for the production of other healthy blood cells produced by the bone marrow. The blast cells may then enter the blood and may also infiltrate the central nervous system (CNS).

The two broad classifications of leukemia are acute and chronic. The most common types of leukemia are

- Acute lymphoblastic leukemia (ALL), which accounts for 75–80 % of childhood leukemia

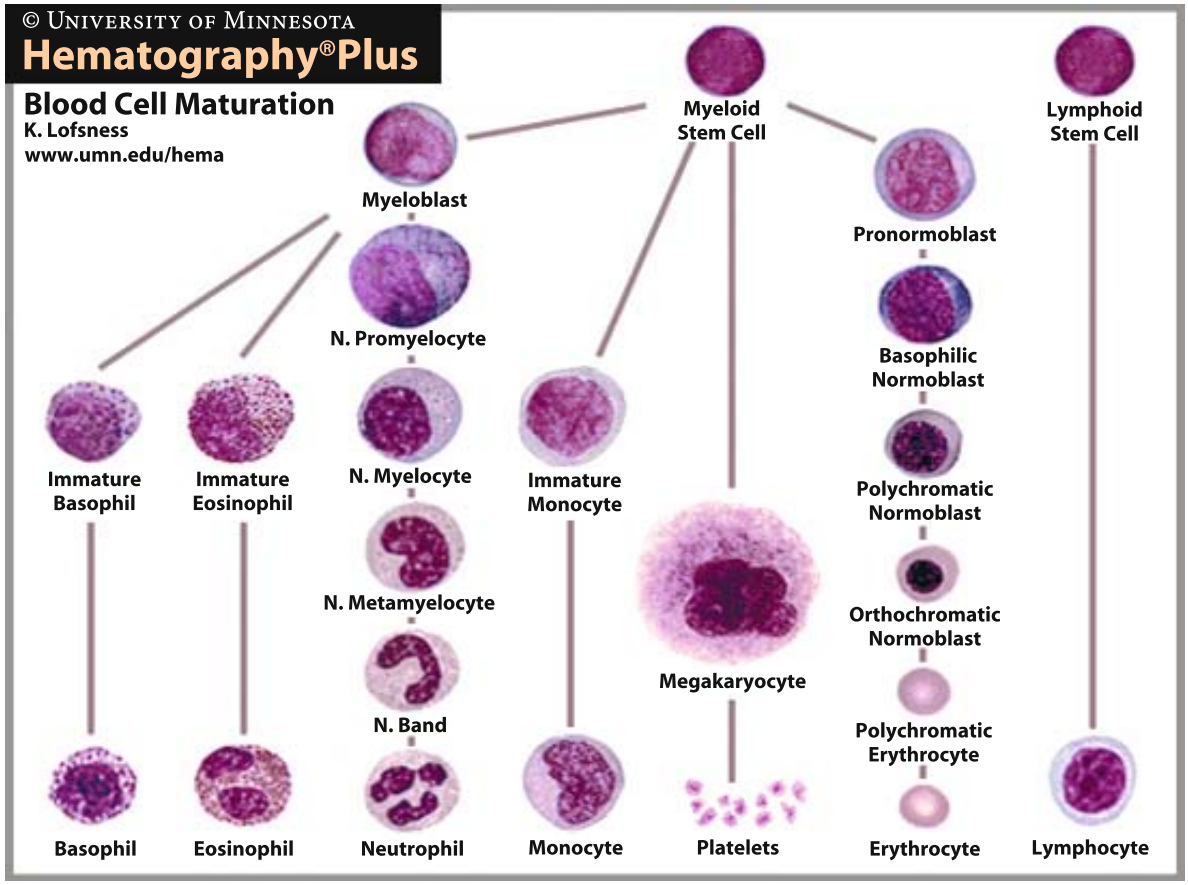

Figure 1.1

Hemopoiesis: The lymphoid stem cell differentiates into T-lymphocytes and B-lymphocytes. Natural Killer (NK) cells are also thought to derive from the lymphocyte stem cell. Image credit: K. Lofsness, University of Minnesota

- Acute myeloid leukemia (AML), also known as acute nonlymphoblastic leukemia (ANLL), which accounts for 20–25% of childhood leukemia
  The most common type of chronic leukemia is
- Chronic myeloid (or myelocytic) leukemia (CML), which accounts for less than 5% of childhood leukemia

1.1 Acute Lymphoblastic Leukemia

1.1.1 Epidemiology

ALL affects slightly more males than females (1.2:1) and peaks between the ages of 2 and 6 years. In infants there is a higher number of females affected.

Globally, the highest incidence of ALL appears to be in Europe and North America, with about 5 cases in 100,000 of 0–14-year-old children. The lowest incidence, of about 0.9 in 100,000, is in Kuwait and Bombay. There may be a lack of clarity regarding some

Table 1.1. Lineage and function of major types of blood cells

Blood cell	Lineage	Function	Half-life
Red blood cells (erythrocytes)	Myeloid stem cells	Transport oxygen from lungs to tissue Transport some carbon dioxide from tissues to lungs	About 120 days
Platelets (thrombocytes)	Myeloid stem cells	Repair blood vessels and participate in clotting mechanism	7–10 days
White blood cells (leucocytes)		Crucial in immunity	
Monocytes	Myeloid stem cells	Can differentiate into macrophages; phagocytosis; antigen presentation; immune regulation	1–3 days in blood 3 months in tissues
Granulocytes			
– Neutrophils	Myeloid stem cells	Phagocytosis, killing bacteria	6–12 hours in blood
– Eosinophils	Myeloid stem cells	Detoxify products from allergic response; phagocytosis	2–3 days in tissues
– Basophils	Myeloid stem cells	Involved in allergic response; source of immune inhibitors (e.g., histamine)	Minutes to hours in blood, then in tissue for about 12 days
– Monocytes	Myeloid stem cells	Contain enzymes that kill foreign bacteria	Undetermined
Lymphocytes	Lymphoid stem cells	Role in immunity	Undetermined; cells can move between blood and lymphoid tissues
– T lymphocytes		Attack invaders directly	
– B lymphocytes		Produce antibodies	
– Others: null cells, natural killer cells, lymphokine-activated killer cells, tumor-infiltrating lymphocytes			

incidence figures due to the lack of true population-based registration of cancer. However, ALL generally has a higher incidence in affluent industrialized nations within white populations. The incidence tends to be lower among the black populations of the same nations.

In a study in the United States, Pan et al. (2002) compared the incidence of leukemia in Asian-Americans and their descendents and in Caucasians. This study reported a lower incidence of leukemia in Asian-Americans irrespective of birthplace. In 1991, Stiller et al. reported that children of Asian and West Indian ethnic origin had patterns of ALL incidence that were similar to those of Caucasians. Interestingly, other later studies of ALL incidence in areas of the United Kingdom have reported an increased risk, although not significantly so, of ALL among South Asian children compared with non-Asian children (McKinney et al. 2003; Powell et al. 1994). However, these increases may be due to socioeconomic status, which has been linked to childhood cancers.

Table 1.2. Syndromes with a predisposition to leukemia

Genetic bone marrow failure syndromes predisposed to leukemia:
Fanconi's anemia
Diamond-Blackfan anemia
Shwachman-Diamond syndrome
Congenital dyskeratosis
Kostmann's infantile genetic agranulocytosis
Genetic syndromes predisposed to leukemia as one of the illnesses:
Chromosomal abnormality:
Down's syndrome (trisomy 21)
Chromosome 8 trisomy syndrome
DNA repair/tumor suppressor deficiency:
Ataxia telangiectasia
Li-Fraumeni syndrome
Neurofibromatosis type 1
Bloom syndrome
Nijmegen/Berlin breakage syndrome
Retinoblastoma:
RB1 gene is important in the histiogenesis of ALL

(Table compiled from Mizutani 1998)

1.1.2 Etiology

The factors involved in the cause of childhood cancers are unclear. Many different etiologies have been suggested and investigated, but few are well established. It would be misleading to associate the cause of any childhood malignancy wholly to genetic or environmental factors, but the study of various factors can improve the understanding of events that may lead to leukemia in children.

1.1.2.1 Genetic Factors

Syndromes that have a component of hereditary or genetic predisposition to leukemia have been identified and are listed in Table 1.2. A study by Mellemkjaer et al. in 2000 has shown that children of parents with autoimmune disease are slightly more susceptible to leukemia.

1.1.2.2 Environmental Factors

It is accepted that ionizing radiation is a causal factor in leukemia. Following the atomic bombs in Japan, children who were exposed acquired an increased risk of developing leukemia. Individuals exposed in utero, however, showed no increase in incidence of leukemia. This finding is in contrast to the suggested results of various studies that showed an increased risk of leukemia and other cancers (by about 40 %) to children exposed in utero to diagnostic radiography (Doll and Wakeford 1997). There is no doubt that ionizing radiation is a causal factor in leukemia; however, there are uncertainties regarding various aspects of its effect on leukemogenesis.

A significant change in thought surrounds the clusters of reported childhood ALL around nuclear installations. The suspicion that background radiation was the cause of these clusters has moved towards Kinlen's theory (1995) that population mixing, herd immunity, and abnormal response to infection of unusually susceptible children increases the risk of ALL. This "delayed infection" or "hygiene" hypothesis suggests that ALL in children is caused by a lack of exposure to infection in infancy, with an abnormal response to a later common infection incurred after mixing with other children in playgroups or schools. Therefore, circumstances that alter the pattern of infections in infants may contribute to the etiology of ALL.

Table 1.3 highlights studies that have been undertaken to investigate various possible factors in the etiology of childhood leukemia and other cancers. All theories surrounding the causes of ALL, or indeed the majority of childhood cancers, leave much unexplained, and further studies are necessary to confirm or reject the conclusions of those available.

Because of the public interest that surrounds the majority of these potential risk factors, parents will continue to form theories regarding their children's illnesses (Ruccione et al. 1994). Nurses have a role in eliciting parents' causal explanations so that the content of these concerns can be related to the parents' adjustment and management of their experience of childhood cancer.

Table 1.3. Reported environmental links to childhood leukemia and current conclusions

Possible environmental link	Current conclusions
Parental use of tobacco	Paternal smoking before pregnancy may be a potential risk factor for the generality of childhood cancers. Studies do not provide significant evidence (Pang et al. 2003; Sorahan et al. 2001)
Vitamin K prophylaxis in infants	Inconsistent associations reported. However, confirmed benefits of vitamin K outweigh the hypothetical association with any childhood cancer (Parker et al. 1998; Passmore et al. 1998; Roman et al. 2002; Ross and Davies 2000).
Living near landfill sites	No excess risk of any cancer reported (Jarup et al. 2002)
Proximity to railways	No association reported between risk of childhood leukemia and railway proximity (Dickinson et al. 2003). Small association with railway density assumed consequence of population mixing and proximity of railways in deprived urban areas
Children born after in-vitro fertilization	No increased risk of childhood cancer reported in studies published (Bergh et al. 1999; Klip et al. 2001)
Prenatal ultrasound	No association with childhood leukemia found (Naumburg et al. 2000)
Supplementary oxygen	Resuscitation with 100% oxygen immediately postpartum is associated with childhood ALL; further studies warranted (Naumburg et al. 2002a)
Breastfeeding	Contradicting reports of association with a reduced risk of acute leukemia (Lancashire and Sorahan 2003; UK Childhood Cancer Study Investigators 2001; Shu et al. 1999)
Pet (healthy or sick) ownership	No relationship (Swensen et al. 2001)
Family cancer history	May be a risk factor for childhood acute leukemia (Perrillat et al. 2001)
Electromagnetic fields (EMF)/ power lines	Do not support hypothesis of an association (Skinner et al. 2002; Steinbuch et al. 1999)
Natural radionucleotides in drinking water, including uranium	Results do not indicate increased risk of leukemia (Auvinen et al. 2002)
In utero exposure to metronidazole	No reported increased risk (Thapa et al. 1998)
Allergies or family history of allergies	Reduced risk of ALL; no such pattern seen with AML (Schuz et al. 2003)
Exposure to pesticides	May increase risk (Ma et al. 2002); further studies needed
Perinatal exposure to infection	Some association reported between maternal lower genitourinary tract infection in utero and risk of childhood leukemia (Naumburg et al. 2002b). This supports hypothesis that an infectious agent is involved in etiology of ALL (Kinlen 1995)
Population mixing	Increased risk of ALL in children 1–6 years old in high tertile of population mixing (Alexander et al. 1999; Boutou et al. 2002). Further support for infectious agents possessing direct or indirect cause

1.1.3 Molecular Genetics

Clonal chromosomal abnormalities (originating in a single cell) are detectable in around 90% of childhood ALL cases. The leukemia then evolves by the accrual of mutations within a clone. The abnormalities are responsible for a loss of controlled cell growth, division, and differentiation.

To review the biology of chromosomes:

- Genes carry instructions to make proteins essential for cell growth, division, and differentiation.
- A deoxyribonucleic acid (DNA) molecule carries the genetic information in coded form.
- DNA is a nucleic acid made of chains of nucleotides.
- Nucleotides have three components – a phosphate group, a pentose sugar, and a base.
- In DNA the sugar is deoxyribose, and the bases are adenine, guanine, thymine, and cytosine.
- DNA consists of two chains of nucleotides linked across their bases by weak hydrogen ions. These two complementary strands of nucleotides are linked in a double helix formation.
- The bases have specific affinities with each other, so that thymine pairs only with adenine, and cytosine pairs only with guanine.
- The base sequence is the key to the control of the cell and is referred to as the genetic code.
- The length of DNA in cells is so great that there is a significant risk of entanglement and breakage. During mitosis, proteins called histones bind to DNA and wrap it into 46 compact manageable chromosomes (23 pairs).
- The complete chromosome complement of a cell is referred to as the karyotype.

Some genes are associated with the transformation of a normal cell to a malignant cell. These are known as oncogenes (or proto-oncogenes) and tumor suppressor genes. Mutations in the DNA of these genes may cause them to produce an abnormal product or disrupt their control so that they are expressed inappropriately, making products in excessive amounts or at the wrong time. Some oncogenes may cause extra production of growth factors, which are chemicals that stimulate cell growth. Other oncogenes may cause changes in a surface receptor, causing it to send signals as though it were being activated by a growth factor.

The exact number of mutations required to transform a normal cell into a malignant cell is unknown, but research indicates that two or more mutations, or "hits," are involved. The first hit is thought to occur in the womb, which in ALL is likely to be a developmental accident affecting a chromosome. This would then suggest that a second hit after birth is necessary before ALL develops. This theory has arisen mainly from observed high concordance rates of leukemia in infant monozygotic twins (that is, if one twin has leukemia, so will the other) and the study of neonatal blood spots or Guthrie cards. In twins, it is considered that the leukemogenic event arises in one twin, and the cells from the abnormal clone then spread to the other via shared placental anastomosis. Polymerase chain reaction (PCR) has been used to identify the same fusion gene sequence in neonatal blood spots as is in patients' leukemic cells at diagnosis. In all cases of infant leukemia, there are fusions of the MLL gene; in many cases of childhood ALL, there are fusions of the TEL-AML 1 gene. These gene fusions would indicate the first hit or mutation. Table 1.4 shows the classification of types of mutation that can occur. In childhood ALL, reciprocal translocations account for approximately 25% of the chromosomal abnormalities. The translocations involve exchanges of tracks of DNA between chromosomes, resulting in the generation of chimeric or fusion genes. There may also be changes in chromosome number (ploidy), gene deletions, or single nucleotide base changes in genes. (The chromosome number is also measurable as the DNA index, in which 46 chromosomes equals a DNA index of 1).

As discussed earlier, the process by which a normal cell transforms into a leukemic cell is unclear. However, improved molecular analysis techniques have assisted in identifying mechanisms regulating cell growth and differentiation. These include the following:

- Polymerase chain reaction (PCR)
- Fluorescence in situ hybridization (FISH)
- Flow cytometry for immunophenotyping

Table 1.4. Types of mutation to genetic code

Mutation	Description	Presentations
Point mutation	Change in DNA sequence Can occur in base substitution, deletion, or addition May result in wrong amino acid being inserted into protein	Mis-sense mutation, usually a decrease in function
Chromosomal mutation	Alteration in the gross structure of chromosomes Results from cell breakage and reunion of chromosomal material during the cell cycle	Translocation Rearrangement
Genomic mutation	Change in number of chromosomes in the genome	Amplification Aneuploidy (loss or gain of single chromosome

- Digitized karyotype imaging/multicolor spectral karyotyping
- Microarray profiling
- Southern blotting
- Western blotting

Molecular analysis has proved indispensable for identifying prognostic factors and therapeutically important genetic subtypes of childhood ALL. The ranges of subtypes are based on gene expression, antigens that delineate cell type, and chromosomal and molecular abnormalities. There is currently a relatively sophisticated understanding of the genetic basis of ALL, which will be discussed further in the following sections.

1.1.4 Symptoms and Clinical Signs

ALL usually presents as an acute illness of short onset, but symptoms are occasionally slow and insidious. Symptoms relate to the infiltration of the bone marrow and other affected organs by the proliferation of lymphoblastic cells. The presenting features often appear like many childhood illnesses. Parents or children may describe the following:

- irritability
- night sweats
- fatigue
- bone pain, which may present as limping
- loss of appetite

Initially, symptoms may fluctuate daily, with the child feeling exhausted one day and fine the next. The child may have suffered from repeated ear or other infections that have been frequently resistant to treatment. This is often associated with a history of frequent visits to the family general practitioner.

Physical findings may include the following:

- pallor and lethargy
- pain at the sites of disease infiltration, especially in long bones
- petechiae
- bruising or unusual bleeding (including nose bleeds)
- enlarged liver or spleen, causing the abdomen to protrude
- enlarged lymph nodes and fever

In less than 10% of cases the disease has spread to the CNS at diagnosis. This may cause related symptoms of

- headache
- poor school performance
- weakness
- vomiting
- blurred vision
- seizures
- difficulty maintaining balance

In 60–70% of children with the T-cell type of ALL, there is involvement of the thymus. Enlargement of the thymus caused by an accumulation of white blood cells can give rise to an anterior mediastinal

mass that can cause pressure on the trachea, causing coughing, shortness of breath, pain, and dysphagia. In some cases the pressure may also compress the superior vena cava and cause swelling of the head and arms.

In rare circumstances acute leukemia may present with extremely high blast cell counts, known as hyperleukocytosis. This state of the disease can cause respiratory failure, intracranial bleeding, and severe metabolic abnormalities, conditions that are the main causes of high early mortality. The process that leads to these complications has become known as leukostasis. It had been thought that leukostasis was caused by overcrowding of leukemic blasts. However, it is now evident that leukostasis results from adhesive interactions between blasts and the vascular endothelium. Damage to the endothelium is likely due to cytokines that are released. The adhesion molecules displayed by the blasts and their response to the environment are probably more important factors in leukostasis formation than numbers of cells. Leukopheresis is routinely used to reduce the leukocyte count in the initial phase when there is hyperleukocytosis. It remains unclear whether this is the most efficient method of treating leukostasis. However, further research should indicate the most appropriate use of this procedure.

1.1.5 Diagnostics

If ALL is suspected following the history and physical examination of the child, initial investigations include a complete blood count, urea and electrolyte counts, and a chest x-ray. The blood count may point to a diagnosis of leukemia with blast cells present or an elevated white blood cell count. Figure 1.2a shows a normal blood film, and Fig. 1.2b is a blood film from a child with ALL. However, the necessary diagnostic investigation is a bone marrow examination. The bone marrow is usually taken from the iliac bone at the iliac crest. Despite the new technologies available, ALL is still usually diagnosed by an experienced pediatric oncologist and/or pathologist examining a Romanowsky-stained bone marrow smear with a high-powered microscope. More than a 25% blast cell count in the marrow confirms a diagnosis of leukemia. A portion of the bone marrow aspirate and the chloroma biopsy/trephine are then analyzed to detect other features of the leukemic cells to help determine what type of leukemia is present. Other techniques are used to extend the diagnosis.

A lumbar puncture is performed to determine any CNS involvement; a sample of cerebrospinal fluid (CSF) is examined for blast cells.

These procedures are most often performed using sedation or anesthetic. Therefore, because of the potential anesthetic difficulties that could develop, a chest x-ray is vital to assist in diagnosing infection or detecting a mediastinal mass.

1.1.6 Staging and Classification

1.1.6.1 Risk Classification

Once a diagnosis of ALL has been confirmed, cell morphology, cytogenetics, and immunophenotyping are determined to elicit more defined prognostic factors. Treatment can then focus on "risk-directed" protocols developed through well-designed clinical trials. This strategy uses the child's likelihood of relapse or resistance to treatment to intensify or reduce the treatment to ensure adequate cell kill within acceptable levels of toxicity. The significance of various reported risk factors has led to some debate. Difficulty also arises when comparing results between different countries and centers using locally-assigned risk categories. However, over the past few decades several features have been determined to be more favorable prognostic factors. In 1993, following a previous initiative in Rome, collaborative groups met to establish those features that would indicate "standard risk" ALL. These are known as the Rome/NCI (National Cancer Institute) criteria:

- WBC <50,000/mm^3
- Female
- 1–9 years of age
- non-T/non-B

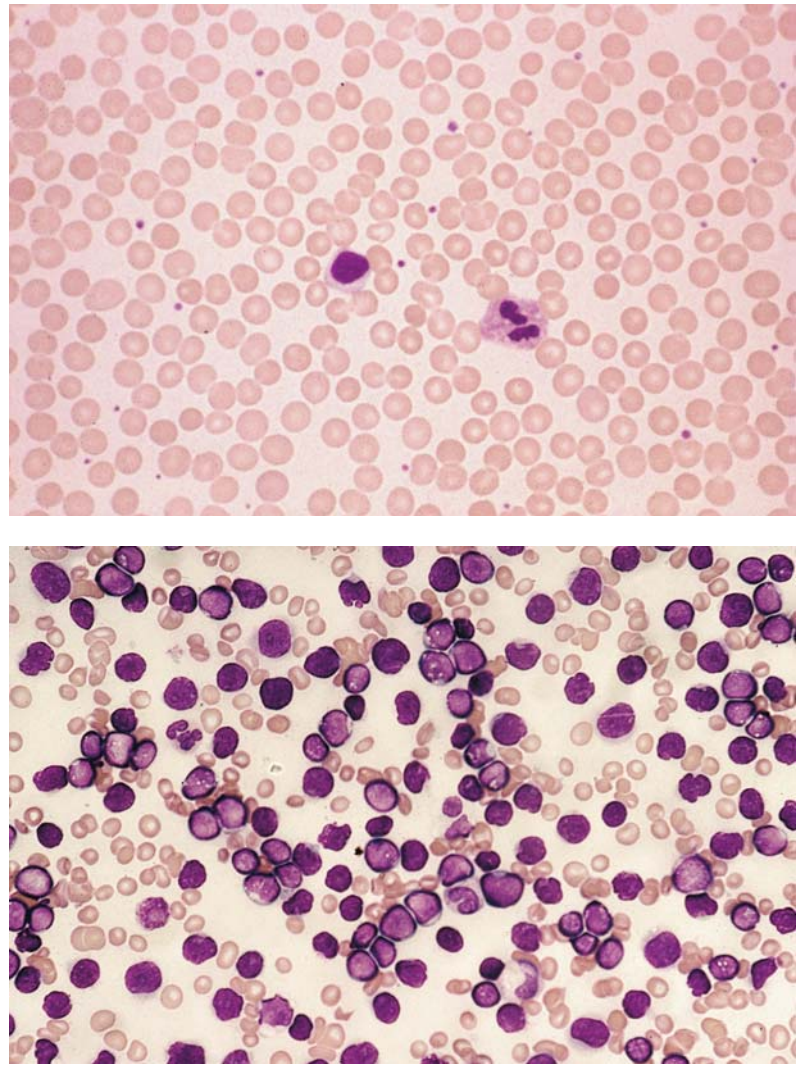

Figure 1.2 a, b

a Normal blood film (×25)
b ALL blood film (×25).
Image credit: Dr Angela Thomas, RHSC, Edinburgh

All other patients are "high risk."

Other factors are used to determine risk classification, but the number and array of factors used to classify ALL make it difficult to establish any one system. Consequently, there is a lack of precision within most risk classification systems. Varying conclusions have been reported with regard to the prognostic significance of other characteristics, including the presence of Down's syndrome; liver and spleen size; the presence of an anterior mediastinal mass; French-American-British subtype; body mass index; and CNS involvement, hemoglobin level, platelet count, and number of blast cells in the CSF at diagnosis. However, subgroups of patients with different outcomes can be predicted by blast karyotype, molecular abnormalities, and early response to treatment, with response to treatment proving to be increasingly more important. The persistence of lymphoblasts in bone marrow following a week of induction therapy is associated with a poor prognosis, with less than 30% survival at 5 years no matter what subsequent therapy is given (Hann 2001).

Table 1.5. French-American-British Classification of acute lymphoblastic leukemia

Category	Definition	Features	% of patients
L1	Small cells with scant cytoplasm	Associated with good treatment response	90%
L2	Large cells with abundant cytoplasm	Indicates more refractory to therapy if 10–20% L2 cells are present	9%
L3	Large cells with prominent nucleoli	Mature B-cell phenotype; frequently presents as lymphoma; poor prognosis	1%

Interestingly, a study by Gajjar and colleagues in 2000 found that traumatic lumbar puncture at diagnosis of childhood ALL indicated adverse outcomes and was an indication to intensify intrathecal (IT) therapy.

1.1.6.2 Cell Morphology

Despite other ways of looking at cells, a morphological classification that is still widely applied is the French-American-British (FAB) system. This classification is based on the morphology (appearance, structure, and cytochemistry) and number of cells, and it defines three categories (Table 1.5). This system is limited due to very unevenly divided numbers of patients in each category and to a morphological feature that correlates with responsiveness to conventional therapy – the presence of cytoplasmic vacuoles – not included in the FAB system. Vacuoles are present in 25–30% of patients and are associated with a lower presenting white cell count and the "common" ALL immunophenotype.

1.1.6.3 Cytochemistry

Several biochemical markers have been identified to assist in the classification of leukemia. However, little is added to the morphology of ALL, with the exception of

- Periodic-acid Schiff positivity, seen in around 15% of cases correlating with common ALL
- Acid phosphatase positivity in T-ALL

Table 1.6. Categories of acute lymphoblastic leukemia

Category of ALL	Percentage (approximately)
Common or pre-B	80%
T-cell	10%
Mature B	7%
Null (early B-precursor)	3%

All forms other than T-cell are considered as B-precursor cell ALL

1.1.6.4 Immunophenotyping

ALL is probably best classified on the basis of immunophenotyping. Antigens on the surface of normal hematopoietic cells express changes as the cells mature in the bone marrow. Technology has produced monoclonal antibodies to many of these cell cluster-of-differentiation (CD) antigen groups. These are each given a classification number prefixed with CD. Some CD antigen groups relate to lymphocyte sublineage (CDs 1–8 mark various stages of T-cell lineage; CDs 19–22, 24, and 79a mark B cells) and some to myeloid lineage, whereas others mark more primitive features (CD10 and CD34). Other useful immunologically defined cell characteristics include the following:

- Cytoplasmic immunoglobulins found in pre-B-cell ALL
- Surface immunoglobulins found in mature B-ALL
- Terminal deoxynucleotidyl transferase (TdT) found in immature lymphoid cells

Using these markers enables the classification of ALL into major categories (Table 1.6).

Table 1.7. Outcome prediction associated with ploidy status of acute lymphoblastic leukemia

Ploidy status	Number of chromosomes per malignant cell	Percentage of childhood ALL cases	Predicted response to treatment
Hyperdiploidy	>50	25–30%	Favorable
Hypodiploidy	<50	5–10%	Poor
Near-haploidy	<30	<1%	Very poor

ALL cells occasionally express cell antigens more usually associated with myeloid lineage. Opinion is divided as to whether this is clinically significant.

1.1.6.5 Cytogenetics

Cytogenetic abnormalities are detectable in most cases of childhood ALL. They can be categorized either by the number of chromosomes (ploidy) or by the structural changes and rearrangements based on detailed analysis of the karyotype. The assessment of ploidy status is clinically useful in predicting prognosis (Table 1.7).

With regard to structural changes, the identification of translocations and marker chromosomes and the delineation of complex chromosome aberrations have been possible with multicolor spectral karyotyping. The most significant chromosome (Ch') translocations identified in childhood ALL include the following:

- Ch'12 and Ch'22; i.e., t(12;22), resulting in the ETV6/AML1 fusion gene
- the Philadelphia chromosome, which is translocation t(9;22) and gives rise to the BCR/ABL fusion gene in ALL that indicates a poor prognosis
- t(1;19), giving rise to E2A/PBX1 which is a translocation of pre-B ALL
- t(12;21), giving rise to TEL/AML1 (also termed ETV6/CBFA2 fusion gene), which has been commonly reported as indicating a good prognosis
- t(4;11), giving rise to MLL/AF4, which is a typical translocation occurring in infant leukemia

Other significant abnormalities include

- rearrangements of the MLL gene
- rearrangements of the MYC gene with immunoglobulin genes
- rearrangements of T-cell receptor genes
- mutations of p16 (a tumor suppressor gene)
- mutations of p53 gene (although uncommon in childhood ALL, these mutations are associated with relapse or refractory leukemia)

The effects of these genetic alterations in leukemia help to explain adverse clinical outcomes. For example, the Philadelphia chromosome results in the production of an active kinase enzyme that drives cell proliferation independently of normal requirements for growth factor and blocks apoptosis (programmed cell death). Therefore, drug responsiveness pathways may be blocked. Normal p53 protein is required to induce cell death following anoxia or DNA damage from exposure to drugs or irradiation. Mutations in the p53, common in relapse of leukemia, may explain drug resistance in more advanced disease.

Although the risk criteria features must be considered important predictors of outcome, it would appear that they are most beneficial in predicting risk groups in B-cell lineage but not consistently in T-cell disease (Eden et al. 2000). Overall, 30–40% of children with T-lineage ALL relapse within the first 18 months after diagnosis, and approximately 20% of children with "standard risk" ALL relapse. Some groups of patients require further intensification of therapy. Consequently, more sophisticated approaches to risk classification that incorporate the molecular genetic findings and minimal residual disease measurement have the potential for identifying higher-risk children.

1.1.7 Treatment

Therapy for ALL has improved to such a degree that about 80% of childhood ALL is curable. The cytotoxic drugs used have been available for over 20 years, but better understanding of the pharmacology of these drugs has led to more effective protocols being devised that also attempt to avoid long-term adverse effects. Improvements have also been made in supportive care to reduce morbidity and mortality. The aim of treatment for ALL is to effectively halt the production of abnormal cells and eradicate the disease. Treatment protocols for ALL are constantly attempting to improve in terms of efficacy and long-term toxicity. Protocols for ALL generally include the following features:

1. Induction
2. Intensification/consolidation
3. CNS-directed therapy
4. Maintenance/continuing treatment

The drugs normally administered during the treatment for ALL are shown in Table 1.8. (Part 3 will detail cytotoxic drugs further). Treatment for ALL continues for a period of 2 or 3 years. However, infant ALL remains a challenge to treat. Most investigators treat infants as a unique subgroup, giving multiple drugs at high doses. Intensive systemic and IT treatments seem to provide adequate therapy for the CNS, even in infants with CNS involvement at diagnosis, thus avoiding cranial irradiation in these infants.

1.1.7.1 Induction

The drugs used initially to induce a remission are vincristine, steroids, and a third drug – L-asparaginase or an anthracycline – given over a 4-week period. This three-drug induction usually produces remission in about 95% of children. CNS prophylaxis/treatment is also started immediately with IT methotrexate. In the past, protocols included daunorubicin during induction. This was later omitted due to treatment-related mortality and potential late cardiotoxicity. However, research suggests that early treatment with daunorubicin could achieve a reduced relapse risk if it is not replaced by alternative intensification strategies (Chessells et al. 2002).

When treatment begins, the lysis of leukemic cells causes an increase in uric acid levels in the blood. Therefore, a uricolytic agent (uric acid depletor) is routinely prescribed. This is usually allopurinol, but investigations continue to seek a more effective agent, such as nonrecombinant urate oxidase.

The steroid of choice is normally prednisolone, but research continues to establish the efficacy of dexamethasone.

L-asparaginase can be derived from several sources, including

- Polyethylene-glycol (PEG) L-asparaginase
- *Escherichia coli (E. coli)* asparaginase
- *Erwinia* asparaginase (derived from *Erwinia carotovora* or *Erwinia chrysanthemi)*.

Each of these L-asparaginase preparations has different pharmacokinetic properties and different toxic tendencies. PEG L-asparaginase has a longer half-life than *E. coli* asparaginase, which in turn has a longer half-life than *Erwinia* asparaginase. Given in equivalent doses, the one with a longer half-life should be more effective but is also more toxic. Reports comparing the efficacy of different preparations have debated the clinical significance of the results. Due to the sources of the preparations, they can all display immunogenicity and cause allergic side effects. However, the presence of antibodies does not necessarily cause an allergic reaction. Other toxicities, including coagulation disorders, liver toxicity, and acute pancreatitis, are related to the inhibition of protein synthesis. Few studies have compared the effect of the various asparaginase preparations on the coagulation proteins. *Erwinia* asparaginase has been reported as having a less pronounced effect on coagulation than *E. coli* asparaginase does. This may be argued to be dose-related rather than preparation-related. Fresh frozen plasma (FFP) was often transfused prior to L-asparaginase if coagulation screening showed a decrease in any coagulation proteins, but this is now thought to be of no clinical benefit. Protocols for the treatment of ALL usually specify one particular preparation of L-asparaginase. However, allergic reactions usually require the discontinuation of thera-

Table 1.8. Drugs commonly used in the treatment of acute lymphoblastic leukemia

Drugs	Route of administration	Induction	Intensification	CNS prophylaxis	Maintenance
Vincristine	Intravenous	*	*		*
L-asparaginase	Subcutaneous/ intramuscular	*			
Prednisolone/ dexamethasone	Oral	*	*		*
Co-trimoxazole	Oral				*
Methotrexate	Oral				*
Methotrexate	Intrathecal	*	*	*	*
Methotrexate (with folinic acid rescue)	Intravenous			*	
Daunorubicin	Intravenous	*possibly	*		
Etoposide or cyclophosphamide	Intravenous		*		
Cytarabine	Intravenous		*		
Thioguanine (may be replaced with mercaptopurine)	Oral		*		
Mercaptopurine	Oral				*

py and subsequent substitution with a different preparation. This substitution is necessary, but it is generally thought that the different preparations are not therapeutically interchangeable, although there is probably no adverse prognostic impact of allergy to asparaginase.

Because of the risk of *Pneumocystis jiroveci* pneumonia (PCP) in immunocompromised patients, sulfamethoxazole/trimethoprim (SMX/TMP) or co-trimoxazole is given as effective prophylaxis. This is normally administered as an oral preparation (usually two or three times per week) but may be given intravenously if the patient's condition requires it. On occasion, due to adverse reactions including prolonged periods of neutropenia, a secondary alternative may be necessary. These alternatives include aerosolized/nebulized pentamidine, oral dapsone, and oral atovaquone. Pentamidine can be given intravenously, but systemic toxicities may be higher with this method of administration.

1.1.7.2 Intensification/Consolidation

This block of treatment is given following induction and again about 4 months later (depending on the protocol). Clinical trials have also investigated the introduction of a third block, which seemed to compensate for the omission of anthracyclines in induction but with possibly little other benefit.

1.1.7.3 CNS-directed Therapy

Prophylactic CNS therapy is based on the premise that the CNS provides a sanctuary site for leukemic cells that are undetectable at diagnosis and that can be protected from systemic therapy by the blood-brain barrier. If preventative therapy were not given to children with ALL, over 50% would develop CNS disease. Regular (usually every 12 weeks) lumbar punctures are performed in order to administer IT methotrexate. Additionally, high-dose methotrexate is given intravenously, usually at 4-weekly intervals between intensification blocks. High-dose metho-

trexate infusions were introduced to protocols to replace cranial irradiation because of its associated adverse side effects, and the benefits are still under investigation. Cranial radiotherapy may be reserved for children thought to be at especially high risk of CNS involvement (T-cell with high white count at diagnosis) or for those with CNS infiltration at diagnosis. Triple IT therapy (including the addition of cytarabine and hydrocortisone) is also under investigation in some protocols.

! Note: It is vital that the IT methotrexate NEVER be confused with the intravenous vincristine that is normally given on the same day. This would result in fatality.

1.1.7.4 Maintenance/Continuing Treatment

Oral methotrexate administered weekly and oral 6-mercaptopurine administered daily are the mainstay of most continuation regimens. Administering these drugs in the evening appears to give a better clinical outcome. This result may be mainly due to issues surrounding compliance; it may be easier for parents or adolescents to remember drugs at this time of day. Studies have indicated the need to give continuation therapy to the limits of tolerance by titrating doses against myelosuppression and reiterating the importance of compliance. This may result in periods of discontinuing therapy during this phase, but this is thought to be a positive event if it is related to neutropenia. Therapy is not usually discontinued if there is an episode of elevated liver enzymes. Maintenance therapy also includes continuing intravenous (IV) vincristine, PCP prophylaxis, and CNS-directed therapy every 4 weeks.

The progression of each stage of the protocol relies on a degree of return of normal bone marrow function, where the blood component levels are within normal limits. Periods of neutropenia are associated with any ALL treatment protocol during which the child/adolescent becomes immunocompromised. Procedures regarding supportive care are adhered to and are as important as the cytotoxic therapy with regard to ensuring the best outcomes for these children and adolescents.

1.1.7.5 Allogeneic Stem Cell Transplant

Some high-risk leukemias may indicate the need for transplantation from the time of diagnosis, such as Philadelphia-chromosome-positive ALL. However, as transplantation and chemotherapy are improving, these patients are continually subject to review. Stem cell transplantation has not been shown to improve outcomes for infant ALL or other very-high-risk ALL.

1.1.8 Prognosis

The prognosis of ALL is one of the highest of childhood malignancies, with a survival rate of around 80%. Studies have investigated the influence on survival of ethnicity and socioeconomic status. Increasing levels of deprivation were associated with poorer survival from all cancers, including leukemia, but only before other prognostic factors were taken into consideration (McKinney et al. 1999). However, despite continuing improved protocols, the rate of relapse has decreased only slightly over the last decade. The main improvements in survival rates have been due to improved management of relapse, especially for those relapsing off treatment. Relapse of ALL is most commonly treated with marrow ablative chemotherapy and allogeneic stem cell transplant following the achievement of a second remission. Late bone marrow relapse of several years may be treated by intense chemotherapy alone, leaving the possibility of transplant in third remission if necessary. Allografts from unrelated donors are an option that has provided encouraging results when there is a lack of suitable related donors. Transplant with umbilical cord blood stem cells is another option.

The survival rate of 80% is the mean that disguises rates that range from 10–90%. The failure of improved rates of survival has been most notable in high-risk groups. However, the relapse that occurs in standard risk groups must also be explained. Reasons may be pharmacological in cases of noncompliance or drug resistance. Drug sensitivity testing and greater vigilance may help to identify those at risk and allow for intervention. Other reasons for treatment failure may be due to intrinsically resistant disease or to recurrence from residual disease. Testicu-

lar relapse of ALL can occur, possibly because this area is a sanctuary site. However, this is a rare event, affecting approximately 1% of boys with ALL, and is normally treated with local radiation therapy and chemotherapy. Approximately 10–13% of pediatric ALL cases have T-lineage phenotype, and 30–40% of these still relapse during treatment. More sophisticated approaches to risk classification and measurement of minimal residual disease to capture patients who would benefit from more intense treatment may go some way to increase overall event-free survival rates (survival free from relapse).

1.1.9 Follow-up

Following the completion of therapy for ALL, it is crucial to monitor these children and adolescents for two reasons:

1. Blood counts will be carried out to ensure that signs of relapse can be detected, but with decreasing frequency over a number of years. Follow-up may also include bone marrow aspiration yearly initially for the same reason.
2. As therapy becomes more successful, late side effects are of increasing concern.

Long-term effects of antileukemic treatment include the following:

- Chronic cardiotoxicity induced by anthracyclines (daunorubicin), which can manifest as sudden onset irreversible heart failure. The severity of cardiac dysfunction is related to the cumulative dose of anthracycline.
- Hypothalamic-pituitary axis and gonadal damage induced by radiation. Growth problems may cause short stature and obesity later in life, and girls may undergo precocious puberty. Growth hormone therapy may be required. It is less clear if chemotherapy alone can impair growth. Testicular radiotherapy renders males sterile, and most will require androgen replacement throughout puberty. Chemotherapy may lead to subfertility, which can improve over time. Ovaries are less sensitive to chemotherapy, but if they are irradiated, estrogen replacement will be necessary. Alkylating agents are also likely to cause gonadal damage.
- Secondary malignancies induced by epipodophyllotoxins (etoposide), radiation, or alkylating agents. Exposure to epipodophyllotoxins has produced an increase in secondary acute myeloid leukemia. There is a marked excess of brain tumors among children who received cranial irradiation before the age of 5.
- Osteonecrosis caused by glucocorticoids (prednisolone, dexamethasone). This is most often seen in adolescents.
- Altered bone density induced by glucocorticoids, which increases susceptibility to fractures.
- Some potential impairment of intellectual development, which is measurable by a fall in IQ of 10–20 points.
- Psychosocial sequelae of a diagnosis of and treatment for leukemia, which are significant. There may be problems regarding relationships, career, insurance, and mortgage application, and emotional issues such as depression, anger, and confusion. Many studies have highlighted the need to include excellent psychosocial care throughout the disease trajectory and beyond.

Approaches to minimize adverse effects without affecting treatment outcome have included the development of new drugs, such as the liposomal formulation of daunorubicin; the use of cardioprotective agents; alternative administration schedules, such as continuous infusions/prolonged infusion times (the advantages of which are debatable); and the monitoring of minimal residual disease, which allows for reduction or optimization of drug doses.

1.1.10 Future Perspectives

The lack of specificity of most prognostic factors, as previously discussed, has led to the search for more relevant features of disease. Minimal residual disease (MRD) – that is, submicroscopic leukemia – can be detected at defined time points by identifying clone-specific T-cell receptors using PCR or immunoglobulin gene rearrangements using flow cytometry. This highly sensitive and highly specific prognostic information allows for definition of new risk groups. Treatment may possibly be reduced in children and adolescents with fast clearance of leukemic cells. Per-

sistent disease could require treatment modification and intensification.

Levels of MRD may be defined as

- Negative – nothing detectable with two markers
- Indeterminate – no result or low positive (1×10^{-5}–1×10^{-4} nucleated bone marrow cells)
- Positive – more than one nucleated bone marrow cell in 10,000 ($>1\times10^{-4}$).

Bone marrow samples from diagnosis and a later defined time point, such as the end of induction therapy, are compared. Treatment can then be assigned according to the clinical trial in place. Sequential monitoring of MRD can also elicit further risk assessment. For example, the persistence of MRD beyond 4 months is associated with an increased risk of relapse.

Remarkable advances have been made by defining molecular abnormalities involved in leukemogenesis and drug resistance. This has led to the development of promising new therapeutic strategies. Recognition of inherited differences in the metabolism of antileukemic drugs has enabled the selection of optimal drug dosages and scheduling. This could be useful to increase antileukemic effects and to reduce late effects. Future strategies will incorporate more specific risk-directed therapy and greater international collaboration. Ultimately, progress made should result in improved clinical management and increased cure rates for childhood ALL.

1.2 Acute Myeloid Leukemia

1.2.1 Epidemiology

Acute myeloid leukemia (AML) is most often seen in adults over age 40, but the annual incidence of childhood AML is approximately 4.7 per 100,000 and is constant from birth to 10 years of age. Incidence peaks slightly in adolescence, and AML is the more common leukemia found in neonates. Boys and girls appear to be affected equally. It is generally reported that AML is equally distributed among ethnic groups, but a study by McKinney et al. (2003) indicated a significantly higher incidence of AML among South Asians in an urban English city.

Children with Down's syndrome have an increased risk of AML, with an estimated 10–15-fold increase in incidence compared with that of the general childhood population (Hasle et al. 2000). These children's risk of ALL is also increased but not to the same degree. The reasons for their predisposition to leukemia are unclear. Presence of the extra chromosome 21 may disrupt the genetic balance, which in turn increases susceptibility to further trauma. However, individuals with Down's syndrome do not appear to have a higher risk of other malignancies. Hypotheses for this may include an increased susceptibility for apoptosis (programmed cell death) in Down's syndrome, causing cell death rather than malignant transformation after cell injuries (Hasle 2001).

1.2.2 Etiology

1.2.2.1 Genetic Factors

The various conditions that have a predisposition to AML are akin to those of any acute leukemia (Table 1.2), with the addition of myelodysplastic syndrome (monosomy 7).

1.2.2.2 Environmental Factors

Similarly, the causal risk factors associated with AML are the same as for ALL (see Table 3). Interestingly, allergy or a family history of allergy (including hay fever, neurodermatitis, asthma, and, to a lesser degree, eczema) have been associated with a decreased risk of ALL but not of AML (Schuz 2003).

Until recently, a Vietnam-era herbicide, Agent Orange (dioxin), was reported to be a parental exposure link to childhood AML. However, subsequent studies have ruled out any increased risk (Ahmad 2002).

1.2.3 Molecular Genetics

The defect that occurs in AML appears to be an arrest in the differentiation pathway of myeloid progenitors or precursors. Fusion genes generated by translocations of chromosomes block cell differentiation. These genes can be detected by PCR, and clonal chromosomal abnormalities of dividing bone marrow cells have been identified in more than 70% of chil-

dren diagnosed with AML. The most common fusion genes detected in AML are

- AML1/ETO from t(8,21), most often seen in acute myeloblastic leukemia
- MLL/AF10 from t(10,11)
- Inversion of ch16, creating CRFB/SMMHC
- Trisomy 8
- Monosomy 7
- PML/RARA from t(15,17), most common in acute promyelocytic leukemia

Fusions of the MLL gene occur in about 50% of cases of AML. These fusions are thought to be fetal in origin, as this fusion is often detected on the Guthrie card or neonatal blood spot of those children who subsequently develop AML. This is possibly the initiating event in childhood AML that requires additional secondary genetic alterations to cause leukemia.

1.2.4 Symptoms and Clinical Signs

AML can have a similar presentation to that of ALL, with symptoms appearing 1–6 weeks before diagnosis. The presenting signs and symptoms include the following:

- Pallor
- Fatigue, weakness
- Petechiae
- Fever, infection
- Sore throat
- Lymphadenopathy
- Skin lesions
- Gastrointestinal symptoms, including pain, nausea, and vomiting
- Gingival changes or infiltrates

The presenting lesions or infiltrates result from chloromas (or granulocytic sarcomas or myeloblastomas), which are localized collections of leukemic blast cells. Presentation with bleeding can be due to disseminated intravascular coagulation (DIC) and may be indicative of acute promyelocytic leukemia. DIC can occur as a result of the release of procoagulants from abnormal promyelocytic granules (see Chapter 16). Complaints of presenting bone pain are less common in AML, and hepatosplenomegaly is more marked in infants with AML.

CNS involvement of AML, occurring in 5–15% of cases, can cause symptoms similar to those of CNS involvement in ALL:

- Headache
- Poor school performance
- Weakness
- Vomiting
- Blurred vision
- Seizures
- Difficulty maintaining balance

Hyperleukocytosis can be present at diagnosis of childhood AML and may or may nor require leukopheresis therapy. Approximately 15–20% of children present with leukocyte counts $>100\times10^9$g/l, which may lead to leukostasis. Testicular infiltrates are uncommon in AML.

1.2.5 Diagnostics

If the history and physical examination suggest leukemia, examination of peripheral blood and bone marrow samples is required, as with the diagnosis of ALL. Bone marrow findings include a hypercellular trephine/biopsy sample and an aspirate sample showing more than 30% blast cells. To confirm a diagnosis of AML, the same procedures as for diagnosing ALL are applied.

1.2.6 Staging and Classification

There is presently no therapeutically or prognostically meaningful staging system for AML. Cytochemical staining of bone marrow smears using Sudan black stain produces a positive result in AML, and esterase stains distinguish further subgroups. Immunophenotyping also assists in determining the originating cell line. Cluster-of-differentiation antigen groups related to myeloid lineage include CD11, CD13–15, and CD33.

If the myeloid cell line is involved and a diagnosis of AML is confirmed, the French-American-British classification system for AML is applied. There are eight different classifications or types of AML (M0 to

M7), based on appearance of the diseased cells under the microscope (Table 1.9). Each subtype refers to the particular myeloid lineage affected and the degree of blast cell differentiation. This standardization began in 1976, but with improvements in treatment outcome, this approach to classification has limited clinical relevance. Approximately 80% of children less than 2 years of age have either M4 or M5 FAB subtypes. M7 is most common in children under 3 years, particularly in those with Down's syndrome.

Table 1.9. French-American-British (FAB) classification of acute myeloid leukemia

FAB group	Cell morphology
M0	Myeloid leukemia with minimal differentiation
M1	Myeloblastic leukemia
M2	Myeloblastic leukemia – undifferentiated
M3	Promyelocytic leukemia with 15;17 translocation
M4	Myelomonocytic leukemia
M5	Monocytic leukemia: M5a – without differentiation M5b – with differentiation
M6	Erythroblastic leukemia
M7	Megakaryoblastic leukemia

Myelodysplastic syndrome (MDS) is a preleukemic syndrome that has a relationship with some types of AML (MDS-related AML or MDR-AML). Approximately half of the cases of AML follow MDS, and these patients generally have a very poor prognosis. The other main group consists of those cases unrelated to MDS, with a suggested name of true de novo AML (TDN-AML). This led to subclassification of AML based on its relationship with MDS. The World Health Organization (WHO) attempted to refine the FAB classification by incorporating the AML/MDS relationship. This classification, shown in Table 1.10, has been a cause for debate over the past few years. However, the WHO classification incorporates subcategories of AML with recurring translocations, AML related to MDS, and subsets of treatment-relat-

Table 1.10. World Health Organization classification of acute myeloid leukemia

Group	Subgroups
Acute myeloid leukemia with recurrent genetic abnormalities	Acute myeloid leukemia with t(8;21) Acute myeloid leukemia with abnormal bone marrow eosinophils inv(16) or t(16;16) Acute promyelocytic leukemia (AML with t(15;17) and variants Acute myeloid leukemia with MLL abnormalities
Acute myeloid leukemia with multilineage dysplasia	Following an MDS or MDS/myeloproliferative disorder Without antecedent myelodysplastic syndrome
Acute myeloid leukemia and MDS, therapy-related	Alkylating agent-related Topoisomerase type II inhibitor-related Other types
Acute myeloid leukemia not otherwise specified	Acute myeloid leukemia minimally differentiated Acute myeloid leukemia without maturation Acute myeloid leukemia with maturation Acute myelomonocytic leukemia Acute monoblastic and monocytic leukemia Acute erythroid leukemia Acute megakaryoblastic leukemia Acute basophilic leukemia Acute panmyelosis with myelofibrosis Myeloid sarcoma

Adapted from Head 2002

ed AML based on their relation to the first two groups. Therefore, this system may assist clinical decisions and be useful in analyzing biologic studies in AML. It is of note that MDS-AML is more prominent in the elderly, with only 15% of cases in children and young adults (Head 2002). The TDN-AML group, related to a set of recurring cytogenetic translocations and inversions, has a median age approximating the median age of the population (Head 2002).

1.2.7 Treatment

The most dramatic outcomes for children with AML have resulted from intensive therapy over a brief period of time. Treatment usually includes a protocol with an induction anthracycline (usually daunorubicin) and cytarabine. An important component of post-remission therapy appears to be several courses of high-dose cytarabine. The addition of mitoxantrone is possibly also beneficial. Intensive therapy usually induces remission in about 90% of children. The challenge then is to prolong the remission. In over 60% of these children, an allogeneic stem cell transplant is the chosen treatment option once first remission has been achieved. However, if cytogenetics are favorable, such as t(15;17), t(8;21) or inv16, intensive chemotherapy consolidation may be the treatment of choice even if a matched sibling donor is available (Sung et al. 2003). These patients would be transplanted after relapse. There is no evidence to suggest that autologous transplant is of any benefit in pediatric acute leukemia. (Part 3 will cover stem cell transplants in detail.) The use of some form of CNS treatment is included. Children with M4 and M5 have the highest incidence of CNS disease.

Acute promyelocytic leukemia (APM) (i.e., FAB subtype M3) can often be treated with all-trans retinoic acid and chemotherapy, which achieves a remission and cure in most children with AML of this type. This outcome is possible due to the translocation t(15;17) involving a breakpoint that includes the retinoid acid receptor. Fatal hemorrhagic complications can occur before or during induction in this subtype. There is a low incidence of CNS disease in children with APM. A lumbar puncture is not performed, and IT chemotherapy is not required.

Down's syndrome patients have a markedly increased responsiveness to therapy. However, this causes an increased treatment-related morbidity and mortality, which has meant that AML protocols have been tailored specifically for this population of children. Stem cell transplant is rarely indicated in these circumstances. Of note are cases when infants with Down's syndrome, usually under 2 months of age, are diagnosed with AML or transient leukemia and achieve complete spontaneous remission.

1.2.8 Prognosis

Despite significant improvements in the outcomes of children with AML, the cure rate is only approximately 50%. About 45% of children with AML relapse, and there remains little information about the best treatment for this group of children.

In 2002 (a), Rubnitz and colleagues reported that the only independent factors indicating a favorable prognosis were

- a presenting leukocyte count of $<50\times10^9$/l
- the genetic factor of translocation t(9;11)

Another favorable prognostic factor, as mentioned previously, is the constitutional trisomy 21 (Down's syndrome), despite the increased risk for developing AML. These children also have a decreased risk of relapse that is unrelated to having the favorable abnormalities of t(15;17), inv16, or t(8;21).

It is worth noting that results of another study by Rubnitz et al. (2002b) debate the favorable outcome of t(8;21) that was previously reported.

1.2.9 Follow-up

Children and adolescents need appropriate and sensitive follow-up, similar to that following ALL treatment. The specific features of follow-up for AML concern the increased incidence of relapse and the increased number of children and adolescents who receive transplant as a standard modality of treatment.

1.2.10 Future Perspectives

The progress in therapy for AML lags behind that for ALL. Allogeneic bone marrow transplant from a matched family donor appears to remain the best option for most patients. Drug resistance is an apparent factor in AML and is being investigated by studying leukemic blast cells or minimal residual disease.

In adult patients with AML, the expression of the multidrug resistance gene (MRD1) defines a poor prognostic group. This is not a similar finding in children with AML (Steinbach et al. 2003). A study by Steinbach et al. (2003) investigated the expression of five of the genes encoding the multidrug resistance-associated proteins (MRP) in children with AML and their response to chemotherapy. Expression of MRP3 was found to be involved in drug resistance, producing a poorer prognosis, and the expression of MRP2 was, to a lesser extent, also associated with poor prognosis. Expression of high levels of both these genes indicated a particularly poor prognosis. This study suggests that these proteins, MRP3 and possibly MRP2, could provide markers for risk-adapted therapy and possible targets for the development of drugs that would overcome multidrug resistance in childhood AML.

Alternative approaches to therapy may include risk-directed therapy based on different prognostic criteria, differentiation therapy with all-trans-retinoic acid, immunotherapy with monoclonal antibodies, or tumor vaccines.

1.3 Chronic Myeloid Leukemia

1.3.1 Epidemiology and Etiology

An increase in the incidence of adult chronic myeloid leukemia (CML) has been seen in three populations:

- The Japanese exposed to radiation released from atomic bombs in Nagasaki and Hiroshima
- Patients with ankylosing spondylitis treated with spine irradiation
- Women with uterine cervical carcinoma who received radiation treatment (Freedman 1994)

Despite this obvious relationship between radiation and CML, only 5–7 % of adult cases of CML have documented exposure to excessive radiation, and previous exposure is infrequent in children with CML (Freedman 1994). In patients younger than 20 years of age, the incidence is less than 1 in 100,000, with 80 % of these cases being over the age of 4 years.

1.3.2 Molecular Genetics

CML is normally a hematological disease of the elderly, characterized by the BCR/ABL oncogene caused by a translocation between the ABL gene on Ch'9 and the BCR gene on Ch'22. The resulting chromosome 22, with a shortening of the long arm, is known as the Philadelphia (Ph') chromosome. The BCR/ABL gene fusion product is thought to be causative in CML and has multiple effects on diverse cell functions, such as growth, differentiation, adhesion, and apoptosis.

1.3.3 Symptoms and Clinical Signs

The "chronic phase" of leukemia that results then evolves into a more rapidly progressive phase known as the "accelerated phase" and ultimately "blast crisis." The chronic phase lasts about 3 years but can range from a few months to 20 years. The accelerated phase generally occurs over a 3–6-month period. The final phase is generally resistant to current treatment and is therefore fatal.

The signs and symptoms of CML can vary depending on the phase the disease has reached:

- The *chronic phase* has a nonspecific onset over weeks to months, with complaints of fatigue, anorexia, weight loss, and excessive sweating. Physical presentation includes pallor, bruising, low-grade fever, sternal bone pain, and splenomegaly that is sometimes accompanied by hepatomegaly.
- Signs and symptoms of the *accelerated phase* present over a few months and are similar to those of the chronic phase but with more episodes of unexplained fever, lymphadenopathy, and bruising and petechiae caused by thrombocytopenia.

- The *blastic phase* presents with symptoms identical to those of acute leukemia

1.3.4 Diagnostics

CML is characterized by the presence of large numbers of granulocytes in the blood, with mild anemia and thrombocytosis. The numbers of basophils and eosinophils are increased. A characteristic laboratory feature is a marked reduction or absence of leukocyte alkaline phosphatase (LAP) activity, which results from a decrease in monocytes that normally secrete a factor that induces LAP activity (Freedman 1994).

Cytogenetic analysis of the marrow cells will display the Philadelphia chromosome in over 90% of new patients with CML. Absence of cytogenetic or molecular abnormalities in chromosome 22 would rule out a diagnosis of CML.

1.3.5 Treatment

In children with CML, allogeneic bone marrow transplant is normally the treatment of choice. This treatment is providing promising survival rates even in the event of advanced disease and histoincompatibility with donor marrow (Sharathkumar et al. 2002). Another treatment that has produced encouraging results, reported by Millot et al. (2002), uses a combination of interferon and cytarabine for children with Philadelphia-chromosome-positive CML. This may offer an alternative to transplantation in children and adolescents in the chronic phase of CML.

1.3.6 Prognosis

For children with the adult form of CML, the importance of prognostic factors is difficult to define due to the low incidence of disease. Remissions can be induced, but relapse is common and long-term survivors are rare.

1.3.7 Future Perspectives

For children with CML, current efforts should aim to reduce transplant-related deaths. Cytogenetic studies to identify further risk factors will assist in the understanding of the cell biology of this disease.

1.4 Juvenile Myelomonocytic Leukemia

A subgroup of CML is juvenile myelomonocytic leukemia (JMML), formerly called juvenile chronic myeloid leukemia (JCML). This subgroup represents less than 1% of cases of childhood leukemia. Controversy surrounds the classification of this subgroup, and it may be termed as chronic myelomonocytic leukemia (CMML). Most patients are less than 2 years of age, with 95% younger than 4 years (Freedman 1994).

Children frequently present with complaints of malaise, bleeding, or fever, often with localized infection. Less common presentations include pulmonary symptoms (cough, wheezing, tachypnea), abdominal distension and discomfort, weight loss, and occasionally bone pain. On examination, splenomegaly is a frequent feature; pallor and hepatomegaly may also be present. Skin manifestations may be seen, with an eczematous rash that is unresponsive to topical treatment. Xanthoma and café-au-lait spots are often associated with JMML. These skins findings are also common in neurofibromatosis, and an interrelationship between neurofibromatosis and JMML has been established (Freedman 1994).

Peripheral blood samples show an increasing number of circulating monocytes in all cases. Immature granulocytes, anemia, and thrombocytopenia are also frequently present. The cells in JMML do not contain the Philadelphia chromosome, although other chromosomal abnormalities are present.

This disease is more progressive and less responsive to treatment than Ph'-chromosome-positive CML. Prognosis is poor, and a bone marrow transplant is required as early as possible for these children, particularly when a matched relative donor is available.

Table 1.11. Common Symptoms of Histiocytosis

System	Symptom
Gastrointestinal	Abdominal pain, vomiting, diarrhea, jaundice, weight loss, esophageal bleeding
Bone	Bone pain, headaches (skull lesions), limp (leg lesions)
CNS (brain)	Diabetes insipidus, mental deterioration, headaches, dizziness, seizures, increased intracranial pressure
CNS (pituitary gland)	Polydipsia, polyuria, dehydration, short stature, delayed puberty
Pulmonary	Feeding problems (infants), chest pain, dyspnea, cough, hemoptysis
Oral	Facial swelling and pain, loss of teeth, swollen and bleeding gingiva, swollen lymph nodes
Skin	Scaly rash
Ear	Inflammed, draining ear canal, rash behind ears

1.5 Langerhans Cell Histiocytosis

Histiocytosis is not defined as a malignancy, but it is treated with cancer therapies (e. g., chemotherapy, radiotherapy) and pediatric oncology nurses may be involved in the care of a child with Langerhan's cell histiocytosis.

A histiocyte is a normal cell in the immune system found in the bone marrow, blood, skin, liver, lungs, lymph glands and spleen. Histiocytosis identifies a group of disorders that have proliferation of cells of the mononuclear phagocyte and dendritic cell systems. In Langerhans cell histiocytosis (LCH), the histiocytes move into tissues where they are not normally found and cause damage to those tissues. The cause of LCH is unknown. Suggested hypotheses include the possibility of clonal abnormalities; cytokine or chemokine abnormality causing abnormal expression of Langerhan's cells; a combination of oncogenesis and immune dysregulation (Egeler et al., 2004); and lesional Langerhans cells that control the persistance and progression themselves (Annels et al., 2003).

The Histiocyte Society, an international body, was formed in 1987 and has outlined morphology, immnohistiochemistry and clinial criteria required for LCH. The symptoms of LCH are dependent on the body system involved and are listed in Table 1.11. Tests to diagnose LCH may include radiographs, CT studies, complete blood count and blood chemistries, and tissue or skin biopsy.

Single-system (localised) LCH usually disappears on its own without any treatment. Although treated with chemotherapy there has been no specific research trial for the use of cytotoxic therapy in LCH. This may occur following a biopsy. In a small number of children, treatment will be needed and low-dose radiotherapy, surgery and steroids may be used. Multi-system (disseminated) disease is usually treated with chemotherapy and steroids. The combination and duration of therapy will vary depending on the severity of the illness. Eighty percent of children who develop LCH will recover from it.

A small number of children may develop side effects many years later, because of the treatment they have received. This is more likely to happen when treatments have been intensive. Possible late side effects include reduced growth, infertility, pulmonary and cardiac abnormalities, and second malignancy.

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Solid Tumors

Eleanor Hendershot

Contents

Solid tumors account for 30% of all pediatric malignancies. Pediatric tumors are most often classified by histology rather than anatomic location, as is done in adult tumors. The most commonly occurring pediatric solid neoplasms are brain tumors, neuroblastoma, and Wilms' tumor. Other malignancies that affect the pediatric population include Hodgkin's lymphoma, non-Hodgkin's lymphoma, Ewing's sarcoma, osteosarcoma, hepatoblastoma, retinoblastoma, and rhabdomyosarcoma. These and other less commonly occurring tumors will be reviewed in this chapter.

2.1 Hodgkin's Disease

Hodgkin's disease (HD) is a malignant disease of the reticuloendothelial and lymphatic systems. It has a predictable pattern of spread through contiguous nodes. It does occur, although rarely, in extralymphatic organs.

2.1.1 Epidemiology

HD comprises 5% of all pediatric malignancies. The overall incidence of HD each year is approximately 6.6 per million children under the age of 15, with a peak in incidence in 14-year-olds of 23.1 per million. (Gurney et al., 1999). There tends to be a male predominance in children less than 15, at which point the incidence becomes more equal between males and females. There is a characteristic bimodal distribution of age of onset that differs geographically. In industrialized nations, there is a peak incidence around the age of 20, followed by a second peak that occurs in the 50s. In developing countries, however, the first peak occurs earlier into childhood. HD is rare in children less than 5 years of age.

2.1.2 Etiology

In general, HD tends to be diagnosed most frequently in patients with abnormal immune systems. There has been a strong association noted between the development of HD and previous Epstein-Barr virus (EBV) infection, especially early and prolonged exposure. The virus has been noted in the Reed-Sternberg cells in 50% of HD patients (Hudson and Donaldson, 2002); HD is characterized by the presence of Reed-Sternberg cells (see section 2.1.5). EBV has been associated with HD to varying degrees based on ethnicity and is found in 93% of Asians, 86% of Hispanics, 46% of whites, and 17% of African-American children who are affected (Hudson and Donaldson, 2002).

The role of HHV6 in disease development is also being investigated. HD has been noted with greater frequency in patients with a family history of HD, ataxia telangiectasia, or immunodeficiency syndromes such as human immunodeficiency virus (HIV).

2.1.3 Molecular Genetics

Cytogenetic abnormalities, often characteristic in other tumors, are not diagnostic in HD.

2.1.4 Symptoms and Clinical Signs

HD usually presents with painless lymphadenopathy. On physical examination the lymph node is usually described as firm and rubbery, and it may be sensitive or painful if it has enlarged quickly. Eighty percent of individuals present with disease in the cervical area, and 60% of those affected have some degree of mediastinal disease. Systemic symptoms are present in 25–30% of children and include

- fever >38°C for more than 3 days
- drenching night sweats
- weight loss comprising 10% of body weight over a period of 6 months (Chauvenet et al., 2000)

Respiratory symptoms of cough or chest pain may be obvious if significant mediastinal disease is present. Superior vena cava syndrome can also occur due to a mediastinal mass. Other systemic symptoms include pruritus, urticaria, and fatigue. Splenic enlargement may be observed with abdominal involvement, and splenic disease is present in one-third of patients. Idiopathic thrombocytopenia purpura occurs in 1–2% of children with HD and is often associated with autoimmune hemolytic anemia (Hudson and Donaldson, 2002).

HD typically spreads via lymphatics rather than hematogenous routes. Extralymphatic organs such as the bone and bone marrow may be involved in advanced disease. Parenchymal lung lesions are also sometimes present.

2.1.5 Diagnostics

Physical examination will demonstrate the presence of any significant lymphadenopathy. Although a chest x-ray can be performed quickly to determine the presence of a mediastinal mass, computerized tomography (CT) of the neck, chest, abdomen, and pelvis is necessary to evaluate the extent of disease. Nuclear imaging such as a gallium scan and, more recently, positron emission tomography (PET) scanning provides additional information on the extent of disease and the response to treatment. Gallium positivity is found in 70% of patients (Chauvenet et al., 2000). Gallium is taken up by underlying pathology, predominantly malignancy; however, it can be taken up by infection and thrombosis as well. Bone scan should be done if clinically warranted; i.e., bone pain, elevated alkaline phosphatase, or metastatic disease. Bilateral bone marrow aspirate and biopsies are necessary to rule out bone marrow involvement. A staging surgical laparotomy is no longer routinely performed in pediatric patients.

A biopsy of the affected node is required for diagnosis. An excisional biopsy is preferred because it preserves the architecture of the node and because the sample must be large enough to locate the presence of Reed-Sternberg cells. HD is characterized by the presence of Reed-Sternberg cells, which are giant multinucleated cells with abundant cytoplasm, the nucleolus having a characteristic "owl's eye" appearance. In most cases the Reed Sternberg cells are B-cells, and in 10–20% of cases, T-cells (Hudson and

Table 2.1. Ann Arbor staging classification for Hodgkin's lymphoma (adapted from Pinkerton et al., 1999)

Stage	Characteristics
I	Involvement of a single lymph node region or a single extralymphatic organ or site
II	Involvement of two or more lymph node regions on the same side of the diaphragm or solitary involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm, which may be accompanied by localized involvement of extralymphatic organ or site or by involvement of the spleen, or both
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement

"B" staging includes subjective symptoms such as fever, night sweats, and weight loss (10% of body weight in previous 6 months) Pinkerton et al., 1999

Donaldson, 2002). Malignant cells comprise less than 1% of tumor cells, with the remainder being inflammatory infiltrates. Histopathological studies carried out on Hodgkin's tumors consist of hematoxylin, eosin, and special immunohistochemical staining for surface markers, including CD15, CD20, and CD30. Immunophenotyping of RS cells indicates expression of certain activation antigens, including the IL2 receptor, Ki-1, the transferrin receptor, and HLA-DR (Hudson and Donaldson, 2002).

Blood work should include a complete/full blood count (CBC) and differential; cytopenias may be seen with bone marrow disease. Liver and renal function tests including alkaline phosphatase, should be done. Elevations of the erythrocyte sedimentation rate (ESR), copper, and ferritin are often seen because of increased activity of the reticuloendothelial system.

2.1.6 Staging and Classification

HD includes four major subtypes: nodular sclerosing, mixed cellularity, lymphocyte-predominant, and lymphocyte-depleted. Nodular sclerosing (NS) is the most common subtype, occurring in 60% of patients; disease is often found in the lower cervical, supraclavicular, and mediastinal lymph nodes. Mixed cellularity occurs in 30% of patients, often in children less than 10 years of age, those with advanced disease, and those with extranodal involvement. Lymphocyte-predominant HD occurs in 10–15% of patients, is more common in males and younger children, and presents as localized disease. Lymphocyte-depleted HD occurs very rarely in children and is more common in HIV infection; it frequently presents as advanced disease involving bone or bone marrow (Hudson and Donaldson, 2002).

The Ann Arbor Staging Classification System is generally used to stage disease (Table 2.1).

2.1.7 Treatment

The goal of treatment for children with HD has become increasingly focused on response-based therapy and on minimizing late effects. Chemotherapy and radiation therapy are the cornerstones of treatment in HD. Surgery is not used in HD treatment; its only role is to obtain tissue biopsy. Children are at an increased risk for late secondary malignancies resulting from having both chemotherapy and radiotherapy at a time when they are still growing. For this reason, attempts to minimize treatment for those children who already do well based on stage and histology are being trialed.

Chemotherapy is an important part of the treatment for HD. Nitrogen mustard was one of the first drugs to be used for treating this disease, but due to subsequently recognized significant toxicities, specifically a relatively high incidence of secondary malignancies (predominantly acute myeloid leukemia) and infertility, it is no longer commonly used. Currently treatment is being modified and efforts made to avoid the use of alkylators and other drugs with

significant long-term sequelae. Drugs that are predominantly used in the treatment of HD include mechlorethamine (M), vincristine (O), prednisone (P), procarbazine (P), adriamycin (A), methotrexate (MT) bleomycin (B), vinblastine (V), etoposide (E), dacarbazine (D), and cyclophosphamide (C). Drug combinations that have and are currently being used in the treatment of HD are MOPP-ABV; ABVD, COPP-ABV, ABVE-PC, VEPA, BEACOPP, and VAMP.

Radiation therapy also plays a vital role in treating HD. Involved field radiation therapy includes the areas that are clinically involved as well as the surrounding lymph nodes. This approach is being used more commonly now in efforts to decrease the radiation field, thereby decreasing late effects. Mantle radiation, involving a larger field (submandibular, submental, cervical, supraclavicular, infraclavicular, axillary, mediastinal, and pulmonary hilar nodes), was typically used in previous protocols. In some instances of mantle radiation, the tumor volume may be enlarged to include the cardiac silhouette or lung fields as well. When pelvic radiation is needed, surgical repositioning of the ovaries to a central midline position is possible, enabling a midline pelvic block to protect ovaries and minimize toxicity.

Tailored therapy considers and evaluates early response to therapy for the purpose of limiting the cumulative chemotherapy doses while maintaining efficacy. Early responders continue to have improved outcomes compared with slow responders. Schwartz (2003) describes a protocol using VEPA (vincristine, etoposide, prednisone, adriamycin) that does not include any alkylators, which has been shown to be effective for low-stage disease without radiation therapy. Donaldson et al. (2002) also studied low-risk children and adolescents with stage I, stage IIa, and IIb without bulky mediastinal disease or peripheral nodal disease. These patients were treated with four cycles of VAMP (vincristine, adriamycin, methotrexate and prednisone) followed by low-dose involved field radiation. Those who had a complete response after two cycles of VAMP were treated with 15 Gy of involved field radiation therapy, and those who had only a partial response to two cycles of VAMP received 22.5 Gy of radiation therapy. The mean follow-up for these patients has been 5–10 years, and the 5 year overall survival is 99%, event-free survival is 93%, and there have been no toxicity concerns. Schwartz describes a North American Pediatric Oncology Group (POG) trial for advanced disease (POG 9425) in which the early responder received three courses of ABVE-PC versus five courses for the slow responders or partial responders, followed by radiation therapy. The results show that the overall 2 year event-free survival is 88.2%, with 90.8% for early responders, which comprised 61% of the children, and 87.7% for slow responders, which represented 38% of the children. Progressive disease was found in 1% of children. These results suggest that tailoring therapy has good outcomes in both cohorts of early and late responders but, by reducing treatment, may avoid late effects in those who respond early.

The treatment for relapsed patients usually consists of high-dose chemotherapy followed by autologous stem cell transplant (ASCT). If radiation therapy has not been used in the initial treatment of the disease, it may have a role in the treatment of the relapsed tumor.

2.1.8 Prognosis

The overall survival of children and adolescents with HD is 90% (Schwartz, 2003). Adverse prognostic features include bulky disease, as defined by a mass greater than 10 cm (6 cm in children) in size, and large mediastinal adenopathy. Smith et al. (2003) describe a prognostic factor analysis as reported in two POG studies. They found that stage IV disease and the male gender showed an inferior event-free survival. In Children's Cancer Group (CCG) trials, they found that elevated ESR, liver size, and mediastinal bulk among stage III patients was prognostic for inferior EFS. They also found that advance stage, bulky mediastinal disease, NS histology, and systemic symptoms were prognostic for both inferior disease-free survival and overall survival. Anemia and leukocytosis may also predict an inferior outcome

2.1.9 Follow-up

The follow up for HD must be long term, due to the many late effects that have affected this cohort of patients. Most relapses occur within the first 3 years off therapy; however, relapse has been documented as long as 10 years post-treatment (Hudson and Donaldson, 2002). Disease should be followed with chest x-ray and CT scanning of the primary site. Gallium scans are sometimes used to follow those who are at high risk for recurrence. PET may play a larger role in this regard in the future as more centers gain access to PET scanners. Scans are often carried out every 3 months for the first year off treatment, every 4 months for the second, and then every 6 months up until 5 years, as per POG protocols. Blood work such as CBC and differential, ESR, TSH, T4, LH, FSH, testosterone, and estradiol must all be monitored.

Late effects of therapy must be monitored carefully. Thyroid dysfunction in the form of nodules, hypothyroidism, and hyperthyroidism occur more frequently in patients who have been treated with radiation therapy as compared with the general population. The incidence of hypothyroidism is four to five times higher in patients treated with radiation therapy for HD compared with the general population (Sklar et al. 2000). Thyroid problems usually present within the first 5 years post-therapy but can occur until 20 years post-therapy. TSH and T4 must therefore be monitored. Echocardiogram and pulmonary function tests must be done to monitor for late cardiomyopathies and pulmonary fibrosis, secondary to anthracycline and bleomycin, respectively (with or without radiation). The risks of secondary tumors at various sites can occur in the two to three decades following treatment (Metayer et al., 2000). Patients treated for HD have the highest incidence of second malignancies of all of the pediatric malignancies. Infertility and primary ovarian failure can occur following chemotherapy and pelvic irradiation. Counseling must be done regarding lifestyle behaviors such as smoking.

2.1.10 Future Perspectives

Future trials for HD treatment will continue to focus on tailored disease protocols in an attempt to minimize late effects while continuing to maintain and exceed current excellent survival data. As more advances are made, immunotherapy and vaccine and monoclonal antibody therapy may be of use in he treating HD in the future. Rituximab is being studied now to determine its effectiveness at targeting lymphocyte-predominant HD (Donaldson, 2003).

2.2 Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphomas (NHL) are a group of malignancies that are derived from cells of the immune system and lymphoid tissue. They are an aggressive form of cancer characterized by rapid cell division and an often high tumor burden at diagnosis.

2.2.1 Epidemiology

Lymphomas in general account for about 12% of all childhood malignancies and are the third most common type of childhood cancer (Sandlund et al., 1996). NHL accounts for 60% of lymphomas; it occurs at an incidence of approximately 8.4 per million children under the age of 20 per year (Gurney et al. 1995). Males are affected twice as often as females, and whites twice as often compared with blacks in the United States. Burkitt's lymphoma, an NHL subtype, is endemic in equatorial Africa and accounts for approximately 50% of all childhood cancers. In other areas of the world, Burkitt's lymphoma occurs sporadically and is less common.

2.2.2 Etiology

There are different etiologies of NHL depending on geographical location. It has become apparent that individuals who are immunocompromised are at a higher risk of developing NHL, including those who are HIV infected and those who have undergone bone marrow transplant. EBV has been implicated in most of these lymphomas. Those individuals who

Table 2.2. Summary of major histological categories, immunophenotypes, common cytogenetic abnormalities, and common sites of disease of non-Hodgkin's lymphomas ((Magrath, 2002; Cairo and Perkins, 2000))

Histological category of lymphoma	Immunophenotype	Cytogenetic abnormalities	Common sites of disease
Burkitt's	B-cell (CD 19, CD 20, CD22, CD79, CD77, CD10)	t(8;14), t(8;2) and t(8;22)	Abdomen, head, neck
Large B-cell	B-cell (CD19, CD20, CD22, CD38, CD79, sometimes CD10) TdT neg	Bcl-6 or bcl-2 t(8;14) in 5–10%	Abdomen, mediastinum
Burkitt's-like	B-cell (MIB-1 positivity)	t(8;14)	Abdomen, head, neck
Lymphoblastic	Pre-T (CD77, CD7, CD5, CD2,CD1, CD3, CD4, CD8, TdT pos)	T-cell t(11;14)	Thorax
	CALLA sometimes observed	t(7;14), t(8;14), t(10;14)	Lymph nodes, bone marrow
	Pre-B (CALLA, B4, HLA-DR)	B-cell t(1;19), t(4;11)	
Anaplastic large cell	T-cell or null (CD 30) Ki-1+	t(2;5), and variants	Lymph nodes, skin, soft tissue, CNS, intrathoracic
Peripheral T-cell lymphoma	T-cell	Unknown	Variable

have been previously treated for HD are also at an increased risk for developing NHL due to cumulative effects of treatment; the risk is increased further if the individual has had a splenectomy. In African Burkitt's lymphoma, there is a very high correlation with those who have been previously infected with both EBV and malaria. In the developed world there has been no clear etiology for the development of NHL.

2.2.3 Molecular Genetics

Cytogenetic abnormalities are commonly found in NHL and assist in their diagnosis. A summary of the major histological categories of NHL with their associated cytogenetic abnormalities is shown in Table 2.2.

2.2.4 Symptoms and Clinical Signs

Like many tumors, the presenting signs and symptoms of NHL vary greatly depending on tumor location. NHL usually presents as extranodal disease in children. The primary presentations are as follows:

- Head and neck: 30%
- Abdominal: 30%
- Intrathoracic, mediastinal, or hilar adenopathy: 25% (Cairo and Perkins, 2000)

Localized disease can present as a firm, nontender mass in virtually any location.

Advanced metastatic disease is present in 70% of children who present with NHL (Cairo and Perkins, 2000). Table 2.3 indicates various presentations of NHL.

2.2.5 Diagnostics

A thorough history, physical exam, radiologic imaging, and tumor biopsy are needed to diagnose NHL. NHL is a rapidly growing tumor and often creates major metabolic disturbances that can be life-threatening. Frequent blood work for biochemistry abnormalities is a necessity while monitoring for signs of tumor lysis syndrome.

The sequence of investigations usually depends on the location of the primary tumor. Table 2.4 shows the possible investigations that may be carried out when a diagnosis of NHL is suspected.

Table 2.3. Presentations of non-Hodgkin's lymphoma

Features	Signs and symptoms	Indication
Meningoencephalitis	Headache Cranial nerve palsies Altered level of consciousness	CNS disease found commonly in Burkitt's lymphoma
Waldeyer's ring involvement	Tonsillar hypertrophy	Burkitt's lymphoma
Jaw lesion	Swelling Pain	Endemic Burkitt's
Systemic features	Fever Weight loss Night sweats Anorexia Malaise	Anaplastic large cell lymphoma
Mediastinal mass	Persistent nonproductive cough Dysphagia Dyspnea Chest pain	Intrathoracic disease, common in T-cell lymphoblastic lymphoma
Superior vena cava syndrome	Swelling of the upper extremities Distended neck veins Decreased breath sounds Dyspnea or stridor due to mass pressing on internal structures, pericardial effusion	Intrathoracic lesion Common in T-cell lymphoblastic lymphoma
Acute abdomen	Abdominal distension Pain Rebound tenderness Shifting dullness Nausea Vomiting GI bleeding Change in bowel habits Intussusception	Abdominal lymphoma B-cell (Intussusception is not an uncommon presentation for abdominal Burkitt's lymphoma)
Bone pain	Local pain Swelling	Bony disease, can occur in large cell lymphomas, lymphoblastic lymphomas, and Burkitt's
Skin involvement	Painful lesions	Particularly anaplastic large-cell lymphoma
Testicular involvement	Pain Swelling	Localized anaplastic large-cell lymphoma or lymphoblastic lymphoma.
Pancytopenia	Infection Fatigue Bleeding	Metastatic disease – bone marrow Lymphoblastic lymphoma or Burkitt's lymphoma common

Table 2.4. Possible investigations in the diagnosis of non-Hodgkin's lymphoma

Investigation	Rationale
Chest x-ray	To detect mediastinal mass and pulmonary lesions
CT of the neck, chest, abdomen, pelvis	For staging and evaluating all sites of potential disease (*tracheal compression would also be noted on the CT and is critical to recognize before administering general anesthetics*)
CT of the head	To detect CNS involvement
Ultrasound of the abdomen	To determine if there are abdominal masses and to ensure patency of the urinary tract system before beginning chemotherapy
Bone scan and skeletal survey	To detect bone metastases
Gallium scan	Often lymphomas show avidity for gallium, and scanning after it is administered outlines tumor throughout the body Also used to assess response to treatment
PET scan	As PET scans become more accessible, they will likely be used in the diagnostic workup and monitoring of patients with NHL
Endoscopy	Indicated if gastrointestinal bleeding is a presenting symptom
Complete/full blood count and differential	If cytopenias are present, bone marrow involvement is likely
Renal function tests	Abnormalities may suggest tumor lysis
Liver function studies	Baseline prior to treatment
Lactate dehydrogenase (LDH)	Nonspecific but can be elevated in NHL, possibly indicating a high tumor burden
Blood cultures	If fever present
Coagulation studies such as PTT, INR, fibrinogen, d-dimers	To evaluate possible disseminated intravascular coagulation
Viral studies for EBV, CMV, HSV, hepatitis A, B, and C	To look for evidence of causation (*HIV testing should be considered in a patient with a primary CNS lymphoma because of the high incidence of CNS lymphomas in the HIV population*)
B- and T-cell function tests	If an underlying immunodeficiency is being considered
Bilateral bone marrow aspirates and biopsies	If the bone marrow has greater than 25% blasts, the lymphoma would be treated as a leukemia based on the cellular phenotype of either B or T lineage (Pinkerton et al., 1999)
Lumbar puncture	To examine the cerebrospinal fluid for malignant cells

A biopsy of the node or mass is necessary to make a definitive diagnosis. NHLs are in the class of blue round cell tumors. They are differentiated from other blue round cell tumors based on immunophenotyping, karyotyping, southern blotting, polymerase chain reaction (PCR), and microarray. The presence of leukocyte common antigen CD45 will confirm lymphoid cell proliferation as it is not present in non-hematologic malignancies (Magrath, 2002). See Table 2.2 to view a summary of immunophenotyping and cytogenetic differences in the various subtypes of NHL.

Table 2.5. St Jude staging systems for childhood non-Hodgkin's lymphoma (adapted from Pinkerton et al., 1999)

Stage I	Single tumor (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen
Stage II	Single tumor (extranodal) with regional lymph nodes Two or more nodal areas on the same side of diaphragm Two single tumors (extranodal) with or without regional lymph node A resectable primary GI tumor with or without involvement of mesenteric nodes only
Stage III	Two single tumors (extranodal) above and below the diaphragm Two or more nodal areas above and below the diaphragm All primary intrathoracic tumors All extensive primary intra-abdominal disease All paraspinal or epidural tumors
Stage IV	Any of the above with the initial involvement of either the central nervous system and/or the bone marrow (<25%)

Pinkerton et al., 1999

Table 2.6. Non-Hodgkin's lymphoma incidence according to subtype and cell of origin (adapted from Pinkerton et al., 1999)

Cell type	Subgroup	Proportion of NHL (%)
B-Cell	I. Precursor B neoplasm	
	B lymphoblastic	5%
	II. Peripheral B neoplasm	
	Follicular	0.4%
	Diffuse large B cell	3%
	Primary mediastinal	0.4%
	Burkitt's	42%
	High-grade Burkitt's and Burkitt's-like	4%
T-Cell	I. Precursor T neoplasm	
	T lymphoblastic	20%
	II. Peripheral T-cell	
	PTL unspecified	1%
	Anaplastic large cell	15%
	Nonspecific/intermediate	9.2%

Pinkerton et al., 1999

2.2.6 Staging and Classification

The classifications of childhood NHL are divided into three main categories:

- Lymphoblastic (30%)
- Large cell (20%)
- Small noncleaved cell, Burkitt's or Burkitt's like (40%).

Staging normally follows the St Jude Children's Research Hospital schema, which was based on the Ann Arbor Hodgkin's classification (see Table 2.5). This staging and classification system is used for all histologic subtypes of NHL. Incidence can also be defined by the B-cell or T-cell lineage of the tumor (Table 2.6). The National Cancer Institute has provided breakdowns of the incidence in which the various forms of lymphoma can present (Table 2.6).

2.2.7 Treatment

Treatment for NHL depends on the histologic subtype and stage of disease. Most protocols now assign patients to risk groups in order to determine intensity of treatment. Surgery is primarily used for diagnosis and staging of NHL, with the exception of abdominal tumors. Radiation therapy is not generally used in treating these tumors except in emergency situations. NHL is primarily treated with chemotherapy. Emergent complications arise quite often in the treatment of NHL based on the tumor's location and size, and therefore must be anticipated, diagnosed, and treated rapidly.

Debulking surgery has demonstrated no benefit to effective chemotherapy (Patte, 1997). Most abdominal lymphomas are the B-cell immunophenotype, and presentation often mimics an acute abdomen. Bowel obstruction or intussusception can also occur. In these cases, gross total excision of the primary is warranted, followed by adjuvant chemotherapy (Patte,1997).

Radiation therapy is not generally a part of NHL protocols. It is used in the urgent treatment of superior vena cava obstruction and for central nervous system (CNS) involvement causing nerve palsies. Prophylactic radiation has generally been shown to have no advantage in active CNS or limited-stage disease and is not used in multiagent chemotherapy regimens (Cairo and Perkins, 2000).

Chemotherapy regimens are based on the immunophenotype of the lymphoma (B- versus T-cell). In general, T-cell lymphomas receive longer and less intense treatments, and B-cell lymphomas are treated for shorter periods but with higher doses of alkylating agents and antimetabolites. NHLs are sensitive to a variety of chemotherapeutic agents, probably due to the aggressive nature of the disease with its rapid doubling time and high growth fractions.

Lymphoblastic lymphomas are most often treated on protocols similar to leukemia protocols. Treatment involves three phases, induction, consolidation, and maintenance, and generally lasts 2–3 years. Patients are usually not divided into risk groups because most patients have advanced disease. Multiple chemotherapeutic agents are used throughout the treatment course (see Table 2.7).

Small noncleaved cell lymphomas are B-cell lymphomas and have much shorter treatments. Treatment consists of two to six cycles of intense chemotherapy with no maintenance therapy. Large B-cell lymphomas are generally treated as per the small noncleaved cell lymphomas protocols as well. (See Table 2.7.)

Anaplastic large-cell lymphomas have been treated by a variety of approaches. Some of the best results have been from the German BFM group, who have used B-cell lymphoma protocols without local radiation therapy. (See Table 2.7.)

CNS prophylaxis is a necessary part of NHL treatment for most patients. Patients who have completely resected abdominal primaries, or stage I disease that is not in close proximity to the CNS, normally do not require CNS prophylaxis. Generally, all others are treated with varying degrees of CNS prophylaxis that consists of intrathecal methotrexate and/or intrathecal cytarabine (Magrath, 2002).

Autologous stem cell transplant is often used for only partial response to therapy in B-cell lymphomas. Allogeneic transplant is indicated for T-cell relapses after response to salvage therapies has been determined. In anaplastic large-cell lymphoma, relapse therapy using retinoic acid and interferon has been used with some effect at maintaining long remissions (Magrath, 2002).

Treatment and tumor complications can occur emergently and must be anticipated. Tumor lysis syndrome is seen frequently in NHL and specifically in Burkitt's and Burkitt's-like lymphoma because of their rapid doubling times. Other complications include respiratory distress, abdominal emergencies, superior vena cava syndrome, esophageal compression, cardiac tamponade, paraplegia, increased intracranial pressure, obstructive jaundice, pancreatitis, renal failure, and infection. The treatment of these complications is discussed further in other sections.

Table 2.7. Treatment summaries for non-Hodgkin's lymphoma (from Cairo and Perkins, 2000; reprinted with permission)

Stage and histology	Chemotherapy regimen	Cooperative group	Length of therapy	% Survival (3–5 years)
Stages I and II (St Jude) or Group A (FAB)	COPADA	SFOP	6 weeks	95
B large or SNCCL	COMP	CCG	6 months	85
Lymphoblastic	CHOP COMP BFM-NHL	BFM	8 weeks	90
Stages III and IV or Group B and C				
SNCCL	LMB-89 Orange NCI-89-C-41 Total-B BFM-NHL	SFOP CCG NCI POG BFM	6 months 8 months 6 months 4 months 4 months	80–90 70–80 70–80 60–70 60–80
Lymphoblastic	(AD)COMP LSA-L2 BFM-NHL	CCG CCG/POG BFM	18–24 months 18–24 months 18–24 months	70 70 90
Large Cell	COMP (D)	CCG	18–24 months	60–70
B cell	APO(+)	POG	18 months	60–70
	LMB-89	SFOP	4–6 months	90
	ORANGE	CCG	4–6 months	90
	BFM-NHL	BFM	4–6 months	70–80
	NCI-89-C-41	NCI	4–6 months	80–90
Anaplastic	CHOP/MACOOP-B BFM-NHL-B HM 89–91	ST JUDE'S BFM SFOP	6 months 6 months 6–8 months	75 80 60–70

2.2.8 Prognosis

The event-free survival for all stages of NHL ranges widely. The overall survival following the treatment of Burkitt's, Burkitt's-like, and large B-cell lymphoma, including advanced stage disease, is 90% (Magrath, 2002). For lymphoblastic lymphoma and anaplastic large cell lymphoma, the overall survival is 80–90%. Children treated for T-cell acute lymphoblastic leukemia as per the BFM Rez protocol have displayed an event-free survival of 92% (Magrath, 2002).

2.2.9 Follow-up

Follow-up for children treated for NHL needs to consider surveillance for disease recurrence and late effects of treatment. Most relapses of Burkitt's lymphoma occur with 12 months. If children with lymphoblastic lymphoma has not relapsed 30 months from the start of treatment, they have a very high probability of cure (Magrath, 2002).

Surveillance scans of the primary tumor can be done using CT or ultrasound, depending on the tumor's location. These should be carried out every 3 months for the first year off treatment and then with decreasing frequency over several years. Gallium or PET scans are very helpful in the surveillance for NHL recurrence and can be done on a similar sched-

ule to primary tumor imaging. CBCs are necessary, especially in lymphoblastic lymphomas, to look for recurrence of bone marrow disease, which is characterized by blasts in the peripheral smear.

Late effects of chemotherapy for NHL include a variety of potential problems because so many different chemotherapeutic agents are used. Cardiotoxicity from anthracycline therapy is a potential; follow-up echocardiograms should be routinely done at least every 2–4 years in the absence of problems. Appropriate attention needs to be paid to growth and development; for unknown reasons a significant group of children treated for NHL go on to become obese. Children who have been treated with significant amounts of intrathecal chemotherapy may be at more risk for learning problems. Neuropsychological testing may be appropriate so that specific help can be given to these children. Secondary malignancies are always a concern following treatment with VP16 and alkylating agents, so surveillance is paramount. Skeletal sequelae are a potential following the use of high-dose steroids. Osteoporosis is a concern, as is avascular necrosis; no specific follow-up is required for this, but awareness is crucial. Infertility and gonadal dysfunction may be a problem following treatment with alkylating agents.

2.2.10 Future Perspectives

Newer techniques such as microarray analysis might be useful in determining the exact rate of response to therapy. Examining gene expression patterns and proteomic analysis may help to determine therapy response rate so that the appropriate intensity of therapy can be given for each histological subtype of lymphoma. Targeting viral proteins in Burkitt's lymphoma is one area of research; it is hoped that a modified Myc gene may be able to induce tumor lysis of these cells. There are thoughts also that the antisense could cause cell death in DNA sequences involving the (8;14) translocation if targeted appropriately.

2.3 Ewing's Sarcoma Family of Tumors

Ewing's sarcoma family of tumors (ESFT) comprises a group of neoplasms that can arise in bone and soft tissue and that share similar histologic and molecular features. These tumors include Ewing's sarcoma, extraosseous Ewing's sarcoma, peripheral primitive neuroectodermal tumor (PPNET), and Askin tumor (a chest wall tumor). Ewing's sarcoma is the more undifferentiated form of the tumor, whereas PPNET is more differentiated. ESFTs are thought to derive from neural crest cells.

2.3.1 Epidemiology

ESFT is the second most frequently seen primary malignant bone tumor in childhood and represents 3 % of all pediatric malignancies (Venkateswaran et al., 2001). The incidence is approximately 2.8 per million annually in individuals less than 20 years of age. ESFT occurs most often in the second decade of life, with the highest age-specific rates occurring at 13 years of age (Gurney et al., 1995). ESFT is extremely rare in individuals over the age of 30 and in Chinese and black children. There is a slight male dominance in the incidence of this tumor.

2.3.2 Etiology

The cause for ESFT is not known. There does not appear to be strong associations with congenital syndromes or familial cancer syndromes.

2.3.3 Molecular Genetics

ESFTs are in the group of small blue round cell tumors. Molecular genetics is invaluable in helping to distinguish ESFT from other small blue round cell tumors. Fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RTPCR) are used to detect cytogenetic changes in the tumor for diagnostic purposes. Immunocytochemical staining also helps in this differentiation.

ESFTs display a characteristic t(11;22) (q24;q12) that fuses the EWS and the FLI1 gene; this genetic translocation is found in most tumors (Pinkerton et al. 1999). A second chromosomal translocation consists of a t(21;22)(q22;q12), which fuses the EWS and the ERG gene (Ginsberg et al., 2002). Less frequently observed changes involve trisomy 8 and 2 and deletions of chromosome 22, 16q, and 1p36 (Ginsberg et al., 2002). These aberrations are though to cause dysfunction in tumor suppressor genes, and their presence might be prognostic of poor outcome.

2.3.4 Symptoms and Clinical Signs

ESFT can occur in both long and flat bones. The incidence anatomically is split almost in half, with tumors arising in extremities (53%) and the central axis (47%).

In the central axis

- 45% occur in the pelvis
- 34% occur in the chest wall
- 12% in the spine
- 9% in the head and neck.

In the extremities:

- 52% of tumors are found in distal bones
- 48% in proximal bones

(Ginsberg et al., 2002)

Children typically present with symptoms caused by the primary tumor. Pain and swelling are often present. A palpable mass is frequently seen, and fractures are evident in 5% of cases (Jurgens et al., 1997). It is not uncommon for a child to present after a prolonged history of increasing pain or mass or after a traumatic injury that does not heal. Neurological impairments or weakness may accompany spinal lesions. Urinary and bowel incontinence may accompany large pelvic tumors.

Twenty percent of patients have metastatic disease at diagnosis (Ginsberg et al. 2002). Metastases usually follow a hematogenous route, spreading to lungs, bone, and bone marrow. Fever may indicate systemic or advanced disease. Infections, bleeding, and lethargy may reflect pancytopenia suggesting bone marrow involvement. Respiratory symptoms, such as cough, dyspnea, unequal breath sounds, and rales, may indicate large pulmonary metastases.

2.3.5 Diagnostics

A plain film of the affected area is usually the first diagnostic test ordered. On x-ray, ESFT will show up as a destructive lesion of the diaphysis of the bone that is poorly marginated. It may also have an onion peel characteristic, which is indicative of a periosteal reaction. CT or magnetic resonance imaging (MRI) of the primary should be performed to achieve better delineation of the soft tissue component of the tumor as well as examine its blood supply and tumor extension. Chest x-ray should be done to look for lung metastases; however, a CT of the chest is needed to look for smaller pulmonary nodules. Fig. 2.1 shows the CT of a patient with Askin tumor (chest wall mass). A bone scan is indicated to look for bony metastases. Fig. 2.2 shows a metastatic PNET on bone scan. Bilateral bone marrow aspirates and biopsies are necessary to rule out bone marrow disease.

A biopsy is indicated to determine definitive diagnosis. Tumor histology may be undifferentiated or differentiated showing Homer-Wright rosettes. The tumor specimen should be evaluated with routine staining and immunohistochemistry. Adrenergic, muscle, and lymphoid markers should be negative, and the tumor should stain positive for CD99 and vimentin (Ginsberg et al. 2002). Cytogenetic studies and RTPCR should be ordered to look for the characteristic t(11;22).

There are no definitive blood tumor markers for the ESFT; however, an elevated lactate dehydrogenase (LDH) may indicate a large tumor burden or rapid tumor growth. Elevated LDH has also been associated with a less favorable outcome. An elevated white blood cell count or ESR can also be seen at times with advanced disease.

2.3.6 Staging and Classification

There is not an elaborate staging system for the ESFT. The tumor is described in terms of the presence or absence of metastases.

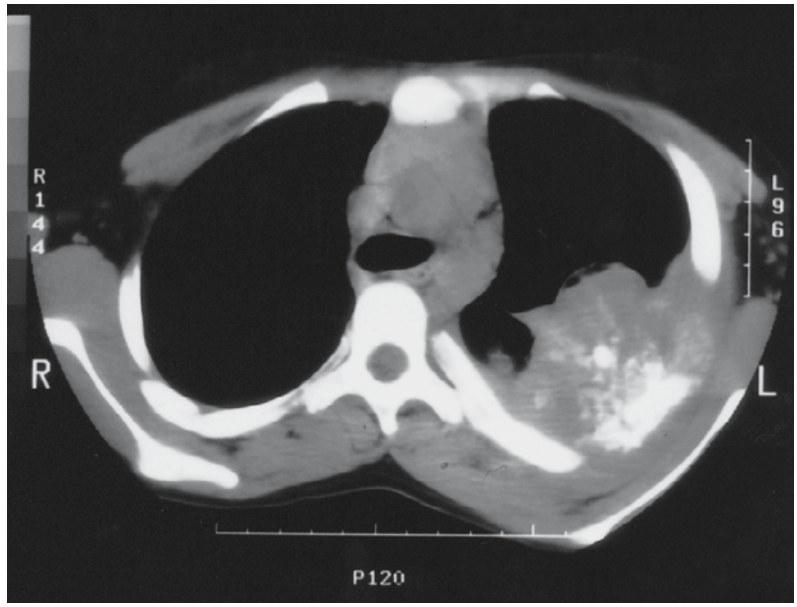


Figure 2.1
CT of a patient with Askin tumor (chest wall mass)

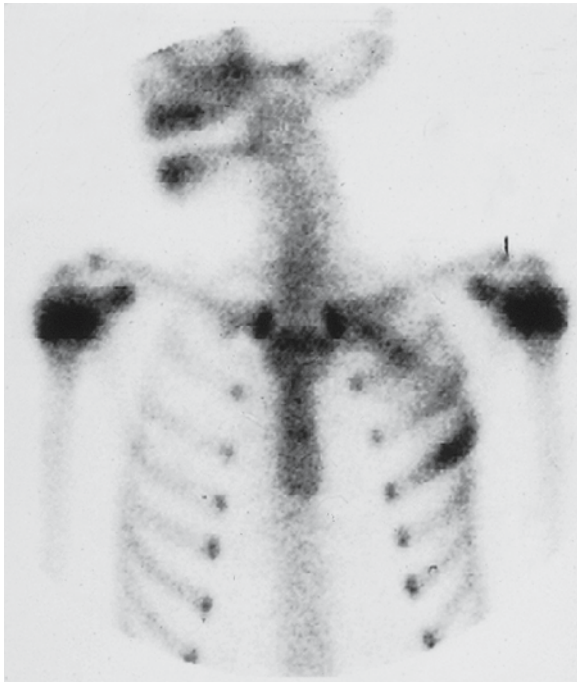


Figure 2.2
Metastatic PNET on bone scan

2.3.7 Treatment

The goals of treatment for the ESFT are threefold:

- Cure the disease
- Preserve useful function in affected area
- Minimize the long-term sequelae

Chemotherapy, radiation therapy, and surgery may all be used in treating this malignancy. Chemotherapy is delivered initially in order to shrink the tumor. Surgery or radiation therapy is then used to establish local control. This is then followed by a maintenance period of chemotherapy. Treatment for ESFT generally lasts up to a year.

Chemotherapy is initially used for cytoreduction in the treatment of the ESFT. After local control has been established, chemotherapy is given to treat micrometastatic disease that may have occurred at the time of surgery or local control. Common chemotherapeutic agents are vincristine, actinomycin, or doxorubicin and cyclophosphamide, alternating with VP16 and ifosfamide. Growth factors such as granulocyte colony-stimulating factor (GCSF) are often used following chemotherapy to hasten white blood cell recovery.

Surgery is the preferred method of establishing local control. It is used most often in local control for tumors of the extremities The entire bony or soft tissue lesion needs to be excised using initial imaging studies ensuring a disease-free margin of approximately 3 cm. Margins of 2 cm are generally acceptable if is near a joint articulation (Ginsberg et al., 2002). Gross or microscopic disease postoperatively is treated with radiation therapy.

Local control following the use of radiation therapy along with systemic chemotherapy delivers a cure rate of 75–90%. Radiation therapy is often the only option that is available for tumors of the central axis, in which radical surgery in not feasible. A total tumor dose of 55–60 Gy is delivered to the whole bony lesion with a 3 cm margin (a smaller margin is used if it avoids radiating an epiphysis); the original imaging studies are used to make this determination (Ginsberg et al., 2002).

Metastases are treated with surgery and/or radiation therapy, depending on the location of the tumors. In the lungs, both surgical resection and radiation therapy can be effectively used, depending on tumor location. Dose intensification regimens for metastatic disease using standard chemotherapy with VACIME (vincristine, adriamycin, cyclophosphamide, ifosfamide, mesna, etoposide) plus peripheral blood stem cell support and GCSF have been attempted with no real increase to disease-free survival (Hawkins et al., 2002). Future Children's Oncology Group (COG) protocols are currently considering the use of antiangiogenic therapies with vinblastine and Celebrex in conjunction with standard chemotherapy therapy for metastatic disease at diagnosis. Angiogenesis is a process by which tumors form new blood vessels; the purpose of antiangiogenic therapies is to target the factors that contribute to the development of new blood vessels, inhibiting or antagonizing them in order to arrest or prevent tumor growth.

2.3.8 Prognosis

Prognosis for the ESFT depends largely on the location of the tumor and the presence of metastases at diagnosis. Cutaneous, subcutaneous, distal bone, and rib tumors tend to have higher cure rates because of the feasibility of surgical resection. Tumors of the pelvis are often associated with poor response. Five-year disease-free survival rates range from 70–75% (Rodriguez-Galindo et al., 2002a). If metastases are present at diagnosis, the 2-year disease-free survival is less than 30% (Hawkins et al., 2002). Prognosis following relapse is poor, with long-term survival less than 25% (Rodriguez-Galindo et al., 2002a). Some children do better with late or local recurrence. Lung metastases tend to respond to treatment more than metastatic disease elsewhere in the body.

The tumor volume, LDH result, and the amount of tumor necrosis at the time of surgery are thought to be of prognostic significance; however, current treatment decisions are not usually based on these criteria. The subtype of fusion gene is also prognostic, with EWS-FLI1 favoring a better outcome than other genetic abnormalities. A retrospective study carried out by Jenkin and colleagues (2002) that looked to determine prognostic factors in localized Ewing's sarcoma and PNET of bone found that age less than or equal to 14, with the primary in a distal extremity or the skull, and tumor volume <200 ml were associated with a favorable prognosis. The amount of neural differentiation did not appear to have a prognostic significance.

2.3.9 Follow-up

Follow-up requires focus on both recurrent disease and late effects of treatment. Recurrent disease is at greatest risk in the first 5 years following treatment for ESFT. Protocols usually request imaging studies including CT or MRI of the primary, CT of the chest, and sometimes bone scan to be done every 3 months following therapy for the first year and then with decreasing frequency over the next several years.

Late effects of therapy must also be considered in the follow-up of these patients. Children are at risk of developing a secondary neoplasm such as a myeloid leukemia (related to the administration of alkylating agents) or a solid tumor in a previously irradiated site. The incidence of secondary malignancies in this group has been reported between 5% and 20% following a period of observation of 20 years (Jurgens et al., 1997). Cardiomyopathy or congestive heart failure

can occur following anthracycline therapy; therefore, cardiac function should be monitored with echocardiograms. Toxicities to the liver, kidney, nervous system, and endocrine system must be considered and any symptoms investigated accordingly.

2.3.10 Future Perspectives

Future therapies may involve targeting cytostatic agents or be immunologically targeted therapies. Monoclonal antibody therapies are also currently being researched. The French group is advocating that future studies be tailored to account for prognostic features such as histological response to chemotherapy (percent of tumor necrosis) and tumor volume (Oberlin et al., 2001). Topotecan plus cyclophosphamide shows promise in 35% of recurrent ESFTs and may continue to play a role in the future (Saylors et al., 1999).

2.4 Osteosarcoma

Osteosarcoma is a primary bone tumor that is thought to arise from mesenchymal bone-forming cells. It is characterized by the production of osteoid.

2.4.1 Epidemiology

Osteosarcoma is the third most common solid tumor of children and adolescents and the most frequently occurring primary bone tumor in this population (Wittig et al., 2002). The peak incidence of osteosarcoma is in the second decade of life, a period characterized by rapid bone growth. It occurs at an annual rate of approximately 3 per million children less than 15 years of age (Gurney et al., 1995). The incidence is slightly higher in African-Americans than whites and in males than females.

2.4.2 Etiology

The etiology of osteosarcoma is largely unknown. There appears to be an association between rapid bone growth and the development of osteosarcoma, as evidenced by its high incidence during the growth spurt in adolescence. There are several associations between osteosarcoma and other pathologies. It is known that osteosarcomas can be caused by ionizing radiation, and this is implicated in 3% of osteosarcomas (Link et al., 2002). It has also been found that osteosarcoma can arise in patients with hereditary multiple exostoses, Paget's disease, fibrous dysplasia, chronic osteomyelitis, multiple osteochondroma, and sites of bone infarcts. A genetic predisposition has been found between hereditary retinoblastoma (Rb) and osteosarcoma. The Rb gene is a tumor-suppressor gene and important in apoptosis. It has been estimated that between 8% and 90% of carriers of the Rb1 mutation will acquire a secondary malignancy, including osteosarcoma by the age of 30 (Link et al., 2002). The Rb1 mutation has also been implicated in the pathogenesis of sporadic osteosarcoma. Mutations of p53 have also been found in osteosarcoma, suggesting that inactivation of p53, which is a tumor-suppressor gene, plays a key role in the development of osteosarcoma. There is a higher incidence of osteosarcoma in Li-Fraumeni syndrome.

2.4.3 Molecular Genetics

The diagnosis of osteosarcoma is primarily based on tumor histology. Although there is not a specific cytogenetic or molecular maker for osteosarcoma, there is a great deal of research in the area of genetics that is focusing on better understanding of the disease and determining prognostic criteria.

It is well known that a relationship exists between osteosarcoma and the Rb1 gene mutation as well as p53 mutations. Loss of heterozygosity at the Rb gene occurs in 70% of sporadic osteosarcomas, and loss of heterozygosity at the Rb locus is thought to be a poor prognostic factor (Ragland et al., 2002). Many other genetic abnormalities continue to be examined to determine their role in the disease. C-Myc is expressed more often in those with osteosarcoma who develop metastatic disease. HER2/neu (human epidermal growth factor receptor 2) is expressed in approximately 40% of patients who develop early pulmonary metastases. Important discoveries are starting to be made in identifying the significance of these abnormalities.

2.4.4 Signs and Symptoms

Osteosarcoma commonly affects the metaphyseal growth plates of long bones. Although osteosarcoma can occur in any bone, the anatomic sites most commonly affected are the distal femur, the proximal tibia, and the proximal humerus. Osteosarcoma metastasizes most frequently to the lung, followed by bone. Gross metastatic disease is present at diagnosis in less than 20% of cases (Kager et al., 2003).

Osteosarcoma typically presents with pain and/or soft tissue swelling in the affected area. The mass itself may be warm, and vascularity over the mass may be found. There is often decreased range of motion in the affected limb. The duration of symptoms prior to diagnosis may range up to 6 months. Respiratory symptoms at diagnosis would only be present in very advanced pulmonary disease and are rare. Systemic symptoms of disease, such as fever and night sweats, are uncommon. Lymphadenopathy in proximal lymph nodes is also very rare.

2.4.5 Diagnostics

The workup up of a patient who presents with pain and/or swelling should start with a thorough health history paying special attention to any pain and the duration of the symptoms. Diagnostic imaging, blood tests and tumor biopsy are all needed.

Plain films of the affected area may reveal a lytic lesion with indistinct margins or ossification in soft tissue with a sunburst pattern that is characteristic of osteosarcoma (see Fig. 2.3). Reactive new bone formation can also be seen frequently under the periosteum forming a "Codman's angle" or "Codman's triangle" (Ragland et al., 2002). An MRI of the affected area would further examine the tumor boundaries, the soft tissue component, and the relationship to joints, blood vessels, and neurovascular bundle. A chest x-ray determines the presence of pulmonary metastases, but CT is more sensitive for smaller pulmonary nodules. A bone scan should also be performed to pick up areas of skeletal metastases. Bony metastases occur in 10% of patients with osteosarcoma at diagnosis (Link et al., 2002).

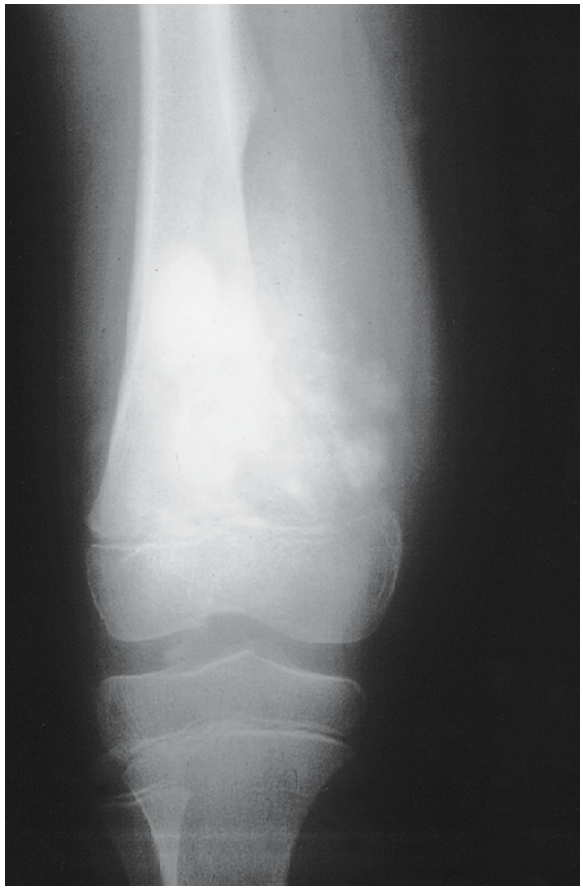


Figure 2.3
Plain film of patient with osteosarcoma

There are no specific blood tumor markers for osteosarcoma. Elevations of LDH are seen in up to 30% of patients at diagnosis (Link et al., 2002). However, LDH is an acute phase reactant and is not tumor-specific. Elevations of alkaline phosphatase are present in over half of patients, but again do not correlate reliably with disease. Abnormalities cannot necessarily be distinguished between bone and liver etiologies, but experience has shown that they may have a poor prognostic significance.

Table 2.8. Enneking system for staging osteosarcomas

Grade 1	Low-grade osteosarcoma
Grade 2	High-grade osteosarcoma
Grade 3	Osteosarcoma with distant metastases
A	Intracompartmental
B	Extracompartmental

A biopsy is necessary for obtaining definitive diagnosis. Open biopsy is preferred so that contamination of skin and surrounding structures is minimized. Histologically, osteosarcoma is characterized by the presence of spindle cells and the production of tumor osteoid (Jurgens et al., 1997).

2.4.6 Staging and Classification

There are varied histological patterns of osteosarcoma with osteoblastic being the most common, with an incidence of 78%, followed, in descending order of frequency, by chondroblastic, fibroblastic, malignant fibrous histiocytoma-like, giant cell-rich, telangiectatic, low-grade intraosseous, small cell, and juxtacortical (Pinkerton et al., 1999).

Staging in osteosarcoma is generally quite straightforward and considers intra- and extracompartmental factors (whether tumor extends through cortex to bone), as well tumor grade and presence of metastases. Table 2.8 shows the Enneking staging system for osteosarcoma. The tumors are divided into low and high-grade variants depending on the number of mitoses, anaplasia, cellularity, and pleomorphism. Stage IIB is the most common presentation of conventional osteosarcoma.

2.4.7 Treatment

Treatment of osteosarcoma consists of surgical resection of the primary and neo-adjuvant chemotherapy. Historically treatment for osteosarcoma consisted only of amputation of the primary. The outcome was poor with long-term survival at 10% (Ferrari et al., 2003). Currently, with use of adjuvant and neoadjuvant chemotherapy, survival has increased dramatically. Chemotherapy agents that are sensitive to osteosarcoma are doxorubicin, cisplatin, and high-dose methotrexate. Agents such as cyclophosphamide, ifosfamide, and VP16 have also shown to be useful. Typically, chemotherapy is given for 2–3 months prior to local surgical control. Dose intensification regimens have become possible with the use of GCSF post-myelosuppressive chemotherapy cycles.

Local control consists of three options:

1. Amputation: Amputation is usually reserved for tumors that cannot be removed with adequate surgical margins. It is also frequently used in large tumors that do not respond well to chemotherapy and to tumors that have produced skip lesions.
2. Limb salvage: Limb salvage procedures can be done for 90–95% of tumors today (Wittig et al., 2002). They are appropriate when the tumors can be removed effectively with negative margins, meaning that the tumor is removed with a rim of healthy tissue around the tumor. In order to reconstruct the limb and/or joint, an endoprosthesis, allograft, arthrodesis, intercalary allograft, or metallic prosthesis can be used.
3. Rotationplasty: Rotationplasty is another procedure that is used when there is a large tumor around the knee joint. The leg is amputated at the distal femur, and the ankle joint is preserved, rotated 180 degrees, and reattached. This produces an artificial knee joint from which the prosthesis can be effectively secured for a greater range of motion (see chapter 21).

Metastatic disease at diagnosis predicts a poor outcome. Treatment aims should be the same: neoadjuvant chemotherapy and surgical resection of disease. Radiation therapy has been used but is not terribly useful. Bone marrow transplant does not currently have a role in osteosarcoma.

Relapse still occurs in 30–40% of patients despite aggressive chemotherapy and surgical resection in nonmetastatic osteosarcoma of the extremities. The post-relapse survival in this group is poor. The majority of relapses occur in the lung. Accepted strategies for treatment include surgical resection, even when this requires multiple thoracotomies. In a

retrospective analysis by Ferrari et al.. (2003), they found that systemic chemotherapy using ifosfamide showed some utility in relapsed osteosarcoma; however, it had little use in pulmonary metastases except in a subset of patients with three or more pulmonary nodules. They also found that relapsed patients with one or two pulmonary nodules did better (5-year event-free survival 24%) than those who had bony metastases or more than two pulmonary nodules. Bony metastases have a poor outcome, but every attempt should be made for complete surgical resection.

2.4.8 Prognosis

The overall survival of patients with nonmetastatic disease at diagnosis, with the tumor located in an extremity, is 60–70%, whereas the survival of patients with metastases at diagnosis remains poor, at 15–20% (Bacci et al. 2002a,b). Prognosis of osteosarcoma depends largely on the extent of disease at diagnosis. Parosteal and intraosseous well-differentiated osteosarcomas tend to have a favorable prognosis. There appears to be no relationship between histological subtypes and overall survival. However, telangiectatic osteosarcomas (which produce lytic lesions) have a poor prognosis (Link et al., 2002). The site of the tumor plays a role in prognosis, with axial tumors faring worse than skeletal, most likely related to the difficulty in surgical resection of axial tumors. The tumor size also has a prognostic significance, with tumors less than 5 cm having better outcomes. Prognosis in children under 10 years old at diagnosis tends to be poorer. Elevations of LDH may have adverse prognosis. Loss of heterozygosity at the Rb gene may indicate that the tumors are more likely to metastasize. HER 2/erbB-2 over expression may be associated with inferior outcome. The response to preoperative chemotherapy is prognostic in that those tumors with greater than 98% necrosis or less than 2% viable tumor at the time of local control have a better outcome. The multidrug-resistance phenotype encodes p-glycoprotein, which if overexpressed may indicate an unfavorable outcome because p-glycoprotein has a propensity to actively pump chemotherapy from tumor cells (Link et al., 2002).

2.4.9 Follow-up

Patients need to be followed for both recurrent and metastatic disease as well as for late effects of the treatment itself. Imaging scans of the primary and the chest are done normally every 3 months for the first year and then at increasing intervals for at least the next several years before finally being done annually.

Late effects of chemotherapy include cardiomyopathies related to anthracycline use and hearing impairments related to cisplatin chemotherapy. Neurological, hormonal, and psychological late effects should also be considered when assessing patients. Infertility and secondary malignancies may result from the use of high-dose alkylating agents.

2.4.10 Future Perspectives

New chemotherapeutic agents have not shown to be effective in phase I and II trials. Dose intensification regimens with current chemotherapeutic agents using cardioprotective agents are being reviewed. There is interest in immunomodulation vaccine therapy and antiangiogenic agents. Antiangiogenic agents are used to target and impede the tumor's ability to form new blood vessels, thereby inhibiting tumor growth. Liposomal muramyl tripeptide-phosphatidylethanolamine (MTPPE) was trialed by the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) and showed some promise when used with conventional chemotherapy. There are current plans for a Phase II trial using inhaled GMCSF to stimulate macrophage activity for lung metastases. There are also research studies in progress attempting to use monoclonal antibodies to target HER2 receptors (Link et al., 2002). Administration of a bone-seeking radioisotope, samarium, is being tested with autologous stem cell transplant for metastatic bony disease.

2.5 Liver Tumors

Approximately two-thirds of all liver tumors are malignant. The most commonly occurring malignant liver tumor is hepatoblastoma followed by hepatocellular carcinoma.

2.5.1 Epidemiology

Malignant liver tumors occur at an annual incidence of approximately 1.5 cases per million children under the age of 15, and they comprise 1.1% of all childhood cancers (Tomlinson and Finegold, 2002). Hepatoblastoma (HB) is the most common malignant liver tumor affecting children and represents two-thirds of all liver tumors in this population. In infancy, the incidence is 11.2 per million, and this steadily decreases throughout childhood. Ninety percent of HBs occur during the first 5 years of life, 68% present within the first 2 years, and 4% are present at birth (Stocker, 2001). The mean age of diagnosis was found to be 19 months in a POG trial. There is a male predominance ranging from 1.4:1–2.0:1, (Tomlinson and Finegold, 2002), and Caucasians are affected up to five times more often than African-Americans. There is an increased incidence of HB in the Far East.

Hepatocellular carcinoma (HCC) accounts for 23% of all childhood liver tumors. It accounts for less than 0.5% of all pediatric malignancies, with an annual incidence of 0.5–1 case per million children (Czauderna et al., 2002). There is a higher male predominance affected by this tumor, and it most often occurs after the age of 10.

2.5.2 Etiology

Some researchers have suggested in recent years that prematurity is linked to HB development. The cause of this is unknown. In Japan's registry for pediatric malignancy the risk for HB is inversely correlated with birth weight (Tomlinson and Finegold, 2002). There is an association with HB and certain conditions such as Beckwith-Wiedemann syndrome (BWS), familial adenomatous polyposis (FAP), Li-Fraumeni syndrome, trisomy 18, and glycogen storage disease.

Hepatitis B infection has been shown to be pathogenic in HCC. HCC also develops in the presence of cirrhosis and underlying liver disease. There is some suggestion that parenteral nutrition in infancy is associated with HCC in childhood. Maternal exposure to oral contraceptive pills, fetal alcohol syndrome, and gestational exposures to gonadotropins are environmental factors implicated as possibly leading to HCC. The following genetic syndromes that are associated with a higher incidence of HCC include glycogen storage disease, hereditary tyrosinemia, Alagille syndrome, other familial cholestatic syndromes, neurofibromatosis, and ataxia-telangiectasia (Tomlinson and Finegold, 2002).

2.5.3 Molecular Genetics

Several chromosomal abnormalities occur in HB, but very few have been linked to HCC.

In HB the most common chromosomal abnormalities involve trisomy 2 and 20, and a translocation between (1;4)(q12;q34), all of which are of unknown significance (Stocker, 2002). Loss of heterozygosity at 11p15, which is a known tumor suppressor gene, has also been shown in HB and BWS. In a German study, 48% of HBs had a mutation at the B-catenin gene; the significance of this requires further exploration (Tomlinson and Finegold, 2002).

Mutations in the tumor suppressor gene (p53) have been reported in HCC and are associated with a shorter survival (Tomlinson and Finegold, 2002).

2.5.4 Symptoms and Clinical Signs

The presentations of HB and HCC are often quite similar to those of other abdominal tumors. Symptoms depend on the size of the tumor and can arise from the mass effect of space-occupying lesions.

Children most often present with an asymptomatic abdominal mass. On physical examination, a firm, irregular mass may be palpated in the right upper quadrant of the abdomen with extension across the midline or down to the pelvis. Pain, weight loss, anorexia, nausea, and vomiting may occur in advanced disease. Jaundice is quite uncommon, occurring only 5% of the time (Stocker, 2001). Infants can

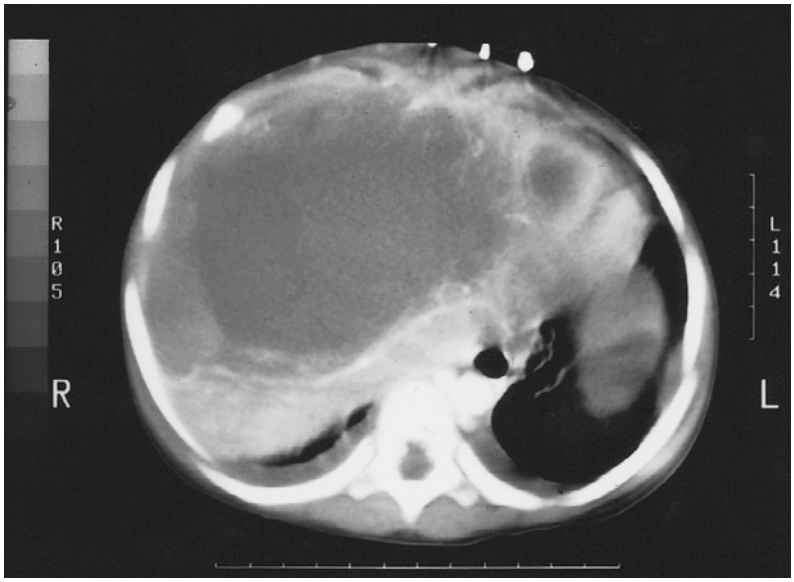


Figure 2.4
CT scan of patient with hepatoblastoma

present with failure to thrive. Severe osteopenia is often seen at diagnosis and is usually picked up incidentally on imaging; however, pathologic fractures occur infrequently. An acute abdomen is present in the case of tumor rupture. Seventy percent of children are anemic at diagnosis, and 35% have thrombocytosis (Stocker, 2001). Precocious puberty may be apparent in children whose tumors secrete beta human chorionic gonadotropin (BHCG). Hypertension can rarely occur in this population due to abnormal rennin secretion. Clinical signs of BWS should be considered, including macroglossia and hemihypertrophy, because of the increased incidence of HB in children with BWS. Patients at risk for developing HB including those with BWS or FAP, are often placed on a surveillance schedule to look for disease.

Metastases tend to spread to lung, bone, and brain.

2.5.5 Diagnostics

The diagnosis of either HB or HCC depends on imaging, blood, physical exam, and ultimately biopsy to determine tumor histology.

x-ray of the abdomen is often one of the first diagnostic tests ordered. A right upper quadrant mass is seen, and sometimes calcification is present. An ultrasound is useful in identifying a mass with increased echogenicity, which is suggestive of malignancy; Doppler will give information about the tumors vascularity. CT or MRI is needed to assess the extent of disease and the presence of local lymph nodes. Fig. 2.4 shows Hb as picked up on CT scan. Tumors often show patchy disease on post-contrast CT, and 50% of tumors show speckled or amorphous calcifications (Tomlinson and Finegold, 2002). CT of the chest is necessary to rule out lung metastases. Bone scan is sometimes ordered to rule out bony metastases, as is MRI of the brain to rule out intracranial spread; however, these are not standard practice.

A biopsy is necessary for definitive diagnosis, and tumor resection at diagnosis is preferred if surgically feasible. HB has two distinct classes based on histology. The first class shows epithelial histology with further variants that include a fetal pattern, a mixed embryonal and fetal pattern, macrotrabecular pattern, and undifferentiated small cell pattern. The second class involves mixed epithelial and mesenchymal histology. Further variants of the mixed histology include variants with teratoid features and those containing mesenchymal elements such as osteoid and cartilage (Stocker, 2001).

Table 2.9. Children's Oncology Group staging of hepatoblastoma (adapted from Tomlinson and Finegold, 2002)

Stage I (favorable histology)	Tumors are those that are completely resected and have a typical histology of a purely fetal histologic pattern with a low mitotic index (<2 per 10 high-power fields
Stage I (other histology)	Tumors that are completely resected with a histological picture other than purely fetal with low mitotic index
Stage II	Tumors are grossly resected with evidence of microscopic residual disease. Such tumors are rare, and patients with this stage have not fared differently from those with stage I tumors. Resected tumors with preoperative or intraoperative spill are classified as stage II
Stage III	(Unresectable) Tumors are those that are considered by the surgeon to be not resectable without undue risk to the patient. This includes partially resected tumors with measurable tumor left behind. Lymph node involvement is considered to constitute stage III disease and may require evaluation with a second laparotomy after the initial four courses of chemotherapy
Stage IV	Tumors that present with measurable metastatic disease to lungs or other organs

HCC has four main histologic types:

- Trabecular pattern is almost always seen in some part of HCC
- Compact and pseudoglandular variants
- Scirrhous is a rare type
- Fibrolamellar carcinoma is another rare variant of HCC that is not associated with cirrhosis; it shows an increased alfa-fetoprotein (AFP) and has a male predilection and a more favorable prognosis (Suriawinata and Thung, 2002)

A CBC should be ordered as well as liver and renal function blood tests. Liver enzymes and bilirubin may be elevated. Coagulation studies should be carried out before any surgical procedure to ensure that liver disease has not interfered with the coagulation pathway. BHCG is sometimes elevated in liver tumors and should be checked; elevations usually correlate with features of precocious puberty. AFP is a protein that is produced by the fetal liver and is elevated in the blood of infants during the first 6–9 months of life (Shafford and Pritchard, 1997). This protein is increased in 90% of HBs and 60% of HCCs (Pinkerton et al., 1999). In infants being worked up for a liver mass, it may be difficult to distinguish between normal AFP and malignant AFP. It is possible to fractionate the malignant and nonmalignant AFP by immunoelectropheresis; however, this lab service in not widely available. The AFP is an important tumor marker in liver tumors and is useful in evaluating response to treatment and recurrent disease. After complete tumor resection, the AFP should return to normal within 6 weeks.

2.5.6 Staging and Classification

Staging of liver tumors has been done by two different methods by two distinct groups. The North American Children's Oncology Group (COG) stages hepatoblastoma by the standard postsurgical tumor status (Table 2.9). The International Society of Pediatric Oncology (SIOP) uses a pretreatment classification schema called PRETEXT, which helps determine feasibility of tumor resection based on the number of liver segments involved using preoperative imaging scans (Tomlinson and Finegold, 2002).

HCC is staged much the same way as HB; however, it is graded differently based on histological differentiation. Stage I HCC resembles normal hepatocytes, stage II and III cells show moderate differentiation, and stage IV tumor cells are very poorly differentiated and often metastatic (Suriawinata and Thung, 2002).

2.5.7 Treatment

For both HB and HCC, surgical resection is crucial for cure and is the single most important factor predicting survival. Chemotherapy often plays a large role postoperatively and sometimes preoperatively if the tumor is unresectable at diagnosis. More recently, liver transplantation is playing a role in unresectable tumors. The use of radiation with these liver tumors is controversial.

Surgery resection is the most important part of curative therapy for children with HB. Forty to 60% of HB tumors are inoperable at diagnosis and 10 to 20% have pulmonary metastases (Stocker, 2001). Surgery is often not possible at diagnosis if both liver lobes are affected, if there is tumor in the porta hepatis, or if bulky lymphadenopathy exists. Presurgical chemotherapy for unresectable lesions renders them resectable 85% of the time (Stocker, 2001). Surgical resection may include a lobectomy or trisegmentectomy based on the extent of disease. Lymph nodes and the porta hepatis should be sampled during surgery; the celiac and paraaortic nodes need only be biopsied if suspicious for disease. In a COG study, surgery alone is the only treatment for stage I tumors with pure fetal histology, which are completely resected at diagnosis (Rowland et al., 2002). Biopsy of any suspicious pulmonary lesions should occur at diagnosis, and residual lesions should be surgically removed at the completion of therapy.

Chemotherapy agents that have shown utility in the treatment of HB include cisplatin, doxorubicin, ifosfamide, vincristine, and 5 fluorouracil. Irinotecan has showed some activity in phase II trials and recurrent disease. Sequential use of carboplatin, carboplatin-vincristine-5FU, and high-dose cisplatin-etoposide in a POG phase II study showed response in metastatic HB and in patients with unresectable disease at diagnosis, similar to other regimens but perhaps with less toxicity (Katzenstein et al., 2002a,b). Table 2.10 shows the most recent chemotherapy regimens for HB.

HCC has traditionally treated with the same chemotherapy agents used in the treatment of HB but with less success. The results of a Pediatric Oncology Group and Children's Cancer Group intergroup study

Table 2.10. Chemotherapy regimens for hepatoblastoma (adapted from Tomlinson and Finegold, 2002)

Study group	Schema	Overall survival (length of follow-up)	Number of patients	Reference
Children's Cancer Group	Cisplatin Doxorubicin day 1–4 Plan: 4 courses	67[a] (2 years)	26	Ortega et al. (1991)
Pediatric Oncology Group	Cisplatin course 1 and then cisplatin, vincristine, 5 FU courses 2–5	67%[a] (4 years)	60	Douglass et al. (1993)
International Society of Pediatric Oncology	Cisplatin 24-hour infusion and doxorubicin 48-hour infusion Plan: 4 courses-surgery-2 courses	75%[b] (5 years)	154	Pritchard et al. (2000)
German Society of Pediatric Oncology and Hematology	Ifosfamide Cisplatin Doxorubicin Plan: 2 or 4 courses-surgery-2 courses	75%[b] (median 64 months)	72	Von Schweinitz et al. (2000)

[a] Includes only patients with unresectable disease at presentation
[b] Includes patients with all stages at presentation
Refer to references to obtain full schema

using a prospective trial using a uniform treatment approach to HCC were published by Katzenstein and colleagues (2002). The treatment involved cisplatin, vincristine and fluorouracil (5-FU), or cisplatin and continuous infusion doxorubicin as determined by randomization. Neither regimen was effective in controlling residual or metastatic disease in children with HCC. For lack of better treatment, most often patients with HCC are usually treated using the same protocols that are used for HB with poor results. Surgery is vital in these patients, but unfortunately, only 10–20% of these tumors are resectable.

Radiation therapy is sometimes used if there is minimal or gross residual disease, but its utility is controversial and not widely accepted. There are high rates of side effects from tumor irradiation as well.

Liver transplantation is now done in the United States, and malignancies account for 2% of liver transplants in children. Transplant is often considered but not limited to instances where tumors are unresectable and show chemosensitivity. A recent study showed that children who had initially unresectable liver tumors and were treated initially with chemotherapy followed by hepatectomy and liver transplant had post-transplant survival rates at 5 years of 83% for HB and 68% for HCC (Tomlinson and Finegold, 2002).

2.5.8 Prognosis

The most important prognostic factor in HB is complete surgical resection. Pure fetal histology and low mitotic count impart an excellent outcome. Small-cell undifferentiated tumors are associated with poor prognosis independent of any other variable. The cure rate for a patient with HB and lung metastases is 70%.

The overall survival for children with HB is 65–70%. The overall survival rates for the various stages of disease are

Stage I: 100%
Stage II: 75–80%
Stage III: 65–68%
Stage IV: 0–27% (Stocker, 2001)

The survival rates for patients with HCC remain very poor. In all reported HCC series, the therapeutic response to chemotherapy is poor and overall survival is less than 30% (Czauderna et al. 2002).

2.5.9 Follow-up

Follow-up should be similar for both HB and HCC, and must consist of physical examination, abdominal ultrasound for tumor recurrence, and chest x-ray for evidence of pulmonary metastases. CT scan may be a more sensitive way to monitor for recurrence and metastases once off treatment, but this should be decided based on individual patient needs. Surveillance should be done every 3 months for at least the first 2 years and then with decreasing frequency. Monitoring of the AFP is essential and is often the first indication that the tumor has recurred.

Monitoring for late effects of the treatment is also necessary. Audiograms should be done periodically to look for hearing loss resulting from cisplatin therapy. Echocardiograms should be done following anthracycline therapy because the potential for cardiac sequelae from treatment exists. Infertility problems may be an issue once children are older. If the patient has undergone liver transplantation, secondary lymphoproliferative disorders may occur. Psychological, endocrine, and hormonal issues may need to be addressed as well.

2.5.10 Future Perspectives

Clearly there needs to be better treatment available for HCC. Studies have proven that HCC does not respond to chemotherapy as HB does. Novel agents need to be examined for their potential role in treating both these liver tumors.

Effort needs to be placed on developing standardized surveillance programs for those who carry a genetic predisposition to developing a liver tumor, as early intervention would hopefully improve outcomes for this group of patients.

2.6 Neuroblastoma

Neuroblastoma (NBL) is a tumor that arises from neural crest cells that make up the sympathetic or peripheral nervous system and can grow in the sympathetic ganglia, adrenal medulla, and other sites. NBL is an undifferentiated and highly malignant tumor, ganglioneuroblastoma is a more differentiated tumor, and ganglioneuroma is a fully differentiated tumor without malignant potential.

2.6.1 Epidemiology

NBL is the most common pediatric extracranial malignancy and the most frequently occurring cancer in infancy. Although it accounts for approximately 10% of all childhood malignancies, it accounts for 15% of all cancer deaths (Alexander, 2000). The incidence is about 9.7 cases per one million children (Gurney et al. 1995). It affects boys at a slightly higher rate than girls, 1.2:1.0, and is slightly more predominant in white children compared with black. The median age at diagnosis is 17.3 months (Brodeur and Maris, 2002).

2.6.2 Etiology

The cause of NBL is unknown. According to current evidence, environment does not appear to play a role. Correlation with intrauterine exposure to several agents such as alcohol, medications, and maternal use of hair-coloring products has been proposed, but none of these hypotheses have not been confirmed. Although most cases of NBL are sporadic, there seems to be a small group, approximately 1–2%, that are familial (Brodeur and Maris, 2002). NBL has been identified in other disorders of neural crest cells, such as neurofibromatosis, Hirschsprung's disease, Beckwith-Wiedemann syndrome (BWS), and DiGeorge syndrome.

2.6.3 Molecular Genetics

Neuroblastoma is a disease in which enormous advances have been made regarding the molecular and genetic aspects. More recently these results have been used to stratify children into low, intermediate and high-risk treatment protocols. Gene amplification, alterations in gene expression, and tumor suppressor gene inactivation are some of the major factors that influence risk determination.

N-Myc amplification occurs in approximately 25% of all NBLs (Matthay and Yamashiro, 2000). N-Myc is an oncogene found on chromosome 2 band q24, and its amplification is associated with aggressive and advanced disease. It is a powerful predictor of outcome regardless of stage and age. Loss of heterozygosity at chromosome 1p36 has also been shown to have an unfavorable outcome and is a very common chromosomal abnormality. 1p is thought to harbor a yet-to-be-identified tumor suppressor gene, and deletion of this may cause tumors to grow uncontrollably. There appears to be an association between a chromosome 1p deletion and N-Myc amplification (Matthay and Yamashiro, 2000). Chromosomal gains of 17q are also a frequent genetic event and often correlate with 1p deletions, therefore pointing to an unfavorable prognosis (Tomioka et al. 2003). Deletions on chromosome 11 and 14 have also been found in some tumors and again the thought is that they may encode tumor suppressor genes. Ploidy, the number of chromosomes pairs, is another important determination. Infants with NBL who have a DNA index (DI) of >1 (more than 46 chromosome pairs) respond well to standard chemotherapy. A DI equal to1 would predict a poorer response to standard therapy and often requires more aggressive treatment. Ploidy does not appear to be as significant in children older than 1 year (Brodeur, 2003). Neurotrophin receptor expression is widely correlated with genetic and biologic features. TrkA, TrkB, and TrkC are tyrosine kinases that code for receptors of the nerve growth factor (NGF) family. High TrkA often corresponds with a lack of N-Myc amplification, and therefore a favorable outcome. TrkB, however, is expressed in higher-stage tumors that show N-Myc amplification and have an unfavorable prognosis. The risk classification table takes into account both clinical features such as stage and age as well as biological risk factors to determine an appropriate treatment intensity protocol. See Table 2.11 for proposed NBL risk groups based on clinical and biologic tumor features for Children's Oncology Group protocols.

Table 2.11. Neuroblastoma risk groups based on clinical and biologic tumor features (Children's Oncology Group Protocols [ANBL0032)]; reprinted with permission)

INSS stage	Age	MYCN status	Shimada histology	DNA ploidy	Risk group
1	0–21	Any	Any	Any	Low
2A/2B	<365 d	Any	Any	Any	Low
	>365–21 y	Non-Amp	Any	–	Low
	>365–21 y	Amp	Fav	–	Low
	>365–21 y	Amp	Unfav	–	High-risk
3	<365 d	Any	Any	Any	Intermediate
	<365 d	Any	Any	Any	High-risk
	>365 d-21y	Fav	Fav	–	Intermediate
	>365 d-21y	Unfav	Unfav	–	High-risk
	>354 d-21y	Any	Any	–	High-risk
4	<365 d	Non-Amp	Any	Any	Intermediate
	<365 d	Amp	Any	Any	High-risk
	>365 d-21y	Any	Any	–	High-risk
4S	<365 d	Non-Amp	Fav	>1	Low
	<365 d	Non-Amp	Any	=1	Intermediate
	<365 d	Non-Amp	Unfav	Any	Intermediate
	<365 d	Amp	Any	Any	High-risk

2.6.4 Symptoms and Clinical Signs

Neuroblastoma can occur anywhere along the peripheral nervous system, so the presentations of the disease vary along with the location of the primary tumor or metastases. Neuroblastoma occurs in various anatomic sites as follows:

- 28.4% in the abdomen
- 32% in the adrenals
- 15% in the thorax
- 5.6% in the pelvis
- 2% in the neck
- 16.9% occur elsewhere

(Ninane and Pearson, 2002)

Infants tend to have more thoracic and cervical spinal tumors than older children. Most children do present before the age of 5 years. Rarely NBL can occur into adulthood.

NBL generally spreads via hematogenous and lymphatic routes and occasionally by regional lymph node invasion. Bone and bone marrow are common areas for metastases, as well as liver and skin in infants. Very rarely, spread to brain and lung occurs. Extensive involvement of the liver, skin, and/or bone marrow (<10%) in infants reflects stage 4S disease. This clinicopathological staging is reserved for infants who, along with favorable tumor biology, can be considered low risk even with advanced disease.

Clinical signs of NBL vary according to the tumor's location. Various presenting signs of neuroblastoma and the possible causes are listed in Table 2.12.

Skin lesions commonly referred to as "blueberry muffin" can occur in infants.

Paraneoplastic syndromes may sometimes be present at diagnosis. One such syndrome is opsomyoclonus. This involves random eye movements, myoclonic jerking movements, and cerebellar ataxia (Bataller et al., 2003). The phenomenon is though to arise because of the production of antineural antibodies that cross-react with neural cells in cerebellum or elsewhere in the brain (Brodeur and Maris, 2002). Children presenting with opsomyoclonus tend to do quite well from the tumor perspective; however, long-term neurological and developmental deficits can be a large problem. Intractable diarrhea can be a rare presentation caused by tumor secretion

Table 2.12. Various presentation signs of neuroblastoma and their possible causes

Clinical sign or symptom	Possible cause
Abdominal pain, abdominal distension, nausea, vomiting, constipation	Abdominal tumor
Anorexia, weight loss	Mass effect of midline tumors
Horner's syndrome (ipsilateral ptosis, miosis, and anhidrosis)	High thoracic and cervical tumors resulting in compromise of descending sympathetic tracks
Proptosis, periorbital ecchymosis	Periorbital tumor
Anemia, thrombocytopenia, frequent infections	Bone marrow involvement
Hypertension	Renal vascular compression
Limp or leg pain	Metastatic bone disease
Decreased motion in legs, muscle weakness, bowel or bladder disturbances	Spinal or paraspinal disease
Weakness or paraplegia	Compression of spinal cord caused by dumbbell tumors

of vasoactive intestinal polypeptide (VIP); this often has a favorable prognosis.

2.6.5 Diagnostics

Several screening tests are useful in diagnosing NBL. Blood and urine testing are done, in addition to tumor biopsy as part of the workup. Diagnostic imaging is used to evaluate the extent of tumor invasion and any tumor dissemination. The information obtained from imaging and biopsy results is used to determine risk stratification based on both clinical and biological factors.

Initially, imaging studies of the affected area may consist of plain films or ultrasound depending on the presenting symptoms. Fig. 2.5 shows a radiograph of a posterior mediastinal mass found in a patient with NBL. Following this, CT of the chest, abdomen, and pelvis should determine the extent of the disease and the presence of metastases. On imaging the tumors often show calcification. In the case of spinal tumors, an MRI should be ordered. Bone scan should determine the presence of skeletal metastases. Metaiodobenzylguanidine (MIBG) scan, using a dye that is taken up by catecholaminergic cells, is extremely useful in identifying NBL metastases but is not available at all centers.

Neuroblastoma tumors produce several substances that can be measured in the blood. Blood should be sent for LDH and ferritin. Neuron-specific enolase (NSE), GD2 (a cell membrane ganglioside), and chromogranin A are produced by NBL tumors, and although not routinely done at most centers, serum levels of these markers can be measured. Highly elevated ferritin levels may be associated with a worse prognosis. Similarly, elevations of LDH and chromogranin A are associated with unfavorable outcomes. GD2 can be found on the surface of NBL; gangliosides shed from the tumor might be important in accelerating tumor progression (Brodeur, 2003). NSE is a protein associated with neural cells; although nonspecific, overall survival is worse in patients with elevations of NSE and advanced disease (Matthay and Yamashiro, 2000). Other blood tests such as a CBC should also be done; any cytopenias that are present may be the result of bone marrow disease. Renal and liver function tests should also be evaluated to ensure normal functioning and to obtain baseline levels prior to chemotherapy.

Urinary catecholamine metabolites are elevated in NBL in 90–95% of patients (Brodeur and Maris, 2002). Urinary vanillylmandelic acid (VMA), formed from norepinephrine, and homovanillic acid (HVA), formed from dopamine, are considered elevated

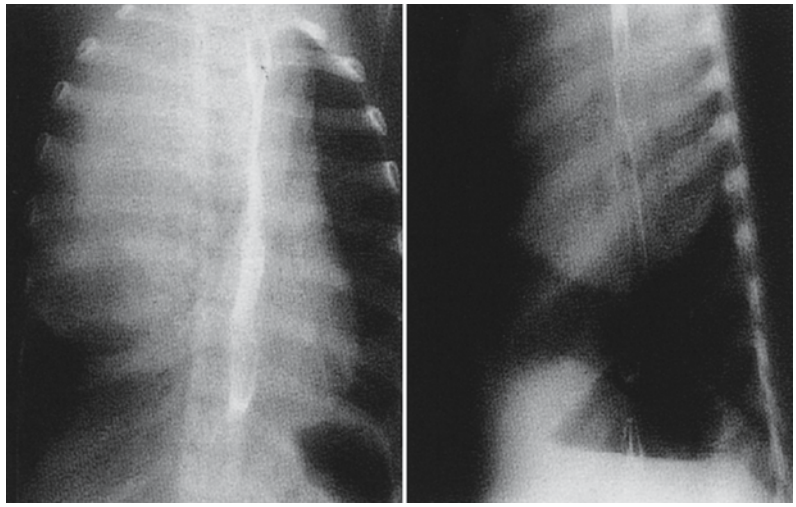


Figure 2.5
Radiograph of a posterior mediastinal mass found in a patient with neuroblastoma

when they are greater than three standard deviations above the upper limit of normal (Brodeur, 2002).

Tumor biopsy and/or tumor resection are done depending on the stage of the tumor. Tissue samples are sent for molecular and histopathological testing. Stage I and II tumors are usually resected at diagnosis, whereas Stage III and IV tumors are only biopsied. Chemoreductive therapy is given in order to facilitate easier removal of higher staged tumors. Bilateral bone marrow aspirates and biopsies are needed to determine the presence of bone marrow disease. It is generally accepted that if tumor is found in the bone marrow studies and the child has an elevated VMA/HVA, it is not necessary to biopsy the primary tumor. However, valuable information gained via biological markers would not be obtained for risk stratification, which may impact patient care.

Histology is an important determinant in risk stratification for these tumors. NBL is a small blue round cell tumor, and Homer-Wright pseudorosettes are often found in the tumor. It can be distinguished from other small blue round cell tumors because of its distinctive monoclonal antibody staining patterns. NBL stains positively for NSE, neurofilament proteins and synaptophysin. Shimada and colleagues (1984) originally developed a pathology staging system; some changes have been made to this earlier system in order to make it internationally useful. The histological determination takes into account the mitotic karyorrhectic index (MKI), patient age, the degree of differentiation, and whether the tumor is schwannian stroma poor. Table 2.13 indicates the pathology classification for NBL.

2.6.6 Staging and Classification

Several staging systems exist for NBL. The international NBL staging system (INSS) is based on post-surgical interventions for low-grade tumors according to location and respectability of the tumor; the Pediatric Oncology Group's staging is similar. The Children's Cancer Group's staging is based on tumor location on imaging. Table 2.14 outlines the various staging systems. Most centers, in North America at least, are using the INSS.

2.6.7 Treatment

Surgery, chemotherapy, radiation therapy and autologous stem cell transplant, and more recently immunotherapy and other biological therapies are all used in the treatment of NBL. Treatment intensity depends on risk stratification (Table 2.11). Essentially, the goals of treatment in those children with advanced disease are to

- Chemotherapy to decrease the size of both the primary tumor and metastases
- Surgical resection of the tumor

Table 2.13. Prognostic evaluation of neuroblastic tumors according to the International Neuroblastoma Pathology Classification/Shimada system (taken from Shimada et al., 1999 with permission; *MKI* mitosis-karyorrhexis index)

	International Neuroblastoma Pathology Classification	Original Shimada classification	Prognostic group
Neuroblastoma	(Schwannian stoma-poor)	Stroma-poor	
Favorable		Favorable	Favorable
<1.5 yr	Poorly differentiated or differentiating and low or intermediate MKI tumor		
1.5–5.0 yr	Differentiating and low MKI tumor		
Unfavorable		Unfavorable	Unfavorable
<1.5 yr	Undifferentiated tumor High MKI tumor		
1.5–5.0 yr	Undifferentiated or poorly differentiated tumor Intermediate or high MKI tumor		
5 yr	All tumors		
Ganglioneuroblastoma, intermixed	(Schwannian stroma-rich)	Stroma-rich intermixed (favorable)	Favorable
Ganglioneuroblastoma, nodular ganglioneuroma	(Composite Schwannian stroma-rich/stroma-dominate and stroma-poor)	Stroma-rich nodular (unfavorable)	Unfavorable
Maturing	(Schwannian stroma-dominant)	Well differentiated (favorable)	Favorable
Mature		Ganglioneuroma	

- Myeloablative chemotherapy followed by autologous stem cell transplantation (ASCT)
- Radiation therapy to areas of residual disease

Surgery is a vital aspect of care for children with NBL. For patients with low-risk disease, often stage I and II, surgical resection may be all that is required for treatment. For intermediate and high-risk disease, including stage III and IV tumors, surgery is done after several courses of chemotherapy have decreased the tumor size.

Chemotherapy is used primarily in tumors that are intermediate to high-risk; i.e., in metastatic disease and locally-spread disease. The most common drug combinations known to be effective are some combination of the following: cisplatin, doxorubicin, cyclophosphamide, carboplatin, ifosfamide, and epipodophyllotoxins (Alexander, 2000; Brodeur and Maris, 2002). In metastatic disease and poor-risk stage III disease, myeloablative therapy is used followed by single or double peripheral stem cell rescue. Melphalan is often an integral part of the ASCT conditioning regimen.

NBL is a radiosensitive tumor. In instances where the primary tumor cannot be fully resected, when there are local lymph nodes, and with microscopic residual disease, radiation therapy plays a vital role. Radiation is often also used for palliative pain control and for bony tumors or spinal cord compression that cause distressing symptoms. Accepted treatment doses of ionizing radiation range to 30 Gy, depending on the tumor size, and fractioned doses range between 150 and 400 cGy (Brodeur and Maris, 2002).

Following myeloablative therapy, maintenance therapy often includes treatment with retinoids. Retinoic acid is used to evoke cellular differentiation of NBL in the cases of minimal residual disease; most children receive 6 months of therapy (Matthay and Yamashiro, 2000). Currently, several groups including the North American study group, COG, are trialing targeted therapies using anti-GD2 antibody, Interleukin II (IL2), and granulocyte macrophage colony stimulating factor (GMCSF) after autologous stem cell transplant to target potential minimal residual disease.

Relapsed disease is very difficult to treat following high-risk disease treatment. Chemotherapy agents that have shown response include topotecan, cyclophosphamide, Taxol, and VP16 (Brodeur and Maris, 2002). Targeted therapy using MIBG radioisotope to deliver radiation therapy is being used at some centers and has shown some response to refractory disease.

2.6.8 Prognosis

The prognosis in NBL varies widely depending on the child's age and the tumor's stage, location, and biology.

- Survival rates are as high as 95% in patients with Stage I disease when the tumor has been completely excised (Alexander, 2000)
- Children with stage II disease who are older than 1 year have an 85% disease-free survival with surgery only
- Children older than 1 year of age with stage III disease treated with surgery and chemotherapy have a 50% disease-free survival; however, if radiation is added to treatment the survival may be increased to 70% (Alexander, 2000).
- High-risk patients with metastatic stage IV disease continue to do poorly and the long term survival rate is less than 15% (Brodeur and Maris, 2002)
- Infants, however, with stage IVS disease and good biological features have survival rates approaching 90%

2.6.9 Follow-up

Close observation for recurrent disease is imperative for these children. Most relapse occurs during the first 2 years following the completion of therapy. Diagnostic imaging of the primary using CT or ultrasound depending on location of the tumor is indicated. MIBG scanning is also useful for monitoring for recurrent disease in high-risk patients. Imaging and physical exam should be done every 3 months for the first few years after completing therapy and then with decreasing frequency over several years, or as clinically indicated. Urinary catecholamines should also be measured with the same frequency as radiological imaging. Blood tests such as LDH and ferritin can be monitored easily, and although nonspecific, can be used for screening along with imaging and physical exam. Those children who remain disease-free for 5 years following treatment of NBL are generally considered cured, although with increased intensity of therapy, late recurrences may be possible.

Follow-up must also consider treatment-related toxicity and late effects. Ototoxicity is usually significant following cisplatin therapy, and hearing aids are often necessary. Growth and development may be impacted, especially if radiation therapy has been delivered to the spinal area; this should be monitored carefully. Organ toxicity is a potential following chemotherapy and should be monitored through blood testing where possible. Echocardiograms should be done to screen for cardiomyopathies from anthracycline therapies. If radiation therapy was received, follow-up with a radiation oncologist is imperative. Second malignancies must be considered a risk for long-term survivors of metastatic disease due to the intensive multimodality therapy including radiation these children would have received. Not a lot of data are available on this cohort because they are such a small group.

Table 2.14. Staging systems for neuroblastoma (adapted from Matthay and Yamashiro (2000)

International Neuroblastoma Staging System	Children's Cancer Study Group System	Pediatric Oncology Group System
Stage 1 Localized tumor with complete gross excision and/or microscopic residual disease	**Stage I** Tumor confined to the organ or structure of origin	**Stage A** Complete gross resection of the primary tumor and/or microscopic residual disease
Ipsilateral lymph nodes negative for tumor (nodes attached to the primary tumor may be positive for tumor)		Intracavitary lymph nodes not ad hered to the primary tumor, which are histologically free of tumor (nodes adhered to the surface of the primary tumor may be positive for tumor)
Stage 2A Localized tumor with incomplete gross resection	**Stage II** Tumor extending in continuity beyond the organ or structure of origin but not crossing the midline	**Stage B** Grossly unresected primary tumor
Representative ipsilateral nonadherent lymph nodes negative for tumor microscopically	Possible regional lymph node involvement on the ipsilateral side	Nodes and nodules the same as in Stage A
Stage 2B Localized tumor and/or complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor		
Enlarged contralateral lymph nodes, which are negative for tumor microscopically		
Stage 3 Unresectable unilateral tumor infiltrating across the midline and/ or regional lymph node involvement	**Stage III** Tumor extending in continuity beyond the midline	**Stage C** Complete or incomplete resection of primary tumor
Alternately, localized unilateral tumor with contralateral regional lymph node involvement	Possible regional lymph node involvement bilaterally	Intracavitary nodes not adhered to primary tumor, which are positive for tumor histologically Liver as in Stage A
Stage 4 Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs (except as defined for stage 4S)	**Stage IV** Remote disease involving the skeleton, bone marrow, soft tissue, and distant lymph node groups (see stage IV-S) bone)	**Stage D** Dissemination of disease beyond intracavitary nodes (e.g., extracavi- tary nodes, liver, skin, bone marrow,
Stage 4S Localized primary tumor (as defined for stages 1, 2A, or 2B) with dissemina- tion limited to skin, liver, and/or bone marrow (<10% involvement)	**Stage IV-S** As defined in stage I or II, except for the presence of metastatic disease confined to the liver, skin, or marrow (<10% involvement) No bone metastases	**Stage DS** Infants <1 year with stage 1 or 2, except for the presence of remote disease confined to the liver, skin, or marrow (<10% involvement) No bone metastases

2.6.10 Future Perspectives

Researchers and clinicians hope to continuously improve risk stratification tools for children with NBL so that treatment intensity may correspond to disease characteristics as more discoveries are made. Gene expression profiling, targeting abnormal transduction pathways, and the use of biologic agents are all areas that are being researched to treat NBL, both in relapsed and primary disease. MIBG therapy is being used at few centers as treatment for refractory disease. Fenretidine, which is thought to induce apoptosis in tumors that may have been resistant to retinoic acid therapy, is being investigated in phase I trials (Brodeur and Maris, 2002). Topotecan has shown activity in relapsed patients and may have a role in first-line therapy. Anti-angiogenic agents, which are used to target and interfere with the tumor's ability to create its own blood supply, are also being researched for a potential role in this disease. Tyrosine kinase inhibitor therapy is being researched to target TRK A, B, and C expression. The intension of current research is to determine agents that are affective against NBL and incorporate these findings into conventional therapy.

2.7 Renal Tumors

The most frequently observed malignant tumor arising from the kidney is Wilms' tumor. Other less frequently occurring renal tumors include renal cell carcinoma, clear cell sarcoma of the kidney, and rhabdoid tumor of the kidney.

2.7.1 Epidemiology

Wilms' tumor is the second most commonly occurring extracranial malignancy in children. It represents about 6% of all childhood cancers (Blakely and Ritchey, 2001). Wilms' tumors can occur bilaterally or unilaterally; bilateral tumors occur either synchronously or at different times. The incidence of Wilms' tumor, or nephroblastoma, in children less than 15 years of age is approximately 7.6 per million. The male to female ratio is 0.92:1 for unilateral tumors and 0.6:1 for bilateral tumors (Grundy et al., 2000). The incidence is slightly higher in African-American children and lower in Asian children compared with Caucasians. Peak age of diagnosis is between 2 and 3 years.

Multiple other tumors arise from the kidney; they are extremely rare and include renal cell carcinoma (RCC), clear cell sarcoma of the kidney (CCSK), and rhabdoid tumor of the kidney (RTK). RCC is a tumor that is distinct from Wilms but also occurs in the kidney at an incidence of 0.1–0.3% of all malignancies, representing 1.8–6.3% of malignant kidney tumors (Indolfe et al.. 2003). CCSK, distinct from Wilms' tumor, was shown to have an incidence of 4% in a National Wilms' Tumor Study (NWTS) (Beckwith, 1998). RTK represents 2% of renal tumors registered with NWTS (Broecker, 2000).

2.7.2 Etiology

Wilms' tumors occur sporadically in 95% of these patients. There is, however, a familial form, comprising 1–2% of all Wilms' tumors, in which tumors tend to occur bilaterally and earlier, suggesting a germ line mutation and a loss of a tumor suppressor gene. The familial form is characterized by an autosomal dominant trait with variable penetrance (Grundy et al. 2002). The disease often occurs in the presence of genetic anomalies or as part of a familial predisposition syndrome. Syndromes often associated with Wilms' are the following:

- Beckwith Wiedemann (BWS) (an overgrowth syndrome)
- Denys-Drash (involving genitourinary abnormalities)
- WAGR (Wilms, aniridia, genitourinary anomalies and mental retardation) (Pritchard-Jones and Mitchell, 1997)

Wilms' tumor has also been described in Bloom syndrome, incontinentia pigmenti, Li-Fraumeni, and genetic instability syndromes, yet no definite link exists (Grundy et al., 2000).

2.7.3 Molecular Genetics

Several genes are described in the development of Wilms' tumor. The first Wilms' tumor suppressor gene, WT1, is located at chromosome (Ch') 11p13. It was cloned in 1990 and is found in patients with WAGR syndrome and involves the PAX 6 gene and WT1 allele (Grundy et al. 2002). Mutations of WT1 have been found also in some sporadic Wilms' cases. WT1 is important in normal kidney development. A second Wilms' tumor putative gene is identified at Ch'11p15, WT2. Children with BWS are predisposed to Wilms' tumor and have mutations at Ch'11p15, the WT2 gene (Neville and Ritchey, 2000). The familial form of the disease has a locus identified at Ch'17q labeled FWT1, and FWT2 is located on chromosome 19q. These genes all appear to have a role in tumor development. Chromosome arms 16q, 1p, 7p, and 17p, the location of p53, have also been associated with Wilms' tumor, but may be linked more to treatment outcome than to tumorigenesis (Grundy et al., 2002). There has been an association also noted between p53 mutations and anaplastic histology in 86% of cases, which may suggest that mutations underlie the anaplastic phenotype (Grundy et al., 2000).

RCC have characteristic translocations involving breakpoint at Xp11.2.

2.7.4 Symptoms and Clinical Signs

Parents are often the first to notice an abdominal mass or abdominal distension in their child. Children are usually asymptomatic. Pain, gross hematuria, fever, and hypertension occur in approximately 25% of children (Grundy et al., 2002). Hypertension is usually attributed to increases in rennin activity. Anemia, fever, and rapid abdominal distension can occur if there has been hemorrhage into the tumor, but this occurs rarely. Syndromes such as BWS and WAGR are linked to Wilms' tumor, so features associated with these syndromes should be noted (e.g., aniridia, GU anomalies, hemihypertrophy). Rarely, extrarenal Wilms' tumors arise; they present as a retroperitoneal mass usually adjacent to the kidney. Symptoms of thrombosis should also be considered and note made of any leg swelling and/or prominent veins over abdomen. Very rarely, a child may present with metastatic disease and may show signs of respiratory difficulty in the presence of advanced pulmonary metastases. Lung, liver, bone, and brain are the major locations of metastases.

2.7.5 Diagnostics

An abdominal ultrasound is usually the first investigation ordered, which will reveal a mass arising from within the kidney. Doppler ultrasound should also be used to assess patency of the renal vein and inferior vena cava, as thrombosis can occur. CT of the abdomen should be ordered to further assess the extent of the mass and assess for smaller lesions in the contralateral kidney. The liver should be thoroughly examined because it is a common site for metastases. A CT of the chest should be ordered to rule out pulmonary metastases. Fig. 2.6 is a chest x-ray demonstrating pulmonary metastases in Wilms' tumor. There is some debate as to whether chest x-ray is sufficient to look for metastases, as smaller nodules are often not picked up.

A CT or MRI of the brain should be done after a diagnosis of CSSK or RTK is made because metastases to the brain can occur. Bone scan and skeletal survey are also indicated in these tumors; bone scan does not always pick up lytic bone lesions, so skeletal survey is also indicated.

Biopsy versus tumor resection at diagnosis remains controversial. There are two major Wilms' tumor study groups: the North American National Wilms Tumor (NWTS) study group and the International Society of Pediatric Oncology (SIOP) in Europe. The NWTS recommends resecting the entire tumor and sampling local lymph nodes at diagnosis. SIOP however, discourages biopsies and recommends chemotherapy with vincristine and actinomycin to shrink the tumor to make surgical resection easier, followed by removal and staging. If pulmonary lesions are noted on CT scan, they should be biopsied at diagnosis prior to treatment.

Histologically, Wilms' tumor can be comprised of blastemal, epithelial, and stromal components, a tumor typically consists of all three components, but one component could predominate. If greater than

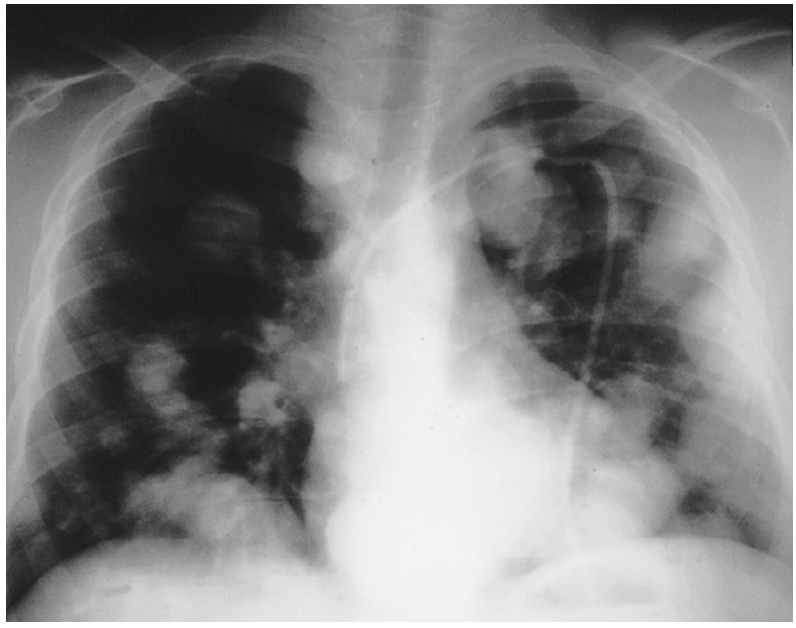


Figure 2.6
Chest x-ray demonstrating pulmonary metastases in Wilms' tumor

two-thirds of the tumor composition is of one component, the histological type is assigned to the tumor, as they can behave quite differently (Neville and Ritchey, 2000). Monophasic blastemal is a highly invasive type of Wilms' tumor. Cystic or partially differentiated cystic nephroma do extremely well and are often cured with surgery alone. Diffuse or focal anaplasia is associated with unfavorable histology and is seen is approximately 5% of tumors (Neville and Ritchey, 2000). Anaplasia is characterized by large nuclei that are three times the size of nuclei of other cells, hyperchromasia of enlarged cells, and the presence of polyploid mitotic features. Diffuse anaplasia is characterized by more than one area of anaplasia in tumor sample or in regional nodes or metastases (Neville and Ritchey, 2000). Nephrogenic rests are precursor lesions to Wilms' tumor and are comprised of abnormally persistent embryonal nephroblastic tissue with small clusters of blastemal, epithelial, or stromal cells. They are seen in kidneys of 35% of unilateral Wilms' tumors and nearly 100% of bilateral. The term nephroblastomatosis describe a clinical situation in which there are multiple nephrogenic rests. Although they are not malignant, it is important to know this information prior to treating tumors, especially with surgery, because if the contralateral kidney has these nephrogenic rests, a Wilms' tumor may develop in the future.

Histologically, RCC in children tends to have a papillary architecture (Broecker, 2000). CCSK have a distinct histological appearance, but several variant patterns such as epithelioid, myxoid, cystic, and spindling exist. Additionally, CCSK can show anaplastic features. This tumor is often misdiagnosed. RTK is thought to be neurogenic in origin. Cells have a prominent acidophilic cytoplasm, resembling rhabdomyoblasts. They are, however, negative for makers of skeletal muscle (Grundy et al., 2000).

There are no specific tumor markers for Wilms' tumor. For the workup of a patient; however, blood should be sent for CBC, liver function tests, renal function tests, and coagulation screen. It has been noted that acquired Von Willebrand's disease occurs in 8% of Wilms' tumor patients at diagnosis, and treatment with DDAVP may be necessary to correct coagulation prior to surgical intervention (Grundy et al., 2002).

Table 2.15. Staging system for renal tumors developed by the National Wilms' Tumor Study Group

Stage	Description
I	Tumor confined to the kidney and completely resected. No penetration of the renal capsule. No involvement of renal sinus vessels
II	Tumor extends beyond the kidney but is completely resected (negative margins and lymph nodes). At least one of the following has occurred: (i) penetration of the renal capsule (ii)invasion of the renal sinus vessels (iii) biopsy of tumor before removal (iv) spillage of tumor locally during removal
III	Postoperatively, gross or microscopic residual tumor remains, including inoperable tumor positive surgical margins tumor spillage involving peritoneal surfaces regional lymph node metastases, or transacted tumor thrombus
IV	Hematogenous metastases or lymph node metastases outside the abdomen (lung, liver, bone or brain)
V	Bilateral disease at diagnosis (with attempts made to stage each side at diagnosis)

2.7.6 Staging and Classification

The NWTS developed a staging system for Wilms' tumor. It is based on surgical resectability and the presence of bilateral and metastatic disease (see Table 2.15).

2.7.7 Treatment

The treatment for Wilms' tumors always involves surgery and chemotherapy and sometimes radiotherapy. As previously stated, controversy surrounds the treatment of Wilms' tumor. SIOP asserts that if preoperative chemotherapy is given, the tumor is easier to remove and fewer complications arise. Diagnosis is therefore made on clinical and diagnostic imaging only. The wrong diagnosis is made in 5% of cases (Grundy et al., 2002). The approach of the NWTS–V is outlined in Table 2.16. Tumors are completely resected at diagnosis, and nodes are sampled.

A transperitoneal surgical approach is recommended for surgical resection so that the contralateral kidney can be examined intraoperatively and local lymph nodes sampled. Spillage during surgical resection results in a six-fold increase in local abdominal recurrence; these patients are therefore upstaged (Grundy et al. 2002). If a tumor is inoperable at diagnosis due to size or thrombosis, after biopsy the tumor is treated as a Stage III with vincristine, actinomycin-D, and doxorubicin, then reevaluated at week 5 and resected as per the NWTS group. Bilateral tumors should be biopsied and staged separately. All efforts should be made to leave any healthy functioning kidney in place by performing a partial nephrectomy and wedge resection; however, this should not be attempted if clear margins are not possible. These patients end up having difficulties with renal dysfunction, and renal failure occurs in 15% of patients 15 years post-treatment, depending on remaining amount of functioning kidney and/or damage related to chemotherapy drugs and radiotherapy (Neville and Ritchey 2000).

Patients with RCC are treated primarily with surgery. There is no standard treatment for advanced stage disease. The tumors are not responsive to radiotherapy, and there is no current chemotherapy that is effective. MacArthur et al. (1994), however, did report complete response to interleukin-2 in one child with metastatic RCC.

2.7.8 Prognosis

The long-term survival is approaching 90% in patients with localized Wilms' tumors and 70% in patients with metastatic disease (Pritchard-Jones, 2002). The results of the NWTS-IV as described by Neville and Ritchey (2000) show 4-year overall survival to be

Table 2.16. Protocol for National Wilms' Tumor Study-V (adapted from Neville and Ritchey, 2000)

Stage of disease	Surgery	Radiotherapy[a]	Chemotherapy
Stage I and II, favorable histology (no anaplasia) Stage I with focal or diffuse anaplasia	Nephrectomy	None	vincristine (18 weeks) Pulse intensive dactinomycin,
Stage III and IV, favorable histology Stage II-IV, focal anaplasia	Nephrectomy	Yes	Pulse intensive dactinomycin, vincristine, doxorubicin (24 weeks)
Stage II-IV, diffuse anaplasia Stage I-IV, CCSK	Nephrectomy	Yes	Dactinomycin, vincristine, doxorubicin, cyclophosphamide, and etoposide (24 weeks)
Stage I-IV, RTK	Nephrectomy	Yes	Carboplatin, etoposide, and cyclophosphamide (24 weeks

[a] Radiotherapy doses are approximately 1,080 cGy for the abdomen and 1,200 cGy for the lung. Only patients with stage IV lung metastases receive whole lung radiotherapy

- 96 % in stage I with favorable histology
- 91 % for stage II with favorable histology
- 91 % for stage III with favorable histology
- 80 % for stage IV with favorable histology
- Stages II-IV with diffuse anaplasia was 82 %

RTK in the NWTS III series had an overall 4-year survival of 25 % and CCSK stages II-IV was 75 %. For patients with stage I RCC, the survival is 90 %; however, with stage IV disease the survival is about 0 % (Broecker, 2000).

2.7.9 Follow-up

Follow-up for Wilms' tumor involves regular physical exams and surveillance scanning, usually with at least abdominal ultrasound and chest x-ray. This is usually done every 3 months for the first 2 years, followed by every 6 months for 2 years and then with decreasing frequency or as clinically appropriate. Renal function does need to be monitored in the remaining kidney quite carefully, especially if bilateral disease existed and radiation therapy was received.

Late effects of radiation therapy and specific chemotherapeutic agents should be assessed. Patients who received anthracycline therapy should be monitored for cardiomyopathy or congestive heart failure; cardiac sequelae might be exacerbated in those patients who also received lung radiation. Patients who have been treated with VP16 need to be screened for second myeloid leukemias, and secondary malignancies are a risk in the radiation field. Ovarian failure is a possible late effect resulting from some of the chemotherapeutic agents.

2.7.10 Future Perspectives

The outcomes for children with Wilms' tumor are relatively favorable. Future efforts will focus on tailoring therapy by decreasing chemotherapy and radiation therapy when possible in order to minimize treatment-related toxicity, based on risk stratification. There is also interest in learning about predisposing factors to Wilms' tumor and whether the use of antiangiogenic agents will have a future role. Topotecan is being currently used in relapsed Wilms' tumors with some effect; it may have a continued role in the future.

New therapies distinct from the protocols for Wilms' tumor need to be developed for RCC and RTK.

2.8 Retinoblastoma

Retinoblastoma (Rb) arises from fetal retinoblasts that normally differentiate into post-mitotic retinal photoreceptor cells and neurons. The tumor tends to outgrow its blood supply, which results in necrosis and calcification.

2.8.1 Epidemiology

Rb is the most frequently diagnosed intraocular malignancy of childhood. It represents 3% of all pediatric malignancies, with an incidence of approximately 1 in 18,000 live births. Eighty percent of cases are diagnosed before the age of 3 or 4 years. Sixty percent of cases are nonheritable and unilateral. Forty percent of cases are heritable (bilateral or multifocal), of which 5% are familial and the rest are sporadic. Metastases can occur in up to 10–15% of patients (Rodriguez and Pappo, 2003).

2.8.2 Etiology

Rb can occur in one or both eyes. Bilateral Rb is generally picked up earlier than unilateral cases. There has been an association between Rb and congenital abnormalities in the 13q- syndrome (Yunis and Ramsay, 1978), and with other abnormalities including cardiovascular defects, cleft palate, infantile cortical hyperostosis, dentinogenesis imperfecta, familial cataracts, Bloch-Sulzberger syndrome, and mental retardation (Hurwitz et al., 2002). The incidence of Rb has been reported to be higher after in vitro fertilization procedures.

The heritable form of Rb is associated with errors in transcription, translocations, or deletions of genetic information on chromosome 13q14. Bilateral Rb can occur at different times, so conservative management should be used in young infants who present with disease in one eye only, as there is potential for tumors to develop in the second eye.

Knudson's two-hit theory of cancer can be used to explain the etiology of Rb. One abnormal chromosome is commonly inherited at conception from an unaffected parent, or rarely inherited from an affected parent, and the second hit occurs after conception. The second hit affects a somatic retinal cell. It can be a mutation in form of a deletion, chromosomal loss by nondysjunction, or somatic recombination (Knudson, 2001). The first hit can either be constitutional (heritable bilateral or multifocal) or somatic (nonheritable unilateral), but the second hit is always somatic. Errors in transcription occur more often in the paternal allele, suggesting that germ line mutations occur more often in spermatogenesis than oogenesis. Predisposition to Rb is imparted by germline mutation in 40% of cases (Hurwitz et al. 2002). It is transmitted as an autosomal dominant trait; penetrance may be as high as 90%, but it is not 100%. There is 50% chance that a child of an affected parent will inherit the disease. A patient's sibling's can present with the disease even if the parents appear to be unaffected, either because of a low penetrance allele or a germline mosaicism (Hurwitz et al. 2002). The heritable form of the disease, characterized by the errors in the Rb1 gene, predisposes children to a small risk for sporadic secondary malignancies and a much higher risk for radiation-induced secondary malignancies.

2.8.3 Molecular Genetics

Molecular analysis has become increasingly sensitive at picking up chromosomal aberrations, although testing is not routinely done at all centers. The Rb1 gene is located at chromosome 13q14. The Rb1 gene is a tumor suppressor gene and is important in apoptosis. It is a key regulator of the cell cycle and therefore governs the proliferation of tumor cells. In Rb, deregulation of cell proliferation occurs as a result of the inactivated or absent Rb1 protein, and constraint that is normally exerted over the cell cycle is lost (Rodriguez-Galindo and Pappo, 2003).

2.8.4 Signs and Symptoms

The most common signs of retinoblastoma are

- Leukocoria (cat's eye reflex) – caused by the tumor, which is white and occludes the normal red retina

- Strabismus – the tumor's placement over the macula causes loss of central vision and disruption of the fusional reflex, causing the affected eye to drift
- Glaucoma – increased intraocular pressure due to the tumor
- Decreased vision in one eye – caused by the tumor covering the macula or retinal detachment

Some other presenting signs include esotropia, painful eyes, and erythematous conjunctivae. Heterochromia (discoloration of the iris) warrants immediate enucleation because it is a sign of advanced disease. Seventeen percent of patients with Rb and 50% of children with advanced Rb requiring enucleation, present with rubeosis iridis, which is neovascularization of the surface of the iris (Hurwitz et al., 2002). Hyphema, blood in the anterior chamber of the eye, can occur secondary to rubeosis iridis, so its presence in the absence of trauma warrants an immediate ocular examination. Glaucoma and closed angle glaucoma are also presenting symptoms that usually indicated advanced disease. Endophytic tumors or diffuse infiltrating tumors may produce pseudohypopyon (cells in anterior chamber).

Metastatic spread of Rb occurs through several mechanisms. Tumor can spread posteriorly through the optic nerve to the brain and cerebrospinal fluid. The second method of extraocular spread occurs through lymphatic dissemination; this can occur anteriorly through the iris and ciliary body. Direct extension can occur through sclera into the orbit. Through the choroid, Rb can spread hematogenously to other sites in the body such as bone, bone marrow, lung, and brain.

2.8.5 Diagnostics

The diagnostic workup for Rb begins with a thorough history, paying particular attention to the duration of symptoms and changes in the eye's appearance. Special attention should be given to familial history and incidence of Rb.

Physical examination should assess visual acuity (cranial nerve II), tracking (cranial nerves III, IV, and VI), strabismus, esotropia, and leukocoria. Direct and indirect fundoscopic examination should be done under anesthesia. The pupils should be well dilated to allow for complete visualization of the fundus. CT of the brain and orbits is needed to detect distal spread of tumor and identify areas of calcification. MRI of the brain has been shown to be an excellent method of localizing intraocular extent of disease as well as visualizing tumor extension into the optic nerve and orbital area. A bone marrow aspirate is often done to detect metastatic disease if there is an apparent risk for hematogenous spread (i.e. choroidal involvement). A lumbar puncture may be done to determine if there is metastatic extension to the cerebrospinal fluid; this is especially necessary when there is optic nerve involvement. Ultrasound is a common test that is performed on eyes affected by Rb and shows the tumor in reference to anatomical structures (Servodidio et al., 1991). Fundoscopic pictures are also taken during the exam under anesthesia.

Retinoblastoma can present as trilateral disease. This is rare, with an incidence of 3%; 6–10% of those affected have a genetic predisposition to the disease. In addition to bilateral ocular tumors, a tumor is also seen on the pineal gland in trilateral retinoblastoma. It is typically associated with an extremely poor prognosis and usually occurs in children ages 4 and younger (Hurwitz et al., 2002). Trilateral disease can even be seen years after successfully treated ocular disease and is a major cause of mortality for these children in the first 5 years after diagnosis of bilateral Rb.

The diagnosis of Rb is made by ophthalmoscopic, radiologic, and ultrasonographic appearance of the tumor; pathological confirmation is unnecessary. Rb is a small blue round cell tumor consisting of densely packed cells. It is mitotically active, and when the eye is enucleated, there are Flexner-Winterstein rosettes, which are highly characteristic of Rb. See Fig. 2.7 for metastatic Rb in the bone marrow.

2.8.6 Staging and Classification

There are several common growth patterns of Rb tumors. With an endophytic pattern, tumor arises from retina and grows into the vitreal cavity. These tumors usually fill the cavity and float in the vitreous and are known as vitreal seeds. Exophytic tumors grow from

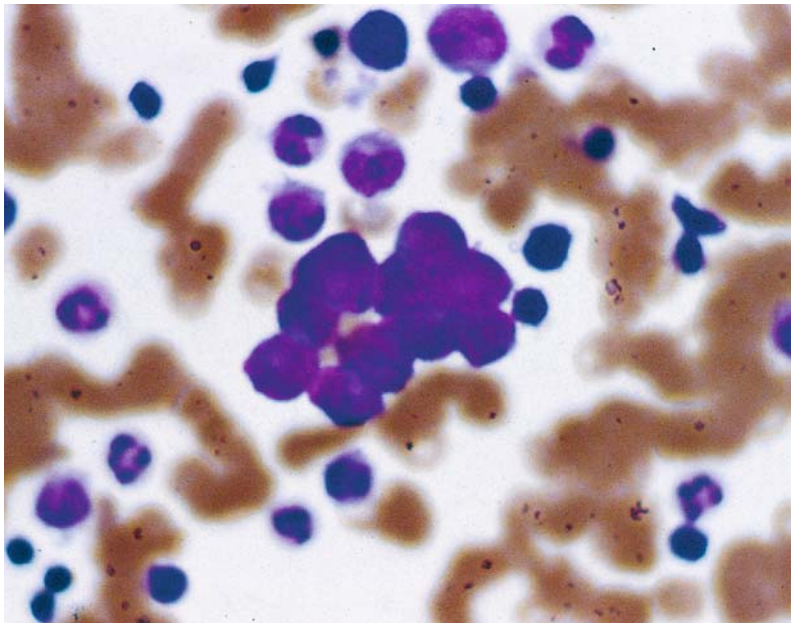


Figure 2.7
Metastatic retinoblastoma in the bone marrow

Table 2.17. The Reese-Ellsworth classification system for retinoblastoma

Group I Very favorable	A: Single tumor, smaller than 4 disk diameters[a] at or behind the equator B: Multiple tumors, none larger than 4 disk diameters, all at or behind the equator
Group II Favorable	A: Solitary tumor, 4–10 disk diameters in size, at or behind the equator B: Multiple tumors, 4–10 disk diameters in size, behind the equator
Group III Doubtful	A: Any lesion anterior to the equator B: Solitary tumors larger than 10 disk diameters behind the equator
Group IV Unfavorable	A: Multiple tumors, some larger than 10 disk diameters B: Any lesion extending anteriorly to the ora serrata
Group V Very unfavorable	A: Tumors involving more than half the retina B: Vitreous

[a] Disc diameter = 1.5–1.75 mm

the retina into the subretinal space and cause serious detachments of the retina. From the retina they can proceed to invade the choroid or the blood supply. A mixed presentation of endophytic and exophytic patterns is the most common occurrence (Hurwitz et al., 2002). Diffuse infiltrating Rb is the least common presentation; it usually occurs in older children and is a diagnostic challenge.

The Reese-Ellsworth classification system is currently the most frequently used tool (Table 2.17). Murphree has developed a simpler staging system, but this has not been adopted widely into practice at this time

2.8.7 Treatment

The goals of treatment for Rb are to preserve useful vision without compromising patient survival. The major treatment modalities for Rb include surgical enucleation, radiation, and chemotherapy, as well as focal cryotherapy and photocoagulation therapy.

Enucleation is used often in the management of Rb. It is used to treat large unilateral tumors with no visual potential. Tumors that invade the optic nerve, choroid, or sclera or those that extend into the orbit need to be removed. Twenty percent of children with bilateral disease lose both eyes eventually (Hurwitz et al., 2002). Enucleation is also used when extensive seeding is evident, as with anterior invasion and secondary glaucoma. When the eye is enucleated, an orbital implant is surgically placed and the rectus muscles are attached to allow for some movement of the eventual prosthesis.

External beam radiation was frequently used in the past treatment of Rb. Its disadvantages include facial hypoplasia, cataract development, retinopathy, and increased risk of secondary tumors in the radiation field. Children who carry the germ line Rb mutation and receive radiation therapy are at a 35% increased risk of developing a secondary malignancy (Gallie et al. 1996). But because Rb cells are very radiosensitive, radiotherapy is sometimes used for the treatment of medium sized tumors. The dose, which ranges 3,500 and 4,500 cGy, is given in 20 fractions (Servodidio et al., 1991). More recently stereotactic radiation has been used to target some intraocular tumors, removing the need to radiate the entire orbit. Incidence of cataracts is lessened with this approach (Hurwitz et al. 2002).

Plaque radiotherapy is another form of radiation therapy. With this form of radiation treatment, cobalt or iodine plaques are surgically implanted at the scleral base of the tumor. The plaque remains in place for 2 to 4 days and then is surgically removed. This treatment is used on medium-sized tumors situated away from the optic nerve and macula (Chan et al. 1996). Plaque radiotherapy is most often used as a secondary treatment after another form has failed.

Focal therapies are used alone or as adjuvant treatment with chemotherapy. Cryotherapy can be effectively used to manage small anterior tumors. Cryotherapy entails freezing the tumor with a probe, allowing the tumor to thaw, and then repeating this process several times. It is usually performed at monthly intervals. Photocoagulation therapy is used for small posterior tumors. Laser burns are made around the tumor, which in effect cut the blood supply to the tumor, ultimately causing cell death.

Until recently, chemotherapy has not played a large role in treating intraocular Rb. A study by Chan et al. (1996) revealed that 30% of already enucleated tumors show resistance to chemotherapy. P-glycoprotein is the multidrug-resistance protein, and was expressed in these chemoresistant tumors (Gallie et al., 1996). P-glycoprotein in vitro has been shown to actively pump chemotherapy out of tumors. Chan et al. (1996) found that high concentrations of cyclosporin reversed this process. A current phase III trial is ongoing to evaluate the efficacy of high-dose cyclosporin in conjunction with the chemotherapy agents vincristine, carboplatin, and etoposide. Preliminary data are showing good results with this approach, which avoids radiation therapy. Adjuvant treatment with photocoagulation and cryotherapy are used in conjunction with the chemotherapy administration. Viable tumor is often left following chemotherapy, so focal therapy is imperative following the cessation of chemotherapy. Other treatment protocols continue to use similar chemotherapy agents in conjunction with focal therapy and without the use of cyclosporin with good success for Reese-Ellsworth eye groups 1, 2, and 3 (Friedman et al., 2000).

Chemotherapy has always played a role in the treatment of metastatic disease. In advanced metastatic disease high-dose chemotherapy followed by stem cell rescue is sometimes being done where available. This is only useful if complete local control of metastatic disease has been obtained. Intrathecal administration of cytarabine and topotecan has also been attempted in efforts to clear metastatic disease in the cerebrospinal fluid.

2.8.8 Prognosis

The overall 5-year survival for Rb is 90% (Hurwitz et al., 2002). Unfortunately, the survival in patients with metastatic disease remains poor. Optic nerve invasion posterior to the lamina cribrosa at time of enucleation is predictive of poor prognosis.

2.8.9 Follow-up

Ongoing follow-up of children with Rb is needed well after tumor control has been established. Children with hereditary disease are at risk of developing new tumors until retinal differentiation is complete, around the age of 7. Following the treatment of Rb, fundoscopic examinations are imperative to pick up recurrent disease quickly. Eye exams are generally done under anesthesia while the child is receiving active therapy. Once a child is only being monitored and is able to cooperate, eye exams can be moved to the outpatient setting.

A child treated with chemotherapy and/or radiation therapy must be followed up for late effects of their treatment. Carboplatin can cause hearing disturbances, so audiograms must be a regular part of the follow-up regimen. Secondary leukemias are a potential following treatment with VP16. Secondary malignancies can arise in fields of prior irradiation. Children with the Rb1 gene mutation are at an increased risk of developing secondary neoplasms. Families must be taught to be conscientious in reporting any changes in their children's health.

2.8.10 Future Directions

Potential future directions in the treatment of Rb include monoclonal antibody, interferon, and gene therapy. There are also international efforts underway for a clinical trial examining the use of chemotherapy and focal therapy in an effort to avoid radiation therapy. The use of cyclosporine in conjunction with chemotherapy and focal therapy will be trialed on a larger scale to help delineate if cyclosporine reverses multidrug resistance and results in superior outcomes compared with chemotherapy alone in treating intraocular tumors. The development of radiosensitizers may act to diminish the resistance of hypoxic cells to radiation, with the hope of increasing the rate of successful radiation.

2.9 Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) develops from a primitive mesenchymal cell committed to muscle differentiation. They can occur anywhere in the body, even in places where skeletal muscle would not be seen.

2.9.1 Epidemiology

Rhabdomyosarcoma is the most common soft tissue sarcoma that occurs in children. It affects approximately 4.5 per million children less than 15 years of age in age (Gurney et al,. 1995). It is the third most common extracranial solid neoplasm of childhood. Males have a very slightly higher incidence, and whites have a 15% increased rate of occurrence compared with blacks (Gurney et al., 1995). Two-thirds of children presenting with RMS do so before the age of 6 (Wexler et al., 2002). Younger children tend to present with the embryonal subtype of RMS, whereas the alveolar subtype occurs throughout childhood.

2.9.2 Etiology

The cause of RMS is unknown. There is association with other genetic syndromes including neurofibromatosis, Li-Fraumeni syndrome, and BWS (Wexler et al. 2002). Parental use of marijuana has shown a three-fold increased risk of developing RMS in some studies (Wexler et al., 2002). Other environmental factors that are being considered as adding to the risk are parental use of cocaine, prior exposure to alkylating agents, intrauterine x-ray, and fetal alcohol syndrome. A higher incidence of RMS has also been noted in patients with congenital anomalies of the gastrointestinal, genitourinary, cardiovascular and central nervous systems.

Table 2.18. The prevalence of rhabdomyosarcoma according to primary site and the correlating clinical symptoms (Wexler et al., 2002)

Site of primary tumor	Prevalence	Clinical symptoms
Parameningeal (Ear, nasal cavity, sinuses, infratem poral fossa, pterygopalatine fossa)	16%	Airway obstruction Respiratory symptoms Nasal congestion Pain Cranial nerve palsies
Orbit	9%	Proptosis Periorbital swelling
Other head and neck	10%	Swelling or mass
Extremities	18%	Swelling or mass
Genitourinary	22%	Prostate: bladder and/or bowel difficulties Paratesticular: scrotal swelling, pain, mass above the testes Uterus, bladder, cervix: menorrhagia, or metrorrhagia Vagina: protruding grape-like cluster (typical for botryoid)
Other	25%	

2.9.3 Molecular Genetics

RMS falls into the category of small round blue-cell tumors. They can be differentiated from tumors with similar morphology based on electron microscopy, immunocytochemistry, and cytogenetic analysis. Sixty percent of RMSs are of the embryonal subtype, and 5% of those are considered the botryoid variant, 20% are the alveolar subtype, and the remaining 20% are undifferentiated (Pappo et al., 1997). A solid variant is referred to as a pleomorphic form revealing the presence of anaplastic cells in large sheets.

Alveolar RMS has a characteristic t(2;13) seen in over one-half of patients and a second t(1;13) translocation seen less commonly (Pritchard-Jones and Mitchell, 1997). In the t(2;13) rearrangement, the PAX3 gene is fused with the FKHR gene, whereas the (1;13) rearrangement causes fusion of PAX7-FKHR. It is thought that PAX3 and PAX7 are vital to muscle development during embryogenesis. Patients with metastatic disease and PAX7 fusion gene tend to have a more favorable prognosis than those with the PAX3 (Pappo et al., 1997). N-Myc is amplified in 10% of the alveolar subtype. A tumor should be treated as alveolar even when it displays only scattered alveolar foci because alveolar imparts a worse prognosis and requires treatment intensification.

The embryonal subtypes have not revealed any translocations but characteristically have shown loss of heterozygosity at 11p15.5 (Pappo et al., 1997).

The undifferentiated sarcomas tend to have a t(11;22), which are seen often in the Ewing's sarcoma family of tumors, and tumors are generally treated similarly.

2.9.4 Symptoms and Clinical Signs

RMS can occur anywhere in the body with the exception of bone and is not limited to those places where skeletal muscle exists. The prevalence of the tumors according to primary and the correlating clinical symptoms are listed in Table 2.18.

RMS spreads via hematogenous and lymphatic routes. The most common sites for metastases are lung, lymph nodes, bone, and bone marrow.

Table 2.19. Clinical group staging system for rhabdomyosarcoma

Clinical group		Extent of disease and surgical result
I	A	Localized tumor, confined to site of origin, completely resected
	B	Localized tumor, infiltrating beyond site of origin, completely resected
II	A	Localized tumor, gross total resection but with microscopic residual disease
	B	Locally "extensive" tumor (spread to regional lymph nodes), completely resected
	C	"Extensive" tumor (spread to regional lymph nodes), gross total resection but with microscopic residual disease
III	A	Localized or locally extensive tumor, gross residual disease after biopsy only
	B	Localized or locally extensive tumor, gross residual disease after "major" resection (>50% debulking)
IV		Any size primary tumor, with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumor

2.9.5 Diagnostics

Necessary diagnostic tests in the workup of a patient thought to have RMS include

- imaging of the affected area
- imaging of likely areas for metastases
- tumor biopsy
- blood work

Initial workup consists of x-ray or ultrasound of the primary, depending on location. Once a mass is identified, CT or MRI scanning should be ordered to evaluate the extent of the mass and look for evidence of bony erosion. A CT of the chest should be done to look for pulmonary metastases. If the tumor is located in a paraspinal or parameningeal area, an MRI should be ordered to assess the extent of disease. A bone scan is ordered to rule out bony metastases. MRI of the head should be considered if the child is symptomatic at diagnosis or has a paraspinal primary.

A biopsy is done to obtain a tumor specimen; this can be either via core or open biopsy. The specimen should be sent for cytogenetics with FISH (or reverse transcription PCR when FISH is not available). Light microscopy reveals rhabdomyoblasts or cross striations, which are both seen in skeletal muscle. RMS cells stain positive for intermediate filaments, desmin, vimentin, myoglobin, actin, and myoD (Pappo et al., 1997). A bilateral bone marrow aspirate and biopsy are also done to rule out bone marrow involvement. A lumbar puncture should be done for children with parameningeal primaries to determine whether the cerebrospinal fluid is infiltrated with tumor cells.

Blood work should consist of a CBC, LDH, and liver function tests. Urinalysis is required. There are no specific tumor markers for RMS. In planning for treatment, it is also prudent to do necessary prechemotherapy surveillance studies such as an echocardiogram and audiogram.

2.9.6 Staging and Classification

Staging normally follows two distinct systems. The first involves the TNM (tumor, node, metastases) system, which takes into account not only surgical outcome, which may be dependent on the surgeon's skill, but also site, size, local invasiveness, and presence of nodes and metastases, and then divides patients into distinct prognostic groups (Andrassy, 2002). (See Table 2.19.). The second grouping system, by the Intergroup Rhabdomyosarcoma Study (IRS) group, looks at pretreatment and operative outcome (Table 2.20). Both stage and group are used to determine appropriate therapy. Survival correlates with clinical group, while TNM staging aids in determining risk stratification to allow for risk-based therapy.

Table 2.20. TNM pretreatment staging classification for rhabdomyosarcoma (*T1* confined to anatomic site of origin; *T2* extension; *NO* not clinically involved; *N1* clinically involved; *NX* clinical status unknown; MO, no distant metastases; *M1* distant metastasis present)

Stage	Sites	Tumor invasiveness	Tumor size	Regional nodes (N)	Metastases
1	Orbit Head and neck[c] Genitourinary[d]	T1 or T2	a[a] or b[b]	NO, N1, or NX	MO
2	Bladder/prostate Extremity Cranial parameningeal Other[d]	T1 or T2	a[a]	NO or NX	MO
3	Bladder/prostate Extremity Cranial parameningeal Other[e]	T1 or T2	a[a] b[b]	N1 NO, N1, or NX	MO MO
4	All	T1 or T2	a[a] or b[b]	No or N1	M1

[a] a <5 or =5 cm in diameter
[b] >5 cm in diameter
[c] Excluding parameningeal
[d] Nonbladder/nonprostate
[e] Includes trunk, retroperitoneum, and so on
Used in Intergroup Rhabdomyosarcoma Study IV

2.9.7 Treatment

Treatment for RMS includes surgery, radiation therapy (sometimes brachytherapy), and chemotherapy. The full treatment plan for RMS depends largely on the location of the tumor. The IRS group has a stratification schema for tumors according to the primary site, stage, TNM and histology. The timing of each depends on the clinical disease group and study protocols. In general, surgery is often followed by radiation therapy and chemotherapy; in cases of complete surgical resection, chemotherapy alone is used.

Surgery depends largely on the site of disease and the feasibility of complete surgical resection. Surgical resection also helps delineate the clinical grouping to be used. Surgery over the years has become more conservative with each intergroup rhabdomyosarcoma study. Treatments in a recent study have used risk stratification based on the likelihood of disease recurrence, and divided patients into low-, intermediate-, and high-risk groups. Risk is determined by examining the site and size of the tumor, nodal disease, and histology.

Radiation therapy is used for microscopic tumor or residual tumor not removed during surgery. The timing of radiotherapy is variable depending on the protocol used. In the IRS V protocols, radiation therapy begins at week 15 for patients in the high-risk group, week 12 for intermediate risk, week 3 for low risk, and immediately for some high-risk patients with advanced cranial tumors (Wexler et al., 2002).

Chemotherapy is used for cytoreduction prior to a gross total resection and for both gross and micrometastatic disease. Chemotherapeutic agents that are used in treating RMS are vincristine and actinomycin D for low-risk tumors. Vincristine, actinomycin, and cyclophosphamide (VAC) is the gold standard for intermediate-risk RMS, although other agents such as ifosfamide, etoposide, and doxorubicin also show activity. Currently, irinotecan is being used in the IRS V protocol to determine its activity in patients with distant metastases at diagnosis (Wexler et al., 2002). Chemotherapy has traditionally been given longer in RMS than in other solid tumors, sometimes for 12–24 months in IRS studies (McDowell, 2003).

Surgery with adequate margins is the treatment of choice for head and neck tumors where possible, although deforming surgery is not warranted. If complete resection is not possible, then radiation therapy is used. Both of these groups of patients receive chemotherapy. For RMS in the orbit, resection without disfiguration is not possible, so chemotherapy and radiation therapy are the treatment of choice (Andrassy, 2002). For bladder and prostate tumors, surgery, with postoperative radiotherapy for both gross or microscopic residual disease, and chemotherapy are used. Those children with bladder tumors often have dysfunction postoperatively, which is lessened somewhat with more conservative surgical approaches and the use of radiation (Andrassy, 2002). For paratesticular RMS, radical inguinal orchiectomy is recommended along with ipsilateral retroperitoneal lymph node dissection. Adjuvant chemotherapy has favorable cure rates. If nodal resections are positive, retroperitoneal radiation and intensified chemotherapy are warranted. Vaginal, vulval, and uterine RMS used to be treated with radical, mutilating surgery; but the IRS now recommends combination chemotherapy post-biopsy followed by conservative surgery and radiation therapy for incompletely resected disease (Andrassy, 2002). RMS of the extremities is treated when possible with limb-sparing surgical resection. At the time of surgery, aggressive lymph node sampling is warranted or, when available, sentinel node biopsy, and postoperative radiation therapy to these sites is recommended

2.9.8 Prognosis

The overall 5-year survival in RMS is 70% (Pappo et al., 1997). A review article by Andrassy (2002) states that 90% of paratesticular tumors are cured, overall survival for bladder/prostate is 85%, and orbital RMS has survival rates greater than 90%. Patients who have limb primaries have an overall survival of 66%. This is because these tumors are often disseminated and the histology is usually of the alveolar subtype. Patients who are high-risk, who have unresectable tumors in unfavorable sites, have an overall survival of 73% (McDowell, 2003). The improved prognosis and survival in this group of patients is attributed to multimodal risk adapted therapy. Patients with metastatic disease at diagnosis (Group IV disease) continue to have a poor prognosis and a 3-year event-free survival of only 25% (Breneman et al., 2003).

2.9.9 Follow-up

Follow-up protocols for children treated for RMS must look for both local recurrence and late effects of treatment. Most protocols generally require follow-up every 3 months for the first year, with physical exam, as well as chest x-ray or chest CT to look for lung metastases, and CT or MRI of the primary. During the second and third years screening may occur with decreasing frequency as clinically appropriate. Follow-up must consider late effects of all treatments including, site-specific radiation and surgery as well as chemotherapy. These children generally have a high risk for developing secondary tumors later in life if they have been radiated and must continue to be followed (Andrassy, 2002)

2.9.10 Future Perspectives

Patients with metastatic alveolar RMS who are PAX3-FKHR positive continue to do poorly on standard treatment protocols, and new targeted therapy needs to be developed. Molecular gene fusions such as the PAX3-FKHR oncogene may be a therapeutic target in the future (Sorensen et al. 2002). Some clinicians believe that radiation therapy that is hyperfractionated, as well as conventional chemotherapy agents such as VP16 and ifosfamide, may have a role in treating advanced-stage RMS (Kaefer, 2002). Others, however, believe that dose escalation of chemotherapy and radiation therapy is futile because these are not tumor-specific (Pappo et al., 1997).

Studies testing the value of antisense, oligonucleotides, and ribozymes in RMS cell lines currently exist, but their value is yet to be determined (Pappo et al., 1997). Irinotecan and topotecan are being used in some clinical phase II trials in patients with metastatic disease. As with many other solid tumors currently, immunotherapy, antiangiogenic agents, and biological agents are thought to have a future role.

Table 2.21. Prognostic factors in the NRSTS (Miser et al., 2002)

	Factors associated with increased risk of local relapse	Factors associated with increased risk of distant metastases	Factors associated with decreased survival
Microscopically positive margins	X		X
Tumor >5 cm	X	X	X
High histologic grade		X	X
Intraabdominal primary tumor	X		X
No radiotherapy	X		
Invasive tumor		X	

2.10 Non-rhabdomyosarcomatous Soft Tissue Sarcomas

Non-rhabdomyosarcomatous soft tissue sarcomas (NRSTS) are a heterogeneous group of tumors. Collectively they account for approximately 4% of cancers occurring in childhood (Spunt et al., 2002). NRSTS are normally staged according to the Intergroup Rhabdomyosarcoma Study Group surgicopathologic staging system. This staging reflects the postoperative tumor status (Table 2.19). The TNM staging system takes into account the presurgical tumor status, including size, local invasiveness, presence of nodes, and metastases. NRSTS are also graded, 1 through 3, and their grade is of important prognostic significance. Grade is based on histological subtype, amount of necrosis, number of mitoses, the degree of cellularity, and nuclear features. Collectively this information is used to determine appropriate treatment stratification.

The treatment approach for NRSTS is similar regardless of tumor type. Primary treatment consists of wide surgical excision of the tumor. A surgical margin of 1 cm is considered adequate if free of all microscopic disease. Radiotherapy is sometimes used as adjuvant treatment in the presence of microscopic residual disease or in the presence of inadequate surgical margins. The long-term survival of patients with surgically resectable tumors treated with or without radiation therapy exceeds 70% (Spunt et al., 1999).

Although the overall survival of children with completely resected tumors is generally excellent, 20% of these children will relapse and die of their disease (Miser et al. 2002). It is important to recognize those tumors with a high potential for local and distant recurrence so that appropriate adjuvant treatment is utilized in their initial treatment. Prognostic factors in NRSTS are described in Table 2.21.

NRSTS in general are not very chemosensitive tumors; however, in some instances adjuvant chemotherapy is warranted. High-grade tumors that are surgically resected but are large (>5 cm) may benefit from adjuvant chemotherapy regardless of surgical margins. Chemotherapy has also been used as neoadjuvant therapy in unresectable tumors, in those that have been incompletely excised, and in metastatic disease. Vincristine, actinomycin, and cyclophosphamide have been used with good response in inoperable infantile fibrosarcoma (Ninane 1991). Ifosfamide and doxorubicin have been used as adjuvant treatment for some NRSTS (especially with synovial sarcoma), with questionable results. Metastatic NRSTS do poorly and require new therapies.

The most commonly occurring NRSTS in children will be briefly discussed, with typical features unique to each tumor summarized.

Alveolar Soft Part Sarcoma (ASPS) This tumor is found most often in late adolescence, with an incidence higher in females. It represents 0.5–1% of all soft tissue sarcomas in adults and children (Pang et al., 2001). Primary sites of disease are the skeletal muscles of the extremities with the deep soft tissue of the thigh and buttocks being the most common (Coffin et al. 1997). The head and neck regions are more common in children. ASPS metastasizes to lung, bone, and CNS. This disease has an indolent course, and relapses can occur very late. Imaging generally shows a large intramuscular mass with prominent vascularity. Chromosomal abnormalities have been identified at t(x;17)(p11.2q25) (Miser et al., 2002). Prognosis is best for head and neck tumors but poor in general.

Fibrosarcoma This spindle cell tumor has two peaks in incidence. It typically affects young infants and children, with the second childhood peak occurring between the ages of 10 and 15 (Carli et al., 1997). Congenital or infantile sarcomas are generally found in the distal extremities and the head and neck regions; these tumors grow rapidly but rarely metastasize. In the adult form, or in children who are older, presentation typically occurs in the proximal extremities, and the deep thoracic and pelvic regions. Adult-type tumors often have cytogenetic abnormalities such a: t(x;18), t(2;5), and t(7;22) (Miser et al., 2002). These tumors are more aggressive and tend to metastasize more often. The overall 5-year survival with infantile fibrosarcoma is 84–93%, but with older children survival correlates with the adult form of the disease, with the 5-year overall survival being 60% (Coffin et al., 1997; Miser et al., 2002).

Hemangiopericytoma This neoplasm represents approximately 3% of all soft tissue sarcomas in children (Miser et al. 2002). This is a vascular tumor that often display the cytogenetic abnormalities of t(12;19) and t(13;22). It is often found in the oral cavity, chest wall, and head and neck of infants and is termed infantile hemangiopericytoma; it is usually associated with an excellent outcome with complete resection. In older children and adults, the tumor is found more often in the lower extremities and retroperitoneum and is usually more aggressive and associated with metastatic disease and poor outcome (Miser et al., 2002). This tumors can metastasize to lung and bone.

Leiomyosarcoma This malignant smooth muscle tumor accounts for less than 2% of NRSTS in children. Radiation therapy may predispose a child to leiomyosarcoma. Incidences of this neoplasm developing in the radiation field of children previously treated for retinoblastoma have been reported. EBV has been linked to leiomyosarcoma in children with HIV. A t(12;14) translocation has been noted in the tumors of children with leiomyosarcoma (Miser et al., 2002). The most common site of occurrence is the gastrointestinal (GI) tract, specifically the stomach, but it can occur in any vascular structure or soft tissue. Gastric epithelioid leiomyosarcomas can occur as part of Carney's triad. When leiomyosarcoma is diagnosed, regular scanning should be done to rule out the presence or development of paraganglioma and pulmonary chondroma. Patients with tumors arising in the GI tract usually have a poor outcome.

Liposarcoma Liposarcoma most commonly affects adolescents in the second decade of life, with a slight male predominance. The deep soft tissues of the extremities account for about half of pediatric cases, and the second most common site of occurrence is the trunk (retroperitoneum). Metastases are not common but can occur in the lymph nodes, lung, liver, and brain. Liposarcomas can be of myxoid, round cell, well-differentiated, or pleomorphic subtypes (Coffin et al., 1997). In the myxoid variant, which is the most common, a characteristic t(12;16)(q13;p11) is often seen (Swanson and Dehner, 1991). Liposarcomas usually have a low malignant potential, and children generally have a low rate of recurrence (Coffin et al., 1997).

Malignant Fibrous Histiocytoma Malignant fibrous histiocytoma (MFH) comprises 2–6% of all soft tissue sarcomas in children under 20 (Coffin et al., 1997). Males and females are affected equally. It presents most often in the head, neck, and extremities as a painless mass. The lungs are a common site of metastases. Associations have been found between

MFH and children who have received prior radiation therapy, as well as those who have DNA repair defects (Coffin et al., 1997). There are four main subtypes of this neoplasm, with the most common being storiform-pleomorphic; the other subtypes are giant cell, myxoid, and inflammatory. This tumor is characterized by p53 immunoreactivity and the amplification of the MDR2 gene (Coffin et al., 1997). The prognosis for this tumor is poor, with a relapse rate of up to 43% and tumor death rate of 44% (Coffin et al., 1997)

Malignant Peripheral Nerve Sheath Tumor (MPNST) MPNSTs arise from the peripheral nerve sheaths, as their name suggests, and they are also referred to as neurofibrosarcomas. They are among the most common of the soft tissue sarcomas occurring during childhood representing 10–20% of all NRSTS. They most commonly occur in the second decade of life, with males and females being affected equally. There is a well-established association between neurofibromatosis and the development of this tumor. Mutations of p53 on chromosome 17 have been noted. There are, however, no characteristic genetic anomalies in this tumor. The most common anatomic sites of presentation of MPNSTs are the extremities and trunk.

Synovial Sarcoma Synovial sarcoma (SS) is the most commonly occurring NRSTS in older children and young adults (Miser et al. 2002). There is a very slight male predominance in the development of SS. It has three histological subgroups: biphasic, which is the most common and represents 60% of cases, monophasic-epithelial, and monophasic-fibrous. SS carries a characteristic genetic alteration t(x;18)(p11;q11) (Coffin et al., 1997). SS normally occurs in close proximity to a joint, tendon, or bursa. The most common site of presentation is the leg near the knee or ankle joint, followed by the arm. The lung is a common site for metastases; lymph nodes are less commonly affected. Diagnostic imaging usually shows a mass with calcification. SS is one of the more chemosensitive NRSTSs.

2.11 Germ Cell Tumors

Germ cell tumors (GCTs) are a heterogeneous group of neoplasms that arise from primordial germ cells. They range from benign teratomas to aggressive malignancies. Extragonadal GCTs result from germ cells migrating aberrantly during fetal development. Presumably the differences in stage of germ cell development at the time of tumorigenesis play a role in the malignant potential of this group of tumors.

2.11.1 Epidemiology

GCTs comprise 3% of all childhood neoplasms and occur at an annual incidence of approximately 2.4 per million children (Gurney et al., 1995). There is a bimodal peak in the ages of occurrence, with the first peak occurring in children less than 5 and the second in adolescents 15–19. Females are affected more often with benign GCTs and males are more often affected by malignant GCTs.

2.11.2 Etiology

Cryptorchidism (undescended testes) and gonadal dysgenesis are known to predispose for GCTs.

2.11.3 Molecular Genetics

Several characteristic genetic abnormalities predominate in GCTs, which can be divided into four groups, each with its distinct molecular characteristics: tumors of the adolescent testes, tumors of infancy, extragonadal tumors of adolescents, and tumors of the adolescent ovary (see Table 2.22).

2.11.4 Symptoms and Clinical Signs

Clinical symptoms of disease depend on the location of the tumor. Tumors arise either in gonadal or extragonadal midline sites. GCTs occur in the ovaries 25% of the time and in the testes 20% of the time. They occur in extragonadal locations more than half of the time: 25% occur in the sacrococcygeal region and 20% occur in the brain, with other sites includ-

Table 2.22. Common genetic alterations associated with germ cell tumors (Cushing and Marina, 2000)

GCT tumor group	Ploidy	Chromosomal alterations
Tumors of the adolescent testes	Aneuploid	Isochromosome 12p Loss of 13 Gain of 8, 21, 1q
Tumors of infancy		
Teratomas	Diploid	Abnormalities at 1, 3, 6
Yolk sac tumor	Diploid or Tetraploid	Abnormalities at 1, 3, 6
Extragonadal tumors of adolescents		
Brain	Diploid or tetraploid	Loss of 13 and 8
Mediastinum		Some have i(12p)[a]; loss of 13 and 8
Tumors of the adolescent ovary		
Mature teratoma		5% show gain or loss of an entire chromosome
Immature teratoma		No consistent changes
Malignant ovarian GCT	Aneuploid	i(12p)[a]; gains of 21 and1q

[a] Two copies of 12p exist, both coming from the same parent

ing the retroperitoneal, pelvic, and neck area (Rodriguez-Galindo and Pappo, 2003). GCTs metastasize via both hematogenous and lymphatic spread. Common sites of metastasis are lung and liver.

Testicular tumors usually present as a mass or swelling in the scrotum and are usually not painful. Ovarian tumors usually present with symptoms such as pain, tenderness, and abdominal swelling. Mediastinal disease may cause symptoms of respiratory distress. Sacrococcygeal tumors can present with symptoms of urinary retention and constipation or as a visible gluteal mass. CNS disease may present with headaches, visual disturbances, precocious puberty, hypothyroidism, and diabetes insipidus.

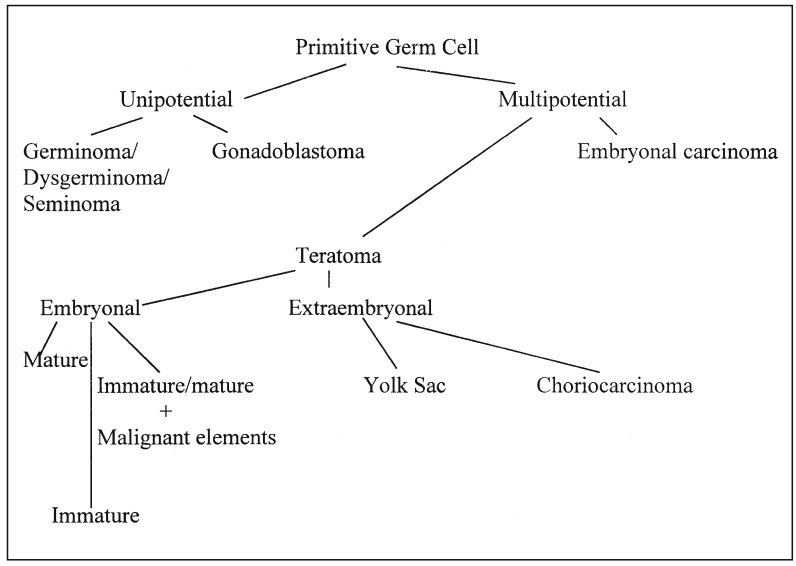
2.11.5 Diagnostics

An ultrasound is usually done initially to investigate abdominal and pelvic tumors and is helpful in differentiating solid from cystic masses. CT of the chest, abdomen and pelvis, is recommended to assess the extent of primary disease and assessing for the presence of metastases. Bone scan may be indicated if bone pain is a presenting feature; however, GCTs rarely metastasize to bone.

There are serum tumor markers for some of the GCTs. Onco-feto-proteins such as alpha feto-protein (AFP) and beta human chorionic gonadotropin (BHCG) are used for screening. Elevations in AFP are seen with endodermal sinus tumor (EST) and embryonal carcinoma; increased BHCG is seen in choriocarcinoma. Serum onco-feto-proteins should decline within a half-life following the removal of a tumor, which for AFP is 7 days,- and for BHCG is 24 hours. Failure of these tumor markers to fall may indicate persistent disease (Pinkerton, 1997a,b). Nonspecific markers such as LDH are often ordered, and elevated levels are thought to correlate with growth of solid tumors (Cushing and Marina, 2000). Placental alkaline phosphatase is the isoenzyme of alkaline phosphatase and is used as a screening test at some centers; increases are seen in seminomas. Pituitary function should be evaluated before and during therapy.

Biopsy and preferably tumor resection (but not mutilating surgery) are necessary for both pathological diagnosis and treatment.

Figure 2.8
Schema for differentiation pathways for germ cell tumors (adapted from Pinkerton, 1997)



2.11.6 Staging and Classification

Germ cells develop from a primordial germ cell. There are many different morphological subtypes, which reflect the pathway of differentiation to which the cell was dedicated prior to malignant transformation. Fig. 2.8 shows the schema of differentiation pathway for GCTs.

Separate staging systems exist for ovarian and testicular tumors. However, staging of both is similar to that for other solid tumors:

- Stage I indicates localized disease confined to primary site, completely resected
- Stage II implies some degree of microscopic residual disease or nodal involvement (<2 cm)
- Stage III is characterized by gross residual disease or lymph node involvement (>2 cm)
- Stage IV denotes distant metastases (Cushing et al., 2002)

Characteristics that are associated with the different histologic subtypes of GCTs are summarized in Table 2.23.

2.11.7 Treatment

The treatment of both malignant and benign GCTs is surgical resection if feasible. Mutilating surgery should be avoided because GCTs are chemosensitive. Radiation therapy is often used for intracranial GCTs either alone or with chemotherapy. Radiation is also used at times for residual disease post-chemotherapy or in the case of bulky mediastinal disease post-chemotherapy.

For malignant GCTs requiring chemotherapy, platinum-containing regimens (cisplatin or carboplatin) are considered the standard of care. Other chemotherapeutic agents that have been used to treat GCTs include actinomycin, vinblastine, bleomycin, doxorubicin, and etoposide. Low-risk patients, those with stage I gonadal, are treated with surgical resection alone and do not require further treatment upfront but need to be closely followed. Similarly, extragonadal tumors that are completely resected may not require further treatment. Those with an intermediate risk, including stages II–IV gonadal and stage II extragonadal disease are treated with standard chemotherapy such as PEB (cisplatin, etoposide, and bleomycin) or JEB (carboplatin, etoposide, bleomycin) for four courses. High-risk patients, those with stage III and IV extragonadal disease, usually re-

Table 2.23. Germ cell tumors (GCT): subtypes, disease sites, and specific characteristics (Cushing et al., 2002)

Malignant category	Subtype	Sites of disease	Specific characteristics
Benign GCT	Mature teratomas	Ovaries Sacrococcygeal area Mediastinum	Mature elements of all three germ cell layers
Benign GCT	Gonadoblastoma	Dysgenic gonad	Mix of gonadal sex cord cells and immature germ cells
GCT of intermediate behavior	Immature teratoma	Ovaries	Graded based on degree of maturation (0–2 show benign behavior)
Malignant GCT	Germinoma	Ovaries (dysgerminoma) CNS (pineal region) Testes (seminoma)	Chemosensitive Radiosensitive
	Yolk sac tumor (endodermal sinus tumor)	Sacrococcygeal Testes	Elevate serum AFP
	Embryonal carcinoma	Testes Mediastinum Ovaries	Major component of mixed GCT
	Choriocarcinoma	Pineal region Mediastinum Ovary Testes	Elevated serum bHCG

quire 6 months of chemotherapy with cisplatin, etoposide, and bleomycin. Intergroup studies (POG and CCG) in the United States have shown that event-free survival can be improved in the high-risk group of GCTs if high-dose cisplatin therapy instead of the standard dosing is used in conjunction with standard dose etoposide and bleomycin (HDPEB) (Rodriguez-Galindo and Pappo, 2003), but the cisplatin-associated toxicity (ototoxicity predominantly as well as nephrotoxicity) is severe.

2.11.8 Prognosis

The 5-year overall survival of those with mature and immature teratoma is 100% (Cushing et al,. 2002). Results of the COG/POG randomized trials of PEB versus HD PEB have shown that the 3-year event-free survival for those with stage II testicular tumors is 100%, and for stage I and II ovarian tumors it is 96.4% (Rodriguez-Galindo and Pappo, 2003). Those with gonadal stages III and IV and extragonadal stages I through IV have an event-free survival of 89.6% with HDPEB (Rodriguez-Galindo and Pappo, 2003).

2.11.9 Follow-up

Close surveillance, clinical as well as regular tumor marker assessment, should occur following the surgical resection of teratomas for up to 5 years because disease recurrence is possible. Malignant GCTs should have regular follow-up with either CT or ultrasound of abdominal and pelvic tumors, or MRI of intracranial tumors, every 3 months for the first year, followed by a decreasing frequency of scanning interval over the next several years. CT of the chest is recommended at regular intervals for metastatic surveillance.

Follow-up must also consider late effects of treatment. Cisplatin, especially high-dose cisplatin therapy, is associated with significant hearing loss, and follow-up audiograms are imperative so that hearing

aids can be ordered if warranted. Nephrotoxicity can also be a problem during and following cisplatin therapy, and renal function studies should be monitored after the completion of therapy. Pulmonary fibrosis may result from bleomycin therapy, and pulmonary function studies should be done regularly in follow-up. Secondary malignancies including myeloid leukemias have been noted after treatment with chemotherapy, especially etoposide. Those who have undergone cranial radiation should receive regular neuropsychological testing. Screening of thyroid, corticotropin, gonadotropin, and growth hormone should also occur regularly following cranial radiation therapy.

2.11.10 Future Perspectives

The use of high-dose cisplatin has led to increased survival in patients with advanced malignant GCTs. Ototoxicity is a problem for these patients. Preliminary data from the recent POG study are disappointing regarding the effectiveness of amifostine to protect against significant ototoxicity. The formal development of risk groups is needed in order to stratify treatment. The role of carboplatin, ifosfamide, and topotecan may also be used to determine their utility in relapsed GCTs. Effective treatment for high-risk patients remains controversial. Future studies are currently being planned that incorporate new agents such as topotecan and paclitaxel.

2.12 Rare Tumors

There are numerous tumors that occur very infrequently in children and adolescents. Most of the rarely occurring neoplasms are those that are seen most often in the adult population. Several more commonly occurring rare tumors will be summarized here.

2.12.1 Adrenocortical Carcinoma (ACC)

Adrenocortical carcinoma is a very rare and aggressive tumor. It occurs more often in females and peaks in the first and fourth decades of life. The incidence of this tumor is very high in Brazil, 10–15 times that observed in the United States. There is a high incidence of Li-Fraumeni syndrome in the families of the children who acquire ACC. Germline mutations of the p53 gene are found in one-third of patients (Kock et al., 2002). Interestingly, in Brazil, children with ACC typically have p53 mutations but they are not germline. Cushing syndrome, reflecting hormonal excess, is a presenting sign of ACC in 68% of children (Plowman, 1997). Evidence of the development of secondary sex characteristics occurs as a presenting sign in 95% of patients younger than 5 (Kock et al., 2002). Other clinical signs are abdominal pain, fever, anorexia, and weight loss. In children, approximately 40% of patients secrete no active hormones, but their inactive steroid precursors such as pregnenolone, 11-deoxycortisone, and 17-hydroxypregnenolone can be found in blood and urine (Kock et al., 2002). ACC can present as localized disease but presents with regional spread to adjacent lymph nodes or the retroperitoneum 20% of the time. Distant metastases to lung and bone can also occur. Curative treatment depends on early wide total excision of the tumor while it is still encapsulated. Repeated surgeries are warranted if isolated recurrences occur. For patients without surgically curable disease, mitotane therapy is often initiated, which is meant to cause necrosis and disease regression while improving the endocrine system (Plowman, 1997). Chemotherapy agents such as fluorouracil, etoposide, doxorubicin, and cisplatin are also sometimes used. These approaches, although they may increase length of survival, are not usually curative. The prognosis is generally quite poor for ACC.

2.12.2 Melanoma

Melanoma accounts for 1.3% of childhood neoplasms; it represents the second most common carcinoma found in children (Rodriguez-Galindo and Pappo, 2003). There is a much higher incidence in whites compared with blacks and in females. Conditions that are associated with melanoma in children include congenital melanomas, giant congenital melanocytic nevi, xeroderma pigmentosum, immunosuppression, neurocutaneous melanosis, and

mole phenotype (atypical moles) (Pratt and Pappo, 2002). Presenting signs may include a mole that has changed in size or color, accompanied by bleeding or itching, with a palpable subcutaneous mass or lymphadenopathy. Common sites are the trunk, head and neck. Metastases generally occur via regional lymph node spread prior to lung, bone, and brain. The American Joint Committee on Cancer staging system of melanoma takes into account tumor thickness, ulceration, nodal disease, and metastases (Balch et al., 2001). Children with thick melanoma >4 mm and those with lymphadenopathy should undergo imaging with CT and MRI to determine the presence of metastatic disease. Wide excision of the lesion is necessary for cure with adequate margins. Interoperative lymphatic mapping with sentinel node biopsy has been shown to be highly sensitive at identifying nodal disease and is usually done for lesions greater than 1 mm in thickness. Alpha interferon therapy has been used in high risk resected melanoma (Pratt and Pappo, 2002). In disseminated disease, agents such as vincristine, dactinomycin, cyclophosphamide, cisplatin, and etoposide, and interleukin 2 have been used with varying rates of success (Pratt and Pappo, 2002). Prognosis depends largely on tumor stage at diagnosis.

2.12.3 Nasopharyngeal Carcinoma

This tumor occurs in the epithelium of the nasopharynx, generally affecting males more often than females. There has been association of EBV infection with this tumor (Plowman, 1997). This tumor has three distinct subtypes, and children are usually affected by the undifferentiated type. It arises in the fossa of Rosenmuller and can spread via direct extension through the oropharynx to the base of the skull and result in cranial nerve palsies (Pratt and Pappo, 2002). The only clinical sign of this disease may be cervical lymphadenopathy, indicating regional metastases. Distant metastases are present in less than 5% of cases, and most common sites include lung and bone (Plowman, 1997). The tumor is staged as per the tumor, node, metastases (TNM) classification system. Surgery is often not possible for nasopharyngeal carcinoma because of its anatomical location. Radiotherapy is the primary treatment modality. Adjuvant chemotherapy is often used in children, and the tumor shows response to agents such as fluorouracil, cisplatin, carboplatin, methotrexate, and bleomycin. Multiple researchers have noted survival rates to be 75% for T1 and T2 tumors, but only 37% for T3 and T4 tumors (Pratt and Pappo, 2002). Late effects of radiation such as xerostomia, muscle atrophy, fibrosis of the neck, and hypothyroidism may be some of the sequelae that affect this group of children.

2.12.4 Thyroid Carcinoma

Thyroid carcinoma is the most commonly occurring carcinoma in children (Rodriguez-Galindo and Pappo, 2003). It generally occurs more often in females, with a peak in incidence between ages 7 and 12. It is well established that neck irradiation is a causative factor in the development of thyroid carcinoma; however, it does also occur sporadically and is associated with some familial syndromes. Cervical adenopathy and thyroid nodules are often the presenting clinical signs; metastases generally occur in the lung and mediastinum. Twenty percent of patients have metastatic disease at diagnosis (Kock et al., 2002). The tumor is characterized by the secretion of T3 and sometimes T4. There are several different subtypes of thyroid carcinoma: papillary, follicular, and anaplastic (Kock et al. 2002). Imaging is generally done with ultrasound and thyroid scintiscan, and chest x-ray or CT is done to rule out lung metastases. A biopsy is needed to confirm malignancy and histology. Complete surgical resection (thyroidectomy) is the treatment of choice for thyroid carcinoma. Radioiodine therapy is used postoperatively if metastatic disease is present and also to ablate any residual functioning thyroid. Thyroid hormone needs to be supplemented in these patients. The prognosis for thyroid carcinoma is generally quite good, with overall survival in some reports approaching 90%, and metastatic disease does not necessarily impart a poor prognosis with the use of radioiodine therapy (Kock et al., 2002).

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Common Central Nervous System Tumors

Nicki Fitzmaurice · Sharon Beardsmore

Contents

Primary brain tumors occur in all age groups but are significantly more frequent in children and adolescents under 15 years old (Turini and Redaelli, 2001). In the United States, central nervous system (CNS) tumors are now the most common malignancy of childhood (Copeland et al., 1999); in the United Kingdom (UK), however, leukaemias are still more prevalent, with paediatric brain tumors continuing to be the most common solid tumor and the most common cause of death from childhood cancer (Bouffet, 2000). They account for 25% of all children's cancers, and around 300 children are diagnosed each year in the UK (CancerBACUP, 2002). In comparison with most other childhood cancers, there have been only moderate improvements in survival rates for children with brain tumors in the past 20 years. Mortality in this group of patients is high, with five-year survival estimated at 50% (CancerBACUP, 2002). Treatment options typically involve a surgical approach, radiotherapy, and chemotherapy, applied in isolation or in various combinations or sequences.

Improvements in imaging, neurosurgical techniques, the delivery of radiotherapy, and the inclusion of chemotherapy in treatment regimens have been reflected in improved survival for some specific histological types of tumors, i.e. cerebella medulloblastoma (Radcliffe et al., 1994). However, there remain major challenges unique to the paediatric arena for those involved in planning and delivering treatment strategies. Aggressive, invasive techniques involving an often immature brain are much more likely to result in devastating late effects, with morbidity estimated at 50% (Macedoni-Luksic et al., 2003). In recognition of this, practitioners have now been undertaking more rigorous appraisal of treat-

ment modalities and the potential risks of cognitive, neuroendocrine, and neuropsychological damage (Plowman and Pearson, 1997)

3.1 Causes/Epidemiology

The cause of childhood brain tumors remains largely unknown, although there is correlation with a family history of cancer, and heredity factors have been implicated. Children with neurofibromatosis, for example, have an increased risk of developing optic gliomas.

Environmental factors such as electric and magnetic fields, radio frequency radiation, chemicals, and mobile phones have all been suggested in the development of brain tumors. There remains, however, insufficient evidence to support these claims. Ionising radiation is a known cause of brain tumors, with secondary local malignancies being a small but significant side effect of cranial radiotherapy (Kheifets, 2003).

3.2 Distribution/Classification

Approximately 60% of childhood brain tumors are infratentorial, including medulloblastoma, cerebellar astrocytoma (WHO grades I–IV), brain stem glioma, and ependymoma (Bouffet, 2000). The remaining supratentorial tumors include low-grade astrocytomas, primitive neuroectodermal tumors, germ cell tumors, hypothalamic and optic nerve gliomas, and craniopharyngiomas.

The most common tumors overall are low-grade gliomas, with cerebellar astrocytomas being the largest of this group. Amongst paediatric malignant brain tumors, medulloblastomas occur most frequently. (See Table 3.1.)

Classification of paediatric brain tumors (shown in Table 3.2) can, however, be misleading, as even the most low-grade tumor may have devastating effects because of the nature of its location. It is therefore often unhelpful to use terms such as benign and malignant to describe specific tumors.

Table 3.1. Incidence of most common brain tumors (Bouffet, 2000)

Tumor	Percentage
Low-grade gliomas	25–40%
High-grade gliomas	5–10%
Brain stem gliomas	8–12%
Medulloblastomas	6–20%
Ependymomas	6–11%
Germ cell tumors	3–15%
Craniopharyngiomas	6–15%

Table 3.2. Classification of paediatric brain tumors (Plowman and Pearson, 1997)

Glial tumors	
Astrocytoma	– Well differentiated cystic cerebellar with mural node Protoplasmic/fibrillary/pilocytic/ gemistocytic – Intermediate – Anaplastic → (glioblastoma multiforme)
Ependymoma	– Well-differentiated – Intermediate to poorly differentiated
Oligodendroglioma	– Well-differentiated – Intermediate to poorly differentiated
Mixed gliomas (may include areas with neuroectodermal features)	
Neuroectodermal tumors	
Medulloblastomas	
Other CNS neuroectodermal tumors (PNETs)	
Pineoblastoma	
Pineocytoma	
Germ cell tumors	
Other primary CNS germ cell tumors (other sites usually midline third to fourth ventricles)	
Craniopharyngioma	
Pituitary tumor	
Choroid plexus tumors (cyst/papilloma/undifferentiated or carcinoma)	
Meningioma	
Others	

3.3 Staging

Staging remains contentious within neuro-oncology with little consensus regarding universal staging systems. The tumor group however, that does utilise a staging process that has prognostic implication is medulloblastoma. Here the Chang operative system is employed (Laurent et al., 1985). For other tumors, histological grade, age, site of disease, and areas of dissemination are the main prognostic factors.

3.4 Molecular Genetics of Brain Tumors

In contrast to other childhood cancers, the molecular genetics of childhood brain tumors are poorly understood, not only in terms of the pathophysiology but also in terms of the characterisation of tumor-specific molecular abnormalities that predict biologically favourable or unfavourable disease. The latter is particularly important in brain tumors because such knowledge may allow a more judicious use of current therapies such as radiotherapy and may also identify molecular targets against which new therapies can be directed. Mutations of chromosome 17 have been associated with medulloblastoma, and mutations of chromosome 10 associated with astrocytoma. Genetic abnormalities are currently used to predict biological behaviour in neuroblastoma and rhabdomyosarcoma. Similar biologicals of tumor behaviour are now required if we are to improve the movements of childhood brain tumors.

3.5 Diagnosis

Diagnosing the presence of a brain tumor may be difficult. Diagnosis is often complicated by a vague history of symptoms that the parents, general practitioner, or local paediatrician may have attributed to common childhood illnesses. Children who have a long insidious history of symptoms are more likely to have a lower-grade tumor. Those who present with a short history and obvious symptoms are much more likely to have biologically aggressive disease. Clearly the site (see Table 3.3), severity of disease, and the child's age and development will have an impact on presenting symptoms. For example, those children with posterior fossa disease often have signs of increased intracranial pressure (ICP):

- Headaches
- Early morning vomiting
- Blurred vision
- Ataxia
- Poor concentration
- Changes in vital signs (late sign)

Children with supratentorial tumors, however, are more likely to present with hemiparesis, hemisensory loss, and/or seizures. Table 3.4 outlines the symptoms and treatment of common CNS tumors in relation to the primary site.

Once the child has presented to a specialist paediatrician, the existence of a brain lesion will generally be confirmed via a thorough neurological examination that includes fundoscopy and a visual assessment, followed by magnetic resonance imaging (MRI) of the head and spine. If the presence of an intracranial germ cell tumor is suspected, serum and cerebrospinal (CSF) levels of alpha-fetoprotein (AFP) and human chorionic gonadotropin (HCG) must be

Table 3.3. Sites of tumors in relation to histology (adapted from Plowman and Pearson, 1997)

Tumor site	Most common histological types of tumors
Cerebellum	Astrocytoma Ependymoma Medulloblastoma/PNET
Brain Stem	Astrocytoma
Hypothalmic/pineal4	Astrocytoma PNET NGGCT Teratoma Dysgerminoma
Supratentorial	Astrocytoma PNET Ependymoma

Table 3.4. Symptoms and treatment of CNS tumors in relation to primary site (adapted from Shiminski-Maher and Shields, 1995)

Site	Tumor	Symptoms	Treatment
Supratentorial	Low-grade astrocytoma	Seizures	With gross total resection: surgical removal and observation
		Visual changes	Partial resection: surgical removal and either observation, radiation [a] or chemotherapy
		Endocrinopathies	
		Hemiparesis	
	High-grade glioma/PNET	Seizures	Maximal surgical resection and radiation [a] and/or chemotherapy
		Increased ICP	
		Mental status change	
		Hemiparesis	
Midline	Optic nerve Chiasmal gliomas	Visual disturbances Endocrinopathies	Observation Surgical debulking, radiation, and /or chemotherapy
		Increased ICP	Treatment is age-dependant and related to site of tumor
		Seizures	
	Craniopharyngiomas	Seizures Visual disturbances Increased ICP Endocrinopathies	Gross total resection: observation Partial resection: observation or radiation[a]
Infratentorial/ posterior fossa		Medulloblastoma	Increased ICP Maximal surgical resection and cranial spinal radiation[a] and chemotherapy
		Headache Morning vomiting Cranial nerve deficits Ataxia	
	Ependymoma	Neck pain	Maximal surgical resection and radiation[a] ± chemotherapy
		Increased ICP	
		Cranial nerve deficits	
	Brain stem glioma	Cranial nerve deficits	Malignant tumors diagnosed by MRI requiring radiation ± chemotherapy
		Increased ICP	
		Hemiparesis	
		Usually short history	
		Long history/minimal symptoms/focal lesion on MRI	Low-grade tumor, surgical debulking, and observation or radiation ± chemotherapy

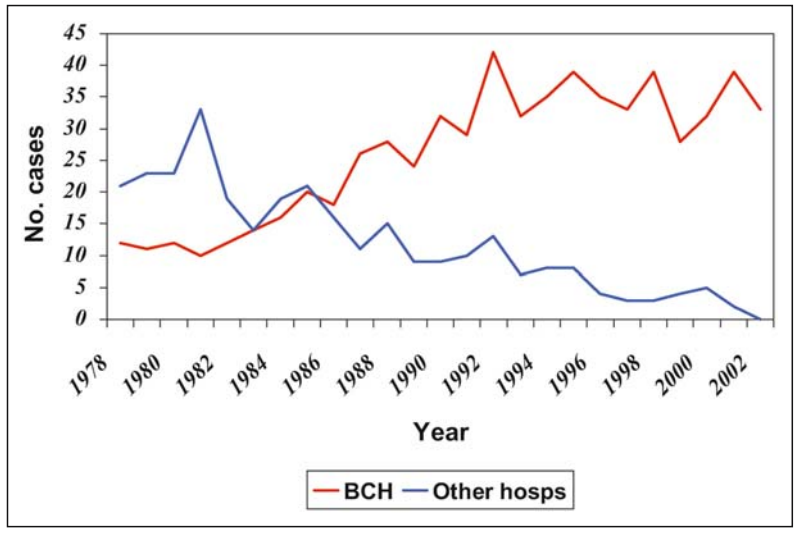
[a] Irradiation should be avoided when possible for children <5 years old

measured. This possibility should be considered in all suprasellar and pineal region tumors. For those tumors with potential to seed along the CSF pathway, CSF cytology should be undertaken at diagnosis or postoperatively.

With some tumors that are impossible to remove, it may be possible to perform stereotactic biopsy to confirm the diagnosis in order to plan treatment.

Figure 3.1

West Midlands brain tumor referrals 1978–2002 (permission to reprint given by Birmingham Children's Hospital, UK)



3.6 Specialist Referral

Whilst other childhood tumors have routinely been referred to specialist paediatric oncology centres since the 1970s, many children with brain tumors continued to receive treatment outside of specialist units. This practice resulted in less than 40% being treated within clinical trials until after 1997 (UKCCSG/SBNS, 1997), when a joint report recommended the centralisation of care for children with brain and spinal disease. Fig. 3.1 demonstrates how the trend has changed in a local region.

3.7 Hydrocephalus

A significant number of children with brain tumors will develop associated hydrocephalus. Noncommunicating hydrocephalus is most commonly seen in paediatric brain tumors and is a result of mass effect. For some children this will present as a surgical emergency around the time of diagnosis, requiring immediate management. The most likely symptoms are headache, early morning vomiting, nausea, and ataxia. The management of hydrocephalus requires the input of a paediatric neurosurgeon with several options available. Debulking or removal of the tumor may be sufficient to relieve the obstruction and allow normal flow of CSF. Other options are high-dose steroids preoperatively, external ventricular drainage, ventriculoperitoneal (VP) shunting, and ventriculostomy.

For those children with VP shunts, potential complications require consideration. Shunt malformation, infection, and, although rare, tumor dissemination should be taken into account when assessing a child who is unwell. Children may experience problems with their shunts during treatment, during periods of good health, and, should they require it, during palliative care.

3.8 Treatment

It is now widely accepted that the best practice for diagnosing, treating, and managing childhood CNS tumors is through a broad-based multidisciplinary team. Such a team includes the collaboration of paediatric neurosurgeons, oncologists, endocrinologists, psychologists, radiotherapists, social workers, and play, physio-, and occupational therapists. Coordinating these services should be a dedicated neuro-oncology nurse specialist. Nursing children with brain tumors is considered more complex and challenging than generic paediatric oncology, with this

patient group often being labelled as the "undesirables" within the discipline (Ryan and Shiminski-Maher, 1995).

Treatment options typically involve surgical removal, radiotherapy, and chemotherapy, applied in isolation or in various combinations or sequences. Tumor type, the extent of disease, the degree of surgical resection, and the individual child will all have an impact on the choice of treatment modality.

3.8.1 Surgery

Primary surgery remains the mainstay of management for paediatric brain tumors. Depending upon the site and extent of the tumor, surgical options range from biopsy alone to complete removal. For most malignant tumors, complete resection is an important surgical goal. There is, however, a balance to be struck between complete excision and the risk of surgical morbidity. For some tumor types, complete surgical excision seems to be of particular prognostic importance (Sutton et al., 1990), i.e. ependymoma medulloblastoma. But in some instances, such as optic nerve gliomas and diffuse brain stem gliomas, surgical excision has little role to play in tumor management.

In other germ cell tumors, chemotherapy now has a primary role, and the indications for surgery are more circumspect (Nicholson et al., 2003).

Increasingly, second-look surgery is an option when it is evident from imaging that excisable tumor remains. Clearly, the surgeon must measure the potential damage to vital structures against the benefits of removing maximum tumor. Debulking alone, however, may relieve local compression and improve the child's symptoms while histology is sought and other treatment modalities are explored.

3.8.2 Radiotherapy

A significant number of children with brain tumors will require radiotherapy, which aims to deliver optimal doses of radiation to tumor cells while sparing surrounding normal tissue.

Conventional Radiotherapy

- 2 cm margin
- Parallel opposed
- Total dose 50–55 Gy
- (craniospinal 25–35 Gy with boost to tumor bed up to a total of 50–55 Gy)

Despite precise planning and delivery of treatment, radiotherapy remains associated with significant long-term sequelae that may lead to significant impairment of quality of life. These sequelae are particularly profound following whole brain treatment and irradiation of pre-school-age children. Internationally, neuro-oncologists recognise the detrimental effects of radiotherapy on the developing brain and have advocated delaying radiation treatment in infants and young children whenever possible (Plowman and Pearson, 1997).

An added complication for young children is their inability to remain still during the delivery of radiotherapy, necessitating the use of daily anaesthetics to ensure dose accuracy. The prolonged use of anaesthetics in an already sick child is not ideal, but it is unavoidable for infants. Every effort should be made via play preparation to obviate the need for anaesthesia

Dose reductions and modified fractionations, to limit the toxicity of craniospinal irradiation, are features of recent investigation

Techniques that have been used to increase the therapeutic index (the tumor to normal tissue dose) include

- Stereotactic radiotherapy
- Brachytherapy
- Radiosurgery

The use of hyperfractionated radiotherapy in medulloblastoma is currently being evaluated in Europe through the SIOP IV trial.

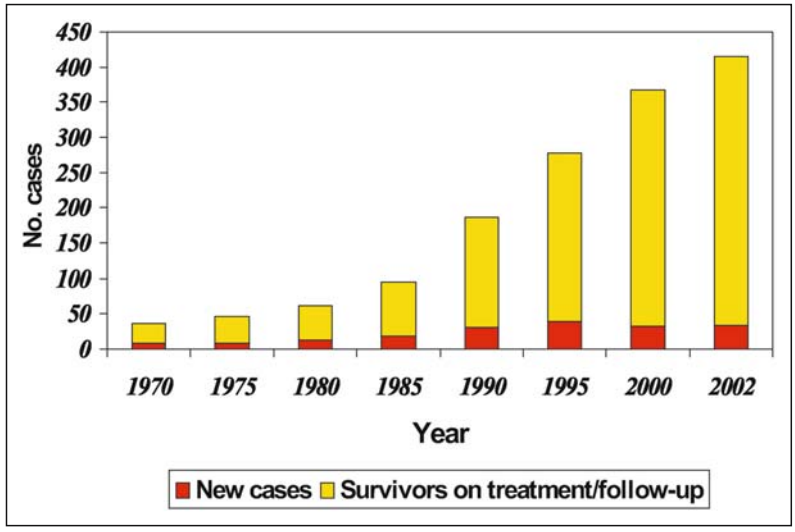


Figure 3.2
BCH brain tumors: cumulative survival 1970–2002 (permission to reprint given by Birmingham Children's Hospital, UK)

The use of conformal radiotherapy is a subject of ongoing debate. Although this type of treatment spares normal brain tissue, an important goal, there is concern that relapse at the margin of the radiotherapy field may increase.

3.8.3 Chemotherapy

The administration of chemotherapy agents to children with brain tumors is a comparatively new treatment development. Until recently, chemotherapy has been considered of little benefit due to the existence of the blood-brain barrier. Recently, however, having established that various degrees of disruption of the blood-brain barrier exist in brain tumors, there has been renewed interest in its role. Significant prejudice did exist regarding the role of chemotherapy and the chemosensitivity of different types of brain tumor, exacerbated by the existence of few randomised and poorly designed trials evaluating the benefits of drug therapy. Chemotherapy is, however, now considered a valuable treatment modality as part of the prospective treatment package facilitating cure. Furthermore, there is now emerging evidence suggesting that chemotherapy is effective in paediatric brain tumor treatment (Taylor, 2002.)

For example, chemotherapy is advantageous in treating those children under 5 years of age who, if diagnosed later in life, would have radiotherapy as a first-line treatment. Multiagent regimens can delay or even obviate the need for radiotherapy and its associated late effects. Likewise, stabilisation of an incompletely resected tumor can be achieved by the use of chemotherapy, allowing second-look surgery.

In addition to management with conventional chemotherapy regimens, children with brain tumors, high-grade gliomas, and medulloblastomas are now being treated with high-dose chemotherapy with stem cell rescue. Intensifying treatment is thought to improve the permeability of the blood-brain barrier, and its role continues to be debated.

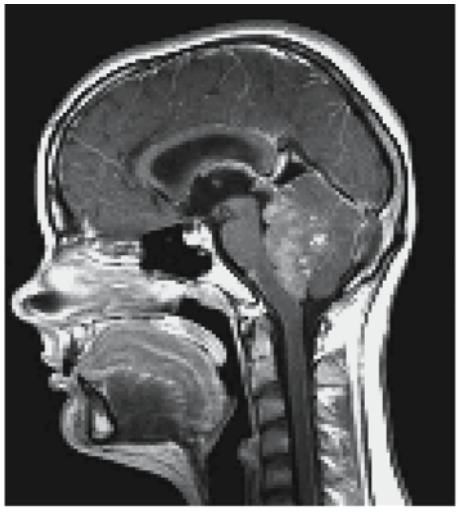
3.9 Prognosis

It is prudent to be wary when discussing survival figures. Percentage figures quoted to families can be misleading because they are often based on the evaluation of treatment strategies that lag behind current practice. Fig. 3.2 demonstrates cumulative survival seen at Birmingham Children's Hospital (BCH), UK.

3.10 Specific Tumors

3.10.1 PNETs/Medulloblastomas

Undifferentiated neuroectodermal tumors of the cerebellum have historically been referred to as medulloblastomas, while tumors of identical histology in the pineal region are diagnosed as pineoblastomas, and cerebral tumors are referred to as primitive neuroectodermal tumors (PNETs). Microscopically, both medulloblastomas and PNETs consist of small round cells with disproportionately large hyperchromatic nuclei. These cells are often clustered into rosettes.



Age at diagnosis	15
Diagnosis	Medulloblastoma
Presenting symptoms	3-4 week of double vision and dizziness Early morning vomiti Reduced conscious level.

Figure 3.3
Craniospinal imaging of medulloblastoma

Medulloblastoma

Epidemiology
- 25 % of paediatric brain tumors
- Most common between 3 and 7 years and in males
- Arises from primitive neuroepithelial cells

Etiology
- Commonly arises in cerebellar vermis
- Invades fourth ventricle with associated hydrocephalus
- Can disseminate via the CSF

Symptoms
- Headache
- Morning vomiting
- Cranial nerve deficits
- Ataxia

Diagnostics
- Craniospinal imaging (Fig. 3.3)
- CSF analysis for free-floating tumor cells
- Bone scan and bone marrow aspiration to detect metastatic spread
- Standard risk: >5 years of age
  - Normal risk: >3 years of age
  - Posterior fossa location
  - Total resection or<1.5 cc of residual disease
  - No dissemination
  - Poor risk: <3 years of age
  - Metastatic disease
  - Subtotal resection (>1.5 cc of residual disease)
  - Non-posterior fossa location (Laurent et al., 1985)

Treatment
- Primary surgery: gross total excision optimal
- Craniospinal radiotherapy + boost to the primary tumor site (optimal dose and mode of administration under investigation) ± chemotherapy
- Children under 5: chemotherapy
- National treatment strategies predominantly seeking to reduce irradiation

Medulloblastoma (continued)

Prognosis

- Nonmetastatic disease: 70–80% overall survival
- Metastatic disease: trials with craniospinal radiotherapy, high-dose chemotherapy, and stem cell rescue are currently being evaluated

Supratentorial PNETs

These are the supratentorial counterpart of medulloblastoma, having the same histological appearance

- Occur mainly <5 years of age
- The majority arise in the cerebral hemispheres/pineal region
- Treatment considerations are similar to medulloblastoma, with survival being lower

Prognosis

Age-related:

- <3 years: Very poor
- 3 years: Site-dependent

3.10.2 Astrocytomas/Glial Tumors

The majority of these tumors are supratentorial and slow-growing and are referred to as low-grade astrocytomas, pilocytic astrocytomas, oligodendrogliomas, mixed gliomas, or gangliogliomas (Shiminski-Maher and Shields, 1995). Less common are malignant gliomas of the supratentorium, i.e. anaplastic astrocytomas and glioblastoma multiforme.

The Kernohan grading system incorporates grade I to grade IV, with I being favourable histology and grade IV being glioblastoma multiforme that carries a fatal outcome.

Anaplastic astrocytomas are histologically recognisable by more frequent mitosis, cellular pleomorphism, and general cellularity of the tumor. Glioblastoma multiforme is diagnosed when areas of necrosis and peculiar cells forms are present.

Cerebellar Astrocytoma

Epidemiology

- Commonly occurs in the first decade of life
- More common in boys

Symptoms

- Midline cerebellar signs

Diagnosis

- History
- Neurological examination
- MRI commonly shows cystic tumor with mural node

Treatment

- Complete surgical removal of the tumor is treatment of choice
- Interval MRI scans to monitor for signs of progression
- Radiotherapy

Prognosis

Over 90% of children with a fully resected pilocytic astrocytoma will survive with only surgical intervention. Those with partially resected diffuse disease who have had radiotherapy have only a 50–60% chance of survival.

Poor prognostic features include

- Diffuse histology
- Incomplete resection
- Brain stem involvement

Supratentorial Astrocytoma

Epidemiology

- Twice as common in boys

Treatment

- Complete surgical removal is optimal
- Radiotherapy is indicated for all than the lowest-grade, completely resected tumors

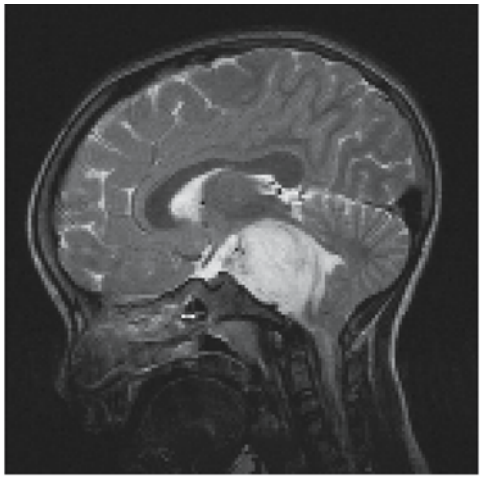
Prognosis

- Varies widely

3.10.3 Malignant Gliomas

Account for 5% of new cases of childhood malignancy each year.

Classified primarily by anatomic location and second by histologic phenotype. For those diagnosed within the supratentorium, treatment consists of optimal surgical excision/radiotherapy and chemotherapy. Despite aggressive treatment strategies, survival in this group of patients remains poor.



Age	5
Diagnosis	Diffuse pontine glioma
Presenting symptoms	3 week history of gradual onset of left sided weakness Headache Increasing difficulty swallowing

Figure 3.4
Diffuse pontine glioma

Brain Stem Glioma

Epidemiology
- Gender incidence equal
- Common presenting age: 5–10 years

Etiology
- Arise in the medulla, pons, midbrain, and cerebral peduncles
- Diffuse pontine gliomas are rapidly infiltrative in nature
- Most commonly found in the pons, with equal distribution of histological varieties
- Low-grade tumors constitute <10% of brain stem tumors

Symptoms
- High-grade disease: short history
  - Multiple cranial nerve palsies
  - Ataxia
  - Hemiparesis
- Low-grade disease: long history
  - Minimal or a focal cranial nerve deficit
  - Raised ICP

Diagnostics
Location, radiological appearance, and clinical features are usually diagnostic (Fig. 3.4)

Treatment
- Treat hydrocephalus
- High-grade disease: steroids to alleviate neurological symptoms in short pulses
  - Radiotherapy is palliative, producing a mean survival of 8–10 months. Chemotherapy and hyperfractionated radiotherapy have failed to make an impact on outcome
- Low-grade disease: surgical debulking
  - Observation
  - Radiotherapy and/or chemotherapy may be indicated

Prognosis
- High-grade disease: median survival 8–10 months

3.10.4 Other High-grade Gliomas

The clinical behaviour of supratentorial and cerebellar gliomas is more difficult to predict on the basis of radiological and clinical characteristics, with prognosis being more related to histologic phenotype and grade. After resection, radiotherapy is the treatment of choice. Long-term survival remains poor, with 40% overall survival for grade III and 10% for grade IV (Lashford, 2002).

Intracranial Ependymoma

Epidemiology
- Paraventricular lesions usually occur in the 1st decade of life
- 50% occurring <5 years of age
- Spinal ependymomas present slightly later

Etiology
- Predominantly arise from ependymal tissue within the ventricular system, most commonly the fourth ventricle
- Can disseminate (more frequently with infratentorial and high grade disease)
- Hydrocephalus common at presentation

Are divided into the following categories:

- Subependymoma (WHO grade I)
- Ependymoma (WHO grade II); variants include cellular, papillary, epithelial, clear cell, and mixed
- Malignant/anaplastic ependymoma (WHO grade III)

Symptoms
Depend on site and extent of disease

Typically
- Neck pain
- Increased ICP
- Cranial nerve deficits
- Ataxia

Diagnostics
- MRI (whole brain and spine) to establish extent of disease
- CSF cytology when possible

Treatment
- Surgery
- Treat hydrocephalus

Adjuvant treatment is age-related:

>5 years of age
- No residual disease or disseminated disease: radiotherapy to the tumor bed
- Residual disease, no disseminated disease: re-resection
  - Radiotherapy (no spinal)
  - Trials are ongoing to determine role of chemotherapy
- CNS disseminated disease: radiotherapy to entire CNS
  - Trials underway looking at role of chemotherapy

<5 years of age
- Chemotherapy
- Second-look surgery

Prognosis
- Overall survival: 40–60% at 5 years
- Good prognostic factors: minimal residual disease post surgery
- Poor prognostic factors: young age
  - Subtotal resection

Craniopharyngiomas

Epidemiology
- 8% of all childhood brain tumors
- Most commonly seen <18 years
- Mean age at diagnosis 8 years

Etiology
- Arise from neural ectoderm and epithelial elements in Rathke's pouch
- Can be located anywhere in the primitive craniopharyngeal duct
- 90% suprasellar, 10% intrasellar
- Benign and slow-growing

Symptoms

Presenting symptoms relate to pressure on adjacent structures:
- Visual fields and acuity defects
- Endocrine dysfunction
- Hydrocephalus is possible

Diagnosis
- History
- MRI scan

Treatment
- Presurgical neuroendocrine and ophthalmic work-up are essential
- Treatment of hydrocephalus
- Complete resection optimal

Prognosis

Although classified as benign, they can result in considerable morbidity.

Problems include
- Endocrine dysfunction
- Diabetes insipidus
- Hypothyroidism
- Growth and sex hormone deficits
- Excessive weight gain
- Visual disturbances
- Neuropsychological dysfunction
- Psychosocial problems

Intracranial germ cell tumors

Germ cell tumors arising intracranially are histologically indistinguishable from the gonadal varieties.

Intracranial germ cell tumors can be divided into two main groups:
- Germinomas: 60% of total number of germ cell tumors
- Nongerminomatous germ cell tumors (NGGCTs; also referred to as secreting germ cell tumors)

Both groups have the potential for CSF dissemination.

Epidemiology
- For all intracranial germ cell tumors there is a male prevalence
- Intracranial germinomas primarily present in the 2nd decade of life
- NGGCTs tend to occur earlier

Etiology
- Germinomas occur predominantly in the suprasellar region
- NGGCTs occur mainly as pineal tumors

Symptoms

Pineal tumors
- Raised ICP is commonly seen
- Headache
- Vomiting

Suprasellar tumors
- Visual disturbances (fields/acuity)
- Diabetes insipidus
- Hypopituitarism
- Headache
- Vomiting

Tumors of the basal ganglia-thalamus area
- Hemiparesis
- Precocious puberty
- Failure of puberty
- Short stature

Intracranial germ cell tumors (continued)

Diagnostics
- Germinoma: MRI and biopsy
- NGGCT: MRI (radiological features are characteristic)
- Serum and CSF levels for AFP and HCG

Treatment
Germinomas
- Highly chemo/radiosensitive tumors
- Surgery has a limited role in their management

Current UK treatment is

- Craniospinal irradiation with boost to the primary tumor site
- Chemotherapy followed by local radiotherapy

NGGCTs
- Chemotherapy has improved rates of cure; nevertheless, local radiotherapy is still considered necessary to achieve cure
- Surgery for difficult residual disease

Prognosis
- Germinomas: 90–100%
- NGGCTs: 60–70%

Visual Pathway Gliomas

Epidemiology
- 75% of isolated optic nerve gliomas occur <10 years
- Peak incidence: 2–6 years
- Occurs in 20% of patients with neurofibromatosis (NF1)

Etiology
- Can present anywhere along optic tracts
- May extend to the pituitary fossa, causing hypopituitarism ,or to the hypothalamus, resulting in precocious puberty
- Hydrocephalus may be present
- Natural history is unpredictable

Symptoms
Symptoms relate to tumor pressure on the optic nerve and adjacent structures and infiltration:

- Decreased visual acuity or fields
- Squint
- Nystagmus
- Precocious puberty

Diagnostics
- MRI
- Neurological examination
- Frequent neuro-ophthalmological testing (see below)

Treatment
- Treat hydrocephalus
- Observation if disease and symptoms are stable (spontaneous regression has been reported)
- Treatment should be considered to stabilise vision
- Surgery has limited role
- <8 years of age + NF1: chemotherapy
- >8 years of age: radiotherapy
- The lack of randomised trials makes it difficult to know whether chemotherapy and radiotherapy make a difference

Prognosis
- Isolated optic nerve tumors have a better prognosis than those that extend along the visual pathway or involve the chiasm
- Children with neurofibromatosis, particularly those who are asymptomatic at diagnosis, have improved prognosis

Neuro-ophthalmological Testing

Visual assessment is frequently used as the critical tool to determine the need for treatment, with deterioration in visual fields and/or acuity indicating the need for intervention. This can be a particular problem with infants and young children as it can be difficult to get consistently accurate results (particularly regarding visual fields). Experience has shown that even in school-age children, results can fluctuate, and it may be unclear whether this fluctuation relates to disease progression or to variable patient compliance.

Germinoma

Comprise 60% of the total number of germ cell tumors

Epidemiology
- Intracranial germinomas primarily present in the 2nd decade of life

Etiology
- Occur predominantly in the suprasellar region

Symptoms
- Visual disturbances (fields/acuity)
- Diabetes insipidus
- Hypopituitarism
- Headache
- Vomiting

Diagnostics
- MRI
- Biopsy

Treatment
- Highly chemo/radiosensitive tumors
- Surgery has a limited role

Current UK Treatment
- Craniospinal irradiation with boost to the primary tumor site
- Chemotherapy followed by local radiotherapy

Prognosis
- 90–100%

Nonsecreting Germ Cell Tumors (NSGCTs)

Epidemiology
- NGGCTs tend to occur earlier

Etiology
- NGGCTs occur mainly as pineal tumors

Symptoms
- Raised ICP is commonly seen
- Headache
- Vomiting

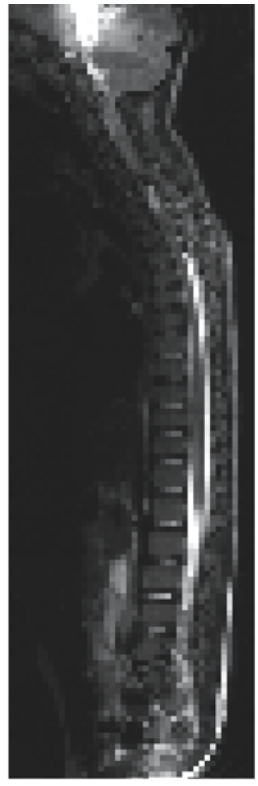
Diagnostics
- MRI (radiological features are characteristic)
- Serum and CSF levels for AFP and HCG

Treatment
- Sensitive to a range of chemotherapy agents
- Chemotherapy has improved rates of cure
- Local radiotherapy is, however, still necessary to achieve cure
- Surgery for difficult residual disease

Prognosis
- 60–70%

Spinal Tumors

Rare in children. Low-grade astrocytomas are usually intramedullary, requiring extensive surgical removal. Radiotherapy and chemotherapy may be required. High-grade astrocytomas of the spine require radiotherapy and, like similar disease in other sites, surgery has little role. Prognosis for spinal ependymoma (Fig. 3.5) is optimal with total surgical excision. Radiotherapy is routine, with residual disease necessitating chemotherapy.



Age	6 years
Diagnosis	Spinal ependymoma
Presenting symptoms	2 month history of intermittent backpain

Figure 3.5
Spinal ependymoma

3.11 Follow-up

Children treated for a brain tumor will require lifelong follow-up care in a specialist centre. Interval MRI scanning and neurological examinations will be important indicators of progress in the early months and years following treatment. Late effects of treatment, such as cognitive deficits and endocrine dysfunction, may only become apparent in subsequent years.

3.12 The Late Effects and Rehabilitation of Survivors

It is clear that children who have been treated for brain tumors may have significant long-term problems relating both to the tumor itself and to treatment (Mostow et al., 1991; Plowman and Pearson, 1997). Radiotherapy, prolonged exposure to raised ICP, and often repeated surgical procedures all incur costs. Side effects are both physical and psychological (Glaser et al., 1997) and include growth problems and weight gain relating to endocrine dysfunction, lack of energy, poor body image, low self-esteem, and decreased overall fitness. Adolescent survivors in particular describe feelings of isolation from their peer group and may lack confidence socially. Problems translate into functional difficulties, such as poor attendance at school, attention deficit, and overt eating disorders. Despite the recognition of how devastating brain tumor treatment can be, this cohort of cancer survivors is rarely included in studies of psychological adjustment during and after treatment (Kline, 1996; Radcliffe et al., 1996). If the overall burden of morbidity is to be addressed for this unique patient group, consideration must to be given to strategies that will facilitate development in both physical and psychological well-being (Glaser et al., 1997). Recent work in the UK suggests that adolescent survivors of brain tumor treatment can benefit psychosocially from a rehabilitation programme targeting their unique needs (Fitzmaurice and Beardsmore, 2003).

3.13 Palliative Care

Palliative care is discussed in detail in chapter 30 of this handbook. It is, however, prudent here to refer to the complexities of symptom control for children with brain tumors. Problems such as steroid dependency, spinal involvement, seizure control, reduced mobility, and speech, language, and swallowing difficulties necessitate the input of palliative care nurses who specialise in the care of these children.

3.14 Future Perspectives/New Innovations

New innovations include the following:

- Boron neutron capture therapy, which is an experimental form of radiotherapy that injects a chemical compound containing boron into the bloodstream, which then concentrates in the brain tumor tissue. Radiotherapy with neutrons is then directed at the cancer, and when the neutrons come into contact with the boron, high-energy radiotherapy is released with low penetrance that spares normal tissue.
- Growth factor inhibitors to prevent the effects of the growth factors that allow a cancer to grow.
- Angiogenesis inhibitors to prevent the formation of new blood vessels that nourish the cancers.
- Immunotherapy to stimulate the body's own immune system to fight the cancer.
- Advanced MR techniques such as MR spectroscopy, diffusion MR, and dynamic contrast-enhanced MR to give noninvasive information on tumor function, i.e. metabolism, relation to white matter, and blood flow.
- Conformal radiotherapy that uses three-dimensional planning. The volume of radiation therapy is irregular and "conforms" to the tumor. Shaped fields of treatment are used, which minimise the amount of normal tissue within the radiotherapy field. This in turn results in a decrease in acute and late morbidity.

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PART II

Anemias

Rosalind Bryant

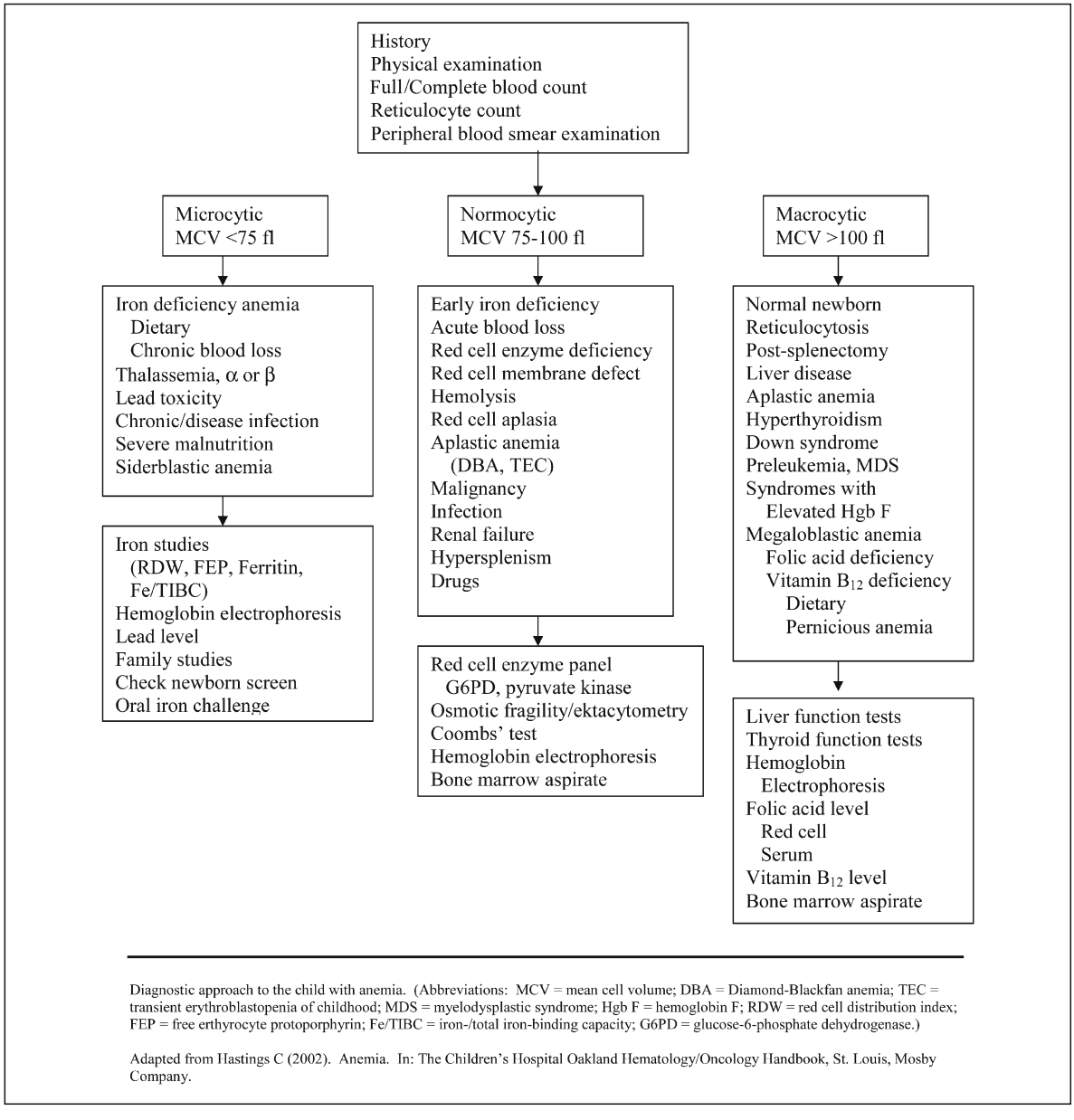
Contents

4.1 Anemia

Anemia is defined as a reduction in red cell mass due to decreased production, increased loss/decreased survival, or increased destruction of red blood cells (RBCs). Because most oxygen is transported by the RBCs to the body tissues, a reduction in the red cell mass causes reduced oxygen supply to body cells. Consequently, anemia is a sign of an underlying pathological process, which is usually discovered during a routine health maintenance visit. The investigation of anemia to determine the underlying diagnosis includes a combination of medical history, family history, physical examination, and the initial laboratory assessment, including the evaluation of the full/complete blood count (FBC/CBC), RBC indices/morphology, reticulocyte count, and the peripheral smear (see Table 4.1). More extensive tests may be needed to verify the diagnosis, such as an iron panel, osmotic fragility, hemoglobin (Hgb) electrophoresis, or even a bone marrow examination (see Fig. 4.1).

Table 4.1. Normal red blood cell values in children (adapted from Hastings, 2002a)

	Hemoglobin (g/dl)		MCV (fl)	
Age	Mean	–2 SD	Mean	–2 SD
Birth (cord blood)	16.5	13.5	108	98
1–3 days (capillary)	18.5	14.5	108	95
1 week	17.5	13.5	107	88
2 weeks	16.5	12.5	105	86
1 month	14.0	10.0	104	85
2 months	11.5	9.0	96	77
3–6 months	11.5	9.5	91	74
0.5–2 years	12.0	10.5	78	70
2–6 years	12.5	11.5	81	75
6–12 years	13.5	11.5	86	77
12–18 years, female	14.0	12.0	90	78
12–18 years, male	14.5	13.0	88	78
18–49 years, female	14.0	12.0	90	80
18–49 years, male	15.5	13.5	90	80



Diagnostic approach to the child with anemia. (Abbreviations: MCV = mean cell volume; DBA = Diamond-Blackfan anemia; TEC = transient erythroblastopenia of childhood; MDS = myelodysplastic syndrome; Hgb F = hemoglobin F; RDW = red cell distribution index; FEP = free erthyrocyte protoporphyrin; Fe/TIBC = iron-/total iron-binding capacity; G6PD = glucose-6-phosphate dehydrogenase.)

Adapted from Hastings C (2002). Anemia. In: The Children's Hospital Oakland Hematology/Oncology Handbook, St. Louis, Mosby Company.

Figure 4.1

Diagnostic approach to the child with anemia. From Wadworth Center, New York State Department of Health. Retrieved 9/13/03 from http://www.wadsworth.org. *From UpToDate webpage. Retrieved 9/17/2003 from www.UpToDate.org

It is important to establish whether the anemia is related to one cell line (i.e., RBCs, white blood cells [WBCs], or platelets) or multiple cell lines (i.e., RBCs, WBCs, and platelets). If multiple cells lines are affected, this may indicate bone marrow production problem (i.e., leukemia, aplastic anemia or metastatic disease). If a single cell line is affected, this usually indicates a peripheral destruction problem such as autoimmune disorders (i.e., immune thrombocytopenic purpura or autoimmune hemolytic anemia).

Anemia is classified into two main categories, which include the morphological and etiological (physiological or functional) basis for the anemia. The mean corpuscular volume (MCV) is the most useful of the RBC indices and is the basis for the morphological category. The morphological category divides the RBC morphology or size into normocytic (normal size RBC), microcytic (smaller than normal RBC), and macrocytic (larger than normal size RBC) anemias (see Fig. 4.1).

These categories are not mutually exclusive for a given anemia because an anemia may present as normocytic and then revert to macrocytic or develop a combination of RBC sizes. The etiological category is divided according to (1) decreased or ineffective production of RBCs, (2) destruction of RBCs, or (3) loss of RBCs. Generally, in the etiological category, there is one basis for the anemia but some anemias may have more than one basis.

Iron deficiency anemia may have more than one basis and more than one morphological presentation (see Fig. 4.1). The usual etiological category for iron deficiency anemia is decreased production of RBCs; however, this anemia may also develop because of an increased loss of RBCs. Iron deficiency is usually morphologically classified as a microcytic anemia, yet early iron deficiency is classified as a normocytic anemia (Fig. 4.1).

Sickle cell hemoglobinopathies represent a group of genetic diseases that are all related to the presence of Hgb S. The most common type of sickle cell disease (SCD) is homozygous Hgb SS, which is morphologically classified as a normocytic anemia when oxygenated but as a macrocytic anemia in the presence of reticulocytosis (an increased number of large immature RBCs). Hgb SS is defined as a protein substitution on the β globin gene that causes destruction of RBC.

Thalassemia is a type of anemia that lacks alpha or beta production and therefore is etiologically classified as ineffective RBC production. Morphologically the thalassemic RBCs are classified as a microcytic anemia.

Hemolytic anemias are divided into intracorpuscular defects (i.e., glucose-6-phosphate dehydrogenase deficiency hereditary spherocytosis) or extracorpuscular defects (i.e., autoimmune hemolytic anemia) that cause RBC destruction. Hemolytic anemia is morphologically classified as normocytic, but if it has more than 20% reticulocytes, it is then classified as macrocytic.

Lastly, aplastic anemia (AA), which is a bone marrow failure syndrome, is divided into inherited (i.e., Fanconi's anemia, Diamond-Blackfan anemia) or acquired anemia (i.e., moderate or severe) characterized by reduced or absent production of RBCs, WBCs, and platelets. Morphologically it is classified as normocytic but most often as macrocytic anemia. The macrocytosis develops because of stress erythropoiesis, which produces erythrocytes with fetal characteristics that tend to be more pronounced in the inherited types of AA (Shimamura and Guinan, 2003).

4.2 Iron Deficiency Anemia

Iron deficiency anemia is defined as a reduction in red cell mass due to decreased production and/or loss of RBCs (see Fig. 4.1). Infants usually have adequate iron stores at birth unless they were born prematurely or maternal iron stores were inadequate. The iron stores of full-term infants gradually deplete in about four months unless replenished with iron-fortified formula or breast milk supplemented with iron.

4.2.1 Epidemiology

Anemia caused by iron deficiency is a major public health problem, affecting 46% of school children globally (United Nations ACC/SCN, 2000). Iron deficiency is the most common form of nutritional deficiency. Its prevalence is highest among young chil-

dren between the ages of 12 months and 3 years and women of childbearing age (particularly adolescent girls and pregnant women).

4.2.2 Etiology

Iron is present in all body cells. Iron balance is maintained between dietary intake (approximately 10% elemental iron is absorbed in the duodenum and jejunum) and iron loss (from sloughing of the skin and mucosal cells). There is no organ that regulates iron excretion (Andrews, 2003). The most common causes of iron deficiency are chronic blood loss and/or inadequate intake of dietary iron during rapid growth periods.

4.2.3 Molecular Genetics

The precise mechanism by which serum iron is loaded onto transferrin (the major protein transporter of iron) as it leaves intestinal epithelial cells or reticuloendothelial cells is unknown. Transferrin binds with the iron (total iron binding capacity = TIBC) and releases the iron into the cell. Once inside the cell, the iron conjugates with free erythrocyte portoporphyrins (FEP or EP) to form heme and binds with the globin protein to form Hgb. The Hgb attracts the oxygen and carries it to body cells for metabolism. The remaining iron is stored as ferritin (soluble protein) or hemosiderin (an insoluble protein complex). Both of these complexes are found in the liver, bone marrow, spleen, and skeletal muscles. Reticuloendothelial cells acquire iron primarily by phagocytosis and breakdown of aging red cells. The iron is then extracted from the heme and returned to the circulation to bind to transferrin and repeat the cycle.

4.2.4 Symptoms/Clinical Signs

Iron deficiency produces a microcytic, hypochromic anemia that impairs tissue oxygen transport to body cells and may cause weakness, fatigue, palpitations, lightheadedness, pallor, lethargy, tachycardia, and tachypnea that may be detected on physical exam and while obtaining a thorough history. Pica, a craving for unusual substances such as starch, clay, toilet paper, and paint chips, may be detected during the history and is frequently associated with iron-deficiency anemia. Adolescents and children less than 36 months are at the highest risk for developing iron deficiency anemia. Severe iron deficiency anemia is associated with impairment of growth and intellectual development and may cause decreased motor activity and social interaction. The lack of iron causes damaged to epithelial cells, which has been associated with gastrointestinal blood loss and/or increase absorption of heavy metals including lead (Andrews, 2003). Therefore iron deficiency may enhance lead absorption and inadvertently cause lead toxicity. Lead is toxic to the bone marrow and affects erythropoiesis by interfering with the heme synthetic pathway in all cells (Andrews, 2003).

4.2.5 Diagnostic Testing

The smear diagnostic of iron deficiency anemia contains microcytic, hypochromic (decreased iron content) RBCs with poikilocytosis (varying red cell shapes), anisocytosis (different red cell sizes) and target cells (which resemble a bull's eye target; see Fig. 4.1). The lead poisoning smear differs from iron deficiency by consisting of coarse basophilic stippling (coarse granules studding the cytoplasm; see Fig. 4.1) with microcytic hypochromic RBCs. In contrast, a chronic disease anemia smear consists primarily of normocytic and normochromic RBCs (see Fig. 4.1) with approximately 20% of microcytic cells.

The iron status of the body can be assessed using several laboratory tests. During mild iron deficiency (Hgb >10 gm/dl) when the stores are depleted, the Hgb may not decrease. Consequently, elevated FEP would be a better screening test for early iron deficiency than Hgb concentration (Mei et al., 2003). The FEP is also elevated in lead poisoning but usually to a greater level than in iron deficiency. Moderate iron deficiency occurs with a decreased Hgb of 7–10 g/dl and decreased MCV compared with the age-matched results. Severe iron deficiency is associated with decreased Hgb (<7 g/dl) and decreased MCV compared with age-matched results (see Table 4.1).

The test most commonly used regardless of whether iron deficiency is mild, moderate, or severe is the Hgb/hematocrit (Hct) concentration. Although Hgb concentration and Hct cannot be used to determine the cause of anemia, if Hgb concentration or Hct increases after a course of therapeutic iron supplementation, the diagnosis of iron deficiency anemia can be made even with mild iron deficiency (Segel et al., 2002a). Other laboratory tests (including decreased reticulocytes, increased RBC distribution width [RDW], decreased serum iron, decreased transferrin saturation, elevated total iron binding capacity [TIBC], positive guaiac, and Hgb electrophoresis) can be used to differentiate iron deficiency anemia from anemia of other causes. Serum ferritin concentration is an early indicator of iron store depletion, yet is also an acute-phase reactant to chronic infection, inflammation, or diseases, which may obscure the results. The MCV is the most useful of the RBC indices and is the basis for the classification of the anemias (Fig. 4.1). A decreased MCV and RBC with increased RDW indicates iron deficiency anemia, whereas a decreased MCV and increased or normal RBC with normal RDW indicates thalassemia minor (Demir et al., 2002).

There are nutritional anemias that affect normal red cell production that must be differentiated from iron deficiency (see Fig. 4.1). Megaloblastic anemia (B_{12} and folate deficiency) may be coupled with iron deficiency anemia. Vitamin B_{12} deficiency may develop in the strict vegetarian diet or the totally breastfed infant. It is treated with cobalamin injections 30 µg/day for 5–10 days, then weaned to 100–200 µg monthly; for adolescents, 100 µg daily for 10–15 days then weaned to 60 µg monthly with the addition of B_{12} dietary sources (Lee et al., 2002). The folic acid dose is 50 µg/day in infants and 1 mg/day for children/adolescents coupled with dietary counseling to promote intake of foods containing folic acid.

4.2.6 Treatment

- Treatment requires the identification of the cause of iron deficiency anemia, whether its due to blood loss from intestinal inflammation/malabsorption, surgery, or medications (e.g., chemotherapy, anticonvulsants) and/or lack of adequate iron intake
- The oral iron dose is 2–6 mg/day elemental iron/kg/day divided bid for child/infant and 60–120 mg/day for adolescents. Iron preparations should be given with vitamin C-fortified juice or with water because vitamin C promotes iron absorption from the gastrointestinal tract. Iron should not be taken with milk, milk products, or antacids because they interfere with iron absorption
- Iron fortified cereal (two or more servings) should be added daily to the diet of the exclusive breastfed full-term infant beginning about 4–6 months after birth
- *Preterm or low birth weight* infants who are exclusively breastfed should take iron drops 2–4 mg/kg/day beginning 2–3 months after birth until age 12 months
- The use of low-iron milk (cow, goat, or soy) should be discouraged until after age 12 months
- The intake of solid foods that are rich in iron should be encouraged in children, along with a decrease in milk consumption to <24 ounces daily
- Dietary counseling regarding the intake of iron-rich foods (e.g., meats, bran, lentils, beans, nuts, and some green leafy vegetables) should be reinforced
- Iron treatment should be continued until iron stores are replenished (approximately 4–6 months of oral iron therapy after Hgb normalizes). Side effects of iron therapy should be explained to the child and parents; these include gastrointestinal discomfort, constipation, bloating, stained teeth (to prevent, give liquid iron with a straw) and dark/black stools

Parenteral iron replacement is

- Used when the patient is unable to ingest oral iron or absorb iron from the gastrointestinal tract
- Available in the United States as iron dextran (elemental iron) and administered as intramuscular (IM) using the z-track technique, or intravenously (IV). The preferable route is intravenous (IV) because the intramuscular injection causes pain and skin discoloration

- Composed of iron dextran and contains 50 mg elemental iron per milliliter. The dose of iron (mg) is calculated by wt (kg) × desired increment Hgb (g/dl) × 2.5 (Hastings, 2002a). A peak reticulocytosis will usually occur 10 days after parenteral iron is given with complete correction of anemia in 3–4 weeks
- Given as a test dose of 12.5–25 mg, with observation of the patient for 30–60 minutes after the dose
- Associated with such adverse effects as anaphylaxis, fever, hypotension, rash, myalgias, and arthralgias
- Not recommended in infants less than 4 months old (Lee et al., 2002)

4.2.7 Transfusion

Depending on whether the child is hemodynamically stable, children with severe anemia (Hgb <5 g/dl) may require red cell transfusion. Common practice is to administer the red cells slowly (2–3 ml/kg/hour) in multiple small volumes (aliquots) with careful monitoring of vital signs and fluid balance to prevent pulmonary edema and congestive heart failure (Glader, 2004).

4.2.8 Erythropoietin (Epotin Alfa, Epogen)

Recombinant human erythropoietin may be used as treatment for mild to moderate anemia to stimulate the proliferation and differentiation of erythroid precursors (Andrews, 2003). The usual subcutaneous dose is 150–300 IU/kg one to three times a week. Sufficient erythroid precursors must be in the bone marrow with adequate iron stores and adequate protein intake for erythropoietin to be effective (Carley, 2003). Common practice is to administer 3 mg/kg/day of supplemental iron concurrently. Erythropoietin has shown efficacy in the treatment of anemia of prematurity and in renal failure and is being investigated as a treatment for transient bone marrow suppression induced by chemotherapy.

4.2.9 Prognosis

Once detected, iron deficiency and other nutritional anemias generally respond positively to supplementation. Follow-up Hgb that fails to show improvement within 4–8 weeks after supplementing with oral iron and dietary iron, or an anemia that recurs despite adequate supplementation warrant, further investigation (Segel et al., 2002). Further investigation may include such disorders as malignancy, copper deficiency, inborn errors of iron metabolism, or other rare disorders.

4.3 Sickle Cell Disease

Sickle cell hemoglobinopathies represent a group of genetic diseases that are all related to the presence of Hgb S. Sickle cell trait is a benign condition that involves approximately 35–45% of Hgb S and the remainder Hgb A. Although complications are rare, they have been described and include an increased incidence of hematuria and hyposthenuria. Vaso-occlusive crisis has also been reported, especially under hypoxic conditions such as shock, strenuous physical activity, and flying in an unpressurized aircraft or at high elevations.

4.3.1 Epidemiology

Sickle cell disease (SCD) has been recognized as a worldwide problem. It is a common hereditary disorder, occurring in 1 in 375 births, with 70,000 cases among African-Americans in the United States. SCD affects a variety of nationalities, including Africans, Hispanics, Arabs, Italians, Native Americans, Caribbeans, Iranians, Turks, and, infrequently, American Caucasians (primarily of Mediterranean descent).

4.3.2 Etiology

Sickle cell disease(SCD) is transmitted as an incomplete autosomal-dominant trait (Karayakin, 2000). When both parents carry the sickle cell trait (heterozygous gene or Hgb AS), there is a 25% chance with each pregnancy of producing an infant with

Table 4.2. Diagnostic tests used in sickle cell disease

Test	Interval
Baseline CBC, differential, and reticulocyte count, pulse oximetry	Each visit
Red cell minor antigen phenotype	Visit at 6 months of age
Hgb electrophoresis	Confirmatory 2–6 months, 2 years of age, and if needed, at 5 years age
Renal and hepatitis function tests, amylase, lipase, LDH, liver function tests, urinalysis	Yearly but more often if abnormal.
Human immunodeficiency virus	Yearly post-transfusion
Blood cultures	If febrile ≥38.5 °C
Transcranial cerebral ultrasonography	Yearly (start at age 2 until 16 years in Hgb SS or comparable sickle hemoglobinopathy
Pulmonary function tests	Age 8 and every 2 years unless abnormal
Electrocardiography/echocardiography	Every 2 years unless abnormal
Abdominal ultrasonography	Age 8–10 years or if symptomatic or
Audiogram	Age 8–10 years or if symptomatic
Plain films, MRI of hips/shoulders	Symptomatic
MRI/angiography of brain as needed	Symptomatic
Neuropsychological testing	Age 6 years and repeat as necessary

SCD (homozygous gene – Hgb SS or heterozygous Hgb S variant). The incidence of the sickle cell trait is about 8 % in African-Americans in the United States, whereas it has been reported to be as 40 % among West Africans.

4.3.3 Molecular Genetics

The molecular defect in Hgb SS occurs due to the substitution of valine for glutamic acid in the sixth position of chromosome 11 of the β-globin chain. The second most common type of SCD is Hgb SC (heterozygous variant) in which the lysine is substituted for the glutamic acid at the sixth position of the β-chain. Other Hgb S variants include a combination of Hgb S trait and β-thalassemia trait, either producing Hgb SB^o thalassemia (no normal β-globin production) or Hgb SB^+ thalassemia (decreased β-globin production). Another frequently seen variant is the combination of Hgb SS with α-thalassemia trait (usually two or three functional α-globin genes).

4.3.4 Symptoms/Clinical Signs

The basic pathophysiology of sickle cell is directly related to the abnormal Hgb S that polymerizes when deoxygenated. Most of the complications of SCD are the result of entanglement and enmeshing of the sticky, rigid, sickle-shaped cells as they block the microcirculation, causing partial to complete vaso-occlusion of vessels. The resultant decreased blood flow to the tissues causes ischemia and infarction which may result in further complications. A thorough history, physical exam, and periodic diagnostic tests tend to identify existing complications (see Table 4.2).

4.3.5 Diagnostic Testing

The following descriptions of peripheral blood smears are correlated with the type of SCD:

- The typical Hgb SS smear contains mild to moderate normochromic, normocytic to macrocytic

Table 4.3. Neonatal hemoglobin patterns (adapted from Hudspeth and Symons, 2002))

Screening phenotype	Confirmed electrophoresis	Possible genotype
FA	Normal newborn pattern	Hgb AA
FAS	Benign sickle cell trait	Hgb AS
FAC	Benign Hgb C trait	Hgb AC
FAA_2	Benign β-thalassemia trait	Hgb AA_2
FS	Fetal and sickle Hgb S	Homozygous Hgb SS or Hgb S/β^o-thalassemia or Hgb S/B^+ thalassemia
FSC	Hgb S and Hgb C	Hgb SC
$FSAA_2$	Heterozygous Hgb S/β^+-thalassemia	Hgb S/β^+ thalassemia
F	Fetal Hgb F or Hgb F with delayed Hgb A appearance	Homozygous β-thalassemia major or homozygous hereditary persistence of fetal Hgb F
FA Barts	Fetal Hgb, Hgb A, and Barts Hgb (ranges 1–2% to 30%)	β-thalassemia silent carrier β-thalassemia trait Hgb H disease
AF	May indicate prior blood transfusion	Retest 4 months post-transfusion

Hemoglobin variants are reported in order of decreasing abundance; for example, FA indicates more fetal than adult Hgb. Repeat blood specimen should be done to confirm original interpretation

cells with sickled cells and increased anisocytosis and poikilocytosis (see Fig. 4.1, plate 8). The average Hgb range is 5–9 g/dl, with an average reticulocytosis 5–>20%

- The Hgb SC smear contains normochromic, normocytic cells with sickle cells, target cells, and spherocytes (see Fig. 4.1, plate 6). The Hgb SC average Hgb range is 9–12 g/dl, with an average reticulocyte count between normal and 10%
- The Hgb S β^o-thalassemia and Hgb SS α-thalassemia smear contains marked microcytosis, and moderate to marked sickle cells with anisocytosis and poikilocytosis. The average Hgb and reticulocytosis are commensurate with Hgb SS
- Hgb S β^+-thalassemia smear contains moderate microcytosis, sickle-shaped cells with anisocytosis and poikilocytosis. The average Hgb is 9–12 g/dl with reticulocytosis 5–10%

The differential diagnoses include disorders such as hereditary spherocytosis (HS), glucose-6-phosphate dehydrogenase (G-6PD), pyruvate kinase, thalassemia, leukemia, and juvenile rheumatoid arthritis, which can all be excluded by obtaining the Hgb electrophoresis (see Table 4.3).

About 2,000 infants with SCD born in the United States are identified by neonatal screening (AAP, 2002). Neonatal screening is included in state screening programs that obtain blood via heel prick to identify primarily sickle and thalassemic hemoglobinopathies (see Table 4.3).

4.3.6 Complications of SCD

The chronic destruction of the RBCs in SCD results in acute and chronic complications; however, this chapter will focus on the acute complications of SCD. Complications of SCD may occur suddenly and can rapidly become severe; therefore, the medical

provider should consult with a hematologist. The most common complication, which is usually not life-threatening, is vaso-occlusive crisis or episode. Other complications that will be discussed are acute sequestration, aplastic crisis, infection, acute chest syndrome, acute abdominal pain, and acute central nervous system events.

4.3.6.1 Vaso-occlusive Crisis/Episode (VOE)

- Definition: Vaso-occlusive episode (VOE) occurs when deoxygenated sticky, rigid sickled-shaped RBCs block microcirculation completely or partially (infarction) causing tissue ischemia or necrosis.
- Signs and symptoms of VOE: Most children with sickle cell anemia experience some degree of acute pain and may express their pain verbally or by crying, grimacing, or maintaining a stoic expression.

  Most of the children are able to describe their severity of pain by using self-reporting methods such as the faces pain scale or the numeric pain scale (see Fig. 4.2). Other behavior indicators may be helpful in the pain assessment of all children, including infants, such as limited movement of a body part, decreased appetite, or increased irritability. The bones and joints are major pain sites, with tenderness, erythema, warmth and swelling frequently present. The initial site of pain in young children and infants is usually the small bones of the hands and feet, called dactylitis or hand/foot syndrome, and may be accompanied by swelling, erythema, and increased warmth. Severe complications may develop after repeated hip/shoulder infarctions (i.e., avascular necrosis of the fibula, femur, or humerus, known as AVN) or repeated skeletal vertebrae infarctions (i.e., lordosis, scoliosis, or kyphosis).

4.3.6.1.1 Diagnostic Test/Differential

A complete blood count, RBC indices, WBC count and differential, reticulocyte count, renal and liver function tests, and, if needed, bone radiographs are usually obtained during severe VOE. The differential includes VOE versus osteomyelitis, which is difficult to differentiate because both are associated with erythema and swelling, low-grade fevers, and joint and bone pain. Osteomyelitis may be excluded by clinical observation, blood cultures, and, occasionally, aspiration of the affected area.

4.3.6.1.2 Treatment

Hydration (oral or intravenous), opioids and NSAIDS (oral or intravenous), incentive spirometry, adjuvant therapy, rest, heat and massage to painful areas, and exercises or diversional activities (school work, friends, meditation, guided imagery) are useful interventions for VOE. Whether VOE is managed by patient-controlled analgesia (PCA) or orally, the pain assessment treatment should be closely monitored to achieve optimal pain management (Jacob et al., 2003).

4.3.6.2 Acute Sequestration Crisis

- Definition: Acute splenic sequestration is a sudden, rapid enlargement of the spleen with trapping of a considerable portion of the red cell mass, leading to acute exacerbation of anemia that drops the Hgb level 2 g/dl or more below baseline
- Signs and symptoms: Sudden weakness, dyspnea, rapidly distending abdomen (spleen or liver enlarging), abdominal pain, lethargy, irritability, pallor, vomiting, headache, tachycardia, and tachypnea are manifestations of acute sequestration. Severe cases of splenic sequestration may lead to circulatory collapse (shock) and death
- Diagnostic tests: Hct may drop to half the patient's usual value. Brisk reticulocytosis with increased nucleated red cells, moderate to severe thrombocytopenia, and leukopenia may be present on the smear
- Treatment: Volume expansion with a fluid bolus and oxygen supplementation are needed immediately. Immediate yet slow transfusion of small aliquots packed RBCs (PRBCs) to restore intravascular volume and oxygen-carrying capacity may be instituted. Prevention of further recurrences is achieved by elective splenectomy after the first major or second minor episode of sequestration, preferably in children >2 years of age

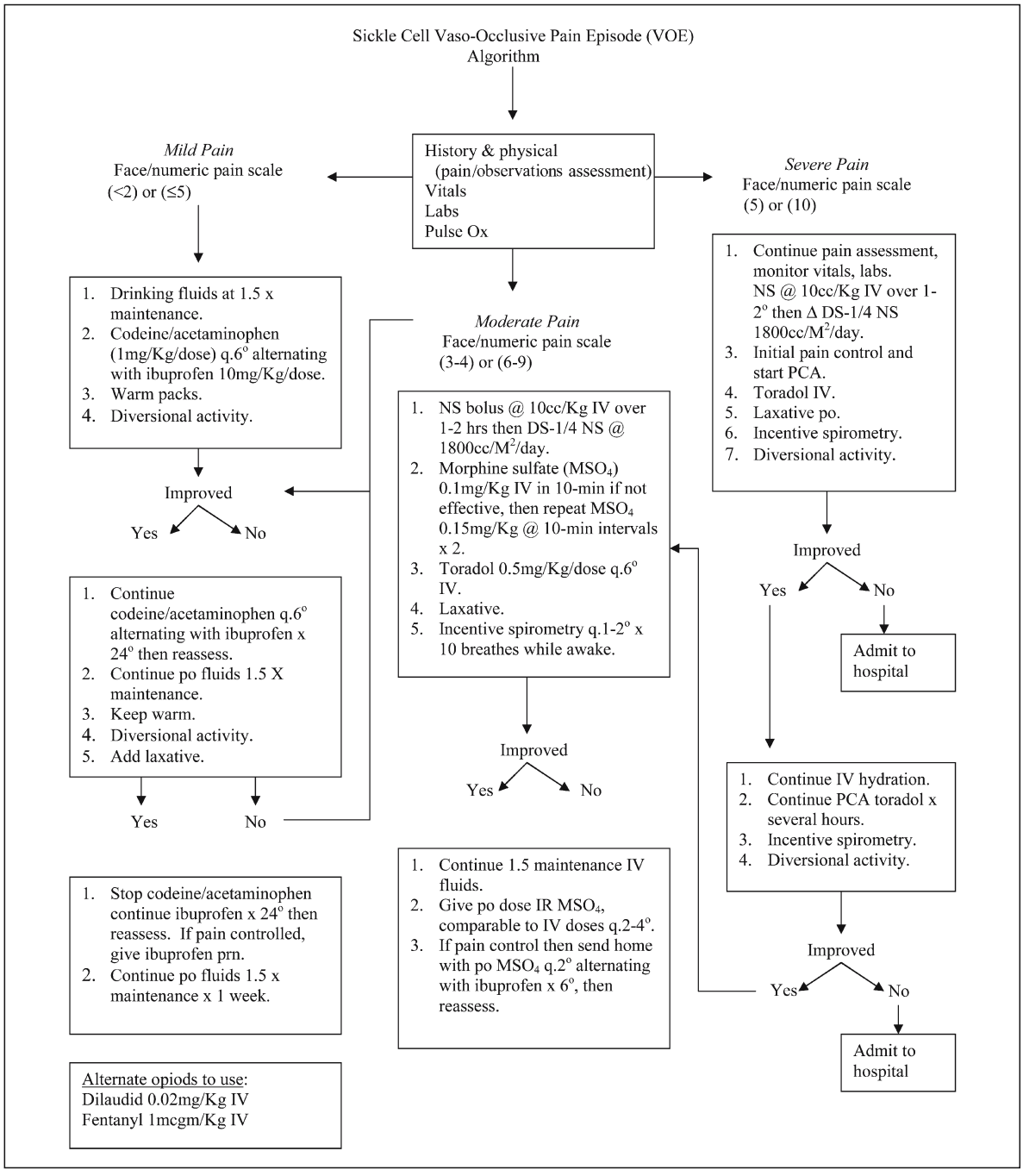


Figure 4.2

Sickle cell vaso-occlusive pain episode (VOE) algorithm

- Education: Parents should be taught splenic palpation and educated about recognizing the signs and symptoms of splenic sequestration to aid in identifying initial episodes of acute sequestration and preventing recurrent life-threatening episodes

4.3.6.3 Aplastic Crisis

- Definition: Temporary cessation of bone marrow activity due to suppression by viral or bacterial infection, which causes a drop in hematocrit without reticulocytosis. Parvovirus B19 is the most common cause of aplastic crisis (Hastings, 2002c).
- Signs/symptoms: Increased pallor, icteric sclera, lethargy, irritability, headache, bone pain, weakness, nausea and vomiting, and dark urine are all manifestations of aplastic crisis.
- Diagnostic tests: The hematocrit decreases as much as 10–15% per day with no compensatory reticulocytosis.
- Treatment: Isolation precautions with oxygen supplementation may be instituted depending on the type of infection. Transfusion of PRBCs may be instituted to prevent congestive heart failure. Folic acid should be given in the recovery phase.

4.3.6.4 Infection

- Definition: The major risk factor for increased susceptibility to infection is splenic dysfunction. The ability of the spleen to clear particles from the intravascular space and provide antibody synthesis is impaired in the patient with SCD. Insidious progressive fibrosis of the spleen (autosplenectomy) occurs in the Hgb SS child, usually by the age of 6 years. Children with splenic dysfunction are 300–600 times more likely to develop overwhelming pneumococcal or *Haemophilus influenzae* sepsis and meningitis than are children without splenic dysfunction. (Karayalcin, 2000).
- Signs/symptoms: Toxic-appearing children with fever ≥38.5 °C, chills, lethargy, irritability, tachypnea, tachycardia, hypoxia, and history of prior sepsis should be treated promptly with parenteral antibiotics after obtaining a blood culture
- Diagnostic tests: A CBC with differential; C-reactive protein (CRP); cultures of blood, throat, and urine; chest x-ray; and oxygen saturation should be obtained. If the chest x-ray shows an infiltrate, a sputum culture should be obtained if possible. After a blood culture is obtained, the child should be started on parenteral antibiotics and admitted to the hospital. If osteomyelitis is suspected, an orthopedics specialist should be consulted regarding needle aspiration and culture of the suspected bone site
- Treatment: A child with SCD and fever ≥38.5 °C must be considered an emergency because of the increased risk for overwhelming sepsis resulting from splenic dysfunction

Children with SCD who have a low risk of sepsis (no high-risk factors, see Table 4.4) and who are older than 2 years of age are treated with outpatient management in several comprehensive sickle cell centers in the United States with close follow-up care (i.e., return clinic visits or telephone contact) (Williams et al., 1996). After blood cultures are obtained, these children are given long-acting parenteral antibiotics such as ceftriaxone (50–75 mg/kg/dose, with maximum dose of 2 g). If the child is allergic to cephalosporin, clindamycin 15 mg/kg is given with a maximum dose of 600 mg. These children are monitored in the clinic or emergency center for several hours prior to being discharged home with close follow-up care (Jakubik and Thompson, 2000).

A SCD child without high-risk factors (see Table 4.4) is discharged on oral antibiotics for 3 days while awaiting blood culture results. The child is prescribed cefprozil 30 mg/kg/day divided twice daily or Pediazole 40 mg/kg/day three times daily if cephalosporin-allergic. Any positive culture obtained from a child being managed on an outpatient basis requires immediate hospitalization and reevaluation of the child. High-risk factors that prevent children from being eligible for outpatient management are listed in Table 4.4.

Table 4.4. Recommended hospital management for the high-risk sickle cell disease patient

Clinically ill-appearing or toxic-looking
Signs of cardiovascular and/or pulmonary compromise
Age less than 12 months
Temperature ≥40 °C
White blood count <5,000/mm^3 or >30,000/mm^3
Platelet count <100,000
Hemoglobin <5 g/dl or reticulocyte count <4%
Dehydration with poor oral fluid intake
Pulmonary infiltrate and/or previous history of acute chest syndrome
Pulse oximetry <92% or 3% below baseline
Central venous catheter
Prior splenectomy
History of previous sepsis
Evidence of acute SCD complications
Prior noncompliance or evidence of inability to comply with outpatient follow-up

- Prevention

  Morbidity and mortality rates have decreased dramatically since the advent of established newborn screening programs (United States), widespread penicillin prophylaxis, timely administration of immunizations, and parental/caregiver education. Parental/caregiver education is aimed at reducing bacterial septicemia and includes such interventions as immediate medical evaluation of febrile illness (≥38.5 °C), twice-daily administration of prophylactic antibiotic, and compliance with immunization schedules. In addition to standard immunizations, the SCD patient should also receives the 23-valent pneumococcal vaccine, the meningococcal vaccine at 2 years of age with boosters at 5 and 10 years of age, and recommended yearly influenza virus vaccines at 6 months and older. Prophylactic penicillin is started at 2 months of age and continued until 5–6 years of age and indefinitely in the child with a history of pneumococcal sepsis (Jakubik and Thompson, 2000). Currently, the child with SCD should be placed on prophylactic penicillin 125 mg twice daily starting at 2 months of age and increased to 250 mg twice daily at 3 years of age. If the child is allergic to penicillin, then erythromycin is substituted at a dosage of 125 mg twice daily starting at 2 months and increased to 250 mg twice daily at 3 years of age (AAP, 2002). Benzathinepenicillin G 300,000 units intramuscularly may be given monthly to the SCD patient with gastrointestinal dysfunction or who is noncompliant with oral antibiotic prophylaxis.

4.3.6.5 Acute Chest Syndrome

- Definition: Acute chest syndrome (ACS) is a common cause of morbidity and mortality in children with SCD and is characterized by fever, chest pain, and a new infiltrate on chest x-ray
- Signs/symptoms: Clinical manifestations of ACS may include extremity pain, rib or sternal pain, abdominal and chest pain, cough, dyspnea, fever (≥38.5 °C), back pain, tachypnea, wheezing, hypoxia (paO_2 <75 mmHg or 3 points of transcutaneous oxygen saturation below baseline) SOB, dyspnea, dullness (palpation), or normal auscultation (Rackoff et al., 1993)
- Diagnostic tests: Chest radiography may be clear initially but should be repeated with increasing respiratory distress or hypoxia. Blood cultures, CBC, differential, reticulocyte count, type and crossmatch, and, if possible, sputum cultures and arterial blood gases should be obtained. It is extremely difficult to differentiate between ACS and pneumonia. The most common organism causing ACS or pneumonia is pneumococcus, followed by *Salmonella, Klebsiella, Haemophilus influenzae,* and *Mycoplasma pneumoniae* and viruses. Martin and Buonomo (1997) reported that pulmonary infiltrates resolve quickly and dramatically in children with ACS not associated with infection, whereas those with infection have a prolonged radiographic course.
- Treatment: Patients may deteriorate rapidly, with progression to pulmonary failure and death; therefore, all patients with ACS should be treated in the hospital. Early recognition of respiratory

Table 4.5. Treatment for acute chest syndrome

Administer oxygen if hypoxic
Monitor continuous pulse oximetry
Encourage incentive spirometry
Administer empiric antibiotics
Cephalosporin (e.g., cefuroxime 150 mg/kg/day divided every 8 h)
Macrolide (e.g., azithromycin 10 mg/kg/day with 5 mg/kg/day on days 2–5)
Administer maintenance intravenous fluids (1,500 cc/m^2/day)
Administer analgesic for pain (see algorithm)
Administer PRBCs if hemoglobin <10 g/dl
Simple transfusion (10 cc/kg)
Exchange transfusion

distress (cough, chest pain, hypoxia with or without fever) and aggressive treatment with oxygen if hypoxic, analgesics (see Fig. 4.2), empiric antibiotics, maintenance intravenous hydration (1,500 cc/m^2/day), bronchodilators, respiratory treatments, and simple RBC transfusion (10 cc/kg) or exchange transfusion are instituted immediately (see Table 4.5). Oxygen treatment is monitored closely by pulse oximetry with an ongoing respiratory assessment of the patient. Incentive spirometry is encouraged every hour while awake, with administered analgesics (see Fig. 4.2) to prevent hypoventilation. After a blood culture is obtained, empiric antibiotics are given, which include a cephalosporin such as cefuroxime 150 mg/kg/day divided every 8 hours (maximum dose 2 g) to eradicate possible pathogens such as pneumococcus. A macrolide such as azithromycin 10 mg/kg on day 1 (maximum dose 500 mg) followed by 5 mg/kg/day on days 2–5 (maximum 250 mg) is given to treat possible pathogens such as *Mycoplasma* or *Chlamydia* (see Table 4.5). Hydration at maintenance rate (1,500 cc/m^2/day) is administered to avoid overhydration (i.e., pulmonary edema). Bronchodilators such as albuterol aerosols are a common treatment that is given every 4–6 hours to decrease airway hyperreactivity. Transfusion of PRBCs as a simple transfusion of 10 cc/kg may be given. However, if the child's respiratory status continues to deteriorate (worsening hypoxia, anemia, chest pain, and worsening infiltrates on chest radiograph), then an exchange transfusion should be performed (see Table 4.5)

- Preventive: Risk factors related to ACS include young age (2–4 years), lower concentration of Hgb F, higher steady-state Hgb concentration, and higher steady-state WBC count should be assessed to prevent development of ACS (Quinn and Buchanan, 1999). Strategies to prevent ACS also include aggressive pain management and the use of incentive spirometry to prevent hypoventilation. Transfusion is generally recommended to decrease the concentration of Hgb S and can theoretically prevent ACS (Quinn and Buchanan, 1999). Hydroxyurea is an agent that is used to upregulate Hgb F and decrease viscosity and sickling of RBC, which decreases the development of ACS. Stem cell transplant is a therapy only available to limited number of donors but is a known cure of SCD (Quinn and Buchanan, 1999).

4.3.6.6 Acute Abdominal Pain

- Definition: The etiology of acute abdominal pain is unknown, although mesenteric sickling and vertebral disease with nerve root compression have been suggested (Dover and Platt, 2003).
- Signs/symptoms: Guarding, tenderness, rebound, distended abdomen, fever, jaundice, right upper quadrant pain, constipation are all manifestations of acute abdominal pain.
- Diagnostic tests: CBC with differential, reticulocyte count, liver enzymes, pancreatic enzymes, hepatitis panel, urinalysis, chest/abdominal films including upright views for perforated viscus, ultrasonography, or biliary scans may be instituted to determine the etiology of the acute abdominal pain. Differential diagnoses may include ACS, ileus, pneumonia, constipation, surgical abdomen, pancreatitis, urinary tract infection, intrahepatic sickling, and cholecystitis.

- Treatment: Maintenance intravenous fluids (1,500 cc/m^2/day), analgesics (see Fig. 4.2), laxatives if constipated, and a surgical consult to rule out surgical abdomen (i.e., appendicitis) are instituted as soon as possible.

4.3.6.7 Acute Central Nervous System Event

- Definition: An acute central nervous system (CNS) event develops from chronically injured cerebral vessels in which the lumen is narrowed or completely obliterated by sickled erythrocytes, causing acute cerebral infarction. Approximately 7–10% of SCD (primarily Hgb SS) patients develop acute cerebral vascular occlusion or stroke, most often between the ages of 2 and 10 years. Cerebral infarction may occur as an isolated event or in combination with such disorders as pneumonia, aplastic crisis, viral illness, painful crisis, priapism, and dehydration
- Signs/symptoms: Sudden and persistent headache, hemiparesis, hemiplegia, seizures, coma, speech defects, gait dysfunction, visual disturbances, and altered mentation are all manifestations of a cerebral infarction
- Diagnostic test: The initial diagnostic test done is a computed tomography scan (CT scan) of the brain without contrast to identify intracerebral hemorrhage, abscess, tumor, or any other pathology that could explain the symptoms. Magnetic resonance imaging (MRI) and angiography aid in assessment of infarcts associated with obstruction of intracranial vessels (i.e., the anterior and/or middle cerebral vessels), and are usually ordered as soon as possible after CT
- Treatment: The standard approach to treating a patient with acute cerebral infarction is exchange transfusion followed by placement on a maintenance monthly transfusion program. The transfusion program is designed to keep Hgb S <30%, which lowers reoccurrence of stroke to 10%. In untreated persons, the mortality rate is approximately 20%, with about 70% of the patients experiencing a recurrence within 3 years of the initial cerebral vascular event (Dover and Platt, 2003). Maintenance monthly transfusion programs are designed to suppress the production of sickle cells, thereby reducing the chance of recurrent strokes. However, the multiple transfusions may cause complications such as hemochromatosis, alloimmunization, and infections such as hepatitis, HIV, and West Nile virus. Hemochromatosis is unavoidable with prolong transfusions and is treated with parenteral desferrioxamine (see section 4.4.6.2)
- Preventive: Transcranial Doppler (TCD) ultrasonography predicts increase risk of stroke in children who have increased flow velocity (>200 cm/sec) in major cerebral arteries that is demonstrated on two consecutive TCDs (Segel et al. 2002; Dover and Platt, 2003). TCDs are done yearly to aid in identifying children who are at high risk for developing stroke or who have asymptomatic brain disease. Neuropsychological testing identifies deficits in intelligence quotient (IQ), which has been instrumental in combination with MRI in discovering SCD children with silent infarcts. Silent infarcts are damage to the brain associated with impaired cognitive abilities secondary to sickling in cerebral vessels without any physical neurological deficits (Dover and Platt, 2003). Recommendations for treatment of silent infarcts may include either hydroxyurea therapy, transfusion program, stem cell transplant or close observation. The best treatment option for silent infarcts is unknown, but the transfusion program is usually recommended as the initial option

4.3.7 Preparation for Surgery

Most children with SCD tolerate chronic anemia well and only require transfusions for severe complications such as splenic sequestration, CNS infarction/ischemia/hemorrhage, aplastic crisis, severe ACS, and preparation for surgery. Because sickling of RBCs is increased during hypoxic periods, it may be necessary to transfuse the patient prior to the surgical procedure that requires anesthesia. If the SCD patient has a history of major complications (i.e., ACS, CNS infarctions, multiple VOE), preoperative transfusion consists of multiple transfusions every 3–4 weeks or exchange transfusion to obtain a goal of <30% Hgb S prior to surgery. Exchange transfusion is used to re-

move sickled cells and replace them with normal cells without increasing blood viscosity. However, if the SCD patient has not sustained any major complications, the patient is transfused to a Hgb of 10 g/dl irrespective of the percentage of Hgb S. A simple transfusion is usually performed 2–5 days prior to the surgical procedure.

4.3.7.1 Hydroxyurea Therapy

- Hydroxyurea (HU) is an S-phase-specific cytotoxic agent that upregulates Hgb F, which interferes with Hgb S polymerization and increases the lifespan of the sickled RBCs. HU decreases blood viscosity, has an increase affinity for oxygen, and releases a byproduct known as nitrous oxide that acts as a potent vasodilator. Therefore, hydroxyurea will aid in decreasing sickling and promoting unobstructed circulation.
- Children with SCD complications such as repeated ACS, or severe VOE are offered HU therapy
- The initial dose of HU is 15–20 mg/kg/day and is escalated to 35 mg/kg/day while monitoring the platelet, neutrophil, and reticulocyte counts (Powars, 2001; Steinberg et. al., 2003)
- Side effects of HU include neutropenia, leukopenia, reticulocytopenia, elevated liver enzymes, nausea and vomiting, hyperpigmentation, alopecia, and a potential mutagenic and carcinogenic effect. All patients of childbearing age must agree to a contraceptive plan prior to starting HU

4.3.8 Prognosis

SCD patients without a history of major SCD complications will have lifespans 10–15 years shorter than the individual without SCD. In an observational study, Miller and colleagues (2002) found a significant correlation between SCD course and adverse outcomes later in childhood in children who developed dactylitis before age 1 year and had a steady-state of Hgb <7 g/dl and leukocytosis in the absence of infection at an early age of 1 year.

4.3.9 Future Perspectives

- Because HU therapy is a lifetime therapy, more studies are needed to determine its long-term side effects in the SCD patient (Steinberg et. al, 2003). Studies to determine long-term additive effects of HU and erythropoietin on Hgb F production are being researched
- A limited number of umbilical cord blood transplants have been successful; therefore, this area is being researched as a possible cure for SCD
- There are studies focused on gene manipulation to correct the SCD defect and cure the disease

4.4 Thalassemia

Thalassemia is a group of inherited heterogeneous anemias associated with the absence or decreased production of normal Hgb (Table 4.6). Two broad classifications of thalassemia are the alpha (α)- and beta (β)-thalassemias, which contain deficits in α- and β-thal globin production, respectively.

4.4.1 Alpha (α)-Thalassemia

4.4.1.1 Epidemiology

The majority of α-thalassemias are located in Southeast Asia, Malaysia, and Southern China.

4.4.1.2 Etiology

The deficit in α-globin production is due to deletion or mutation of one or more of the four α-globin genes located on chromosome 16.

4.4.1.3 Molecular Genetics

More than 30 different mutations affecting α-globin genes have been described (Nathan and Orkin, 2003).

- Silent carrier has three functional α-globin genes (-α/αα)
- α-thalassemia trait has two functional α-globin genes (-α/α or αα/–)

Table 4.6. Classification of thalassemias (adapted from Nathan and Orkin, 2003)

Syndrome	Phenotypes	Clinical findings
Silent carrier (α and β-thalassemia)	α: 1–2% Hgb Barts or 1–2% Hgb CS at birth only β: Hgb A_z ≥3.5 80–90% of Hgb F / Hgb A	Normal or slightly microcytic RBCs; no signs or symptoms
Thalassemia trait (α- and β-thalassemia trait)	α: 5–10% Hgb Barts or 1–2% Hgb CS at birth 80–90% Hgb F / Hgb A β: Hgb A_z ≥3.5 80–90% Hgb F / Hgb A	Mild anemia to elevated RBCs; microcytosis/hypochromic
Hgb H or Hgb CS (constant spring)	α: 5–30% Hgb Barts or 1–2% Hgb CS at birth Hgb F 70–90%	Microcytic/hypochromic anemia (7–10 g/dl); pale, icteric, jaundiced; hepatosplenomegaly
Hydrops fetalis	α: combination of Hgb Barts, Hgb H. Hgb Portland usually death in utero	Severe anemia (6.2 g/dl average Hgb); pale, icteric, edematous due to congestive heart failure; hepatosplenomegaly
Thalassemia intermedia	Hgb A_z 2–7% Hgb F 20–100% Hgb A 0–80% (depends on phenotype)	Anemia (6–10 g/dl) microcytosis hypochromic; pale, icteric, and with hepatosplenomegaly; rarely transfused
Thalassemia major	Hgb Az 2–7% Hgb F 20–100% Hgb A 0–80% (depends on phenotype)	Anemia average 6 g/dl with microcytic/hypochromia; pale, failure to thrive, frontal bossing, thalassemic facies, short stature, hepatosplenomegaly; transfusion-dependent

- Hemoglobin H disease has one functional α-globin gene (–/-α) and a Hgb H variant = Hgb constant spring (–/$\alpha^{cs}\alpha$)
- Hydrops fetalis has no functional α-globin gene (–/–)

4.4.2 Beta (β)-Thalassemia (Cooley Anemia)

4.4.2.1 Epidemiology

β-thalassemia mutations are found worldwide in regions including the Mediterranean, Africa, Southeast Asia, India, Italy, Greece, Spain, and North America, but are uncommon in Northern Europe, Korea, and Japan.

4.4.2.2 Etiology

The deficit in β-globin production is due to mutation of the β-globin genes located on chromosome 11.

4.4.2.3 Molecular Genetics

Within the β-globin gene, 170 mutations affect the transcription, translation of β-globin messenger, and stability of β-globin product (Olivieri, 1999; Nathan and Orkin, 2003). β-thalassemia includes four clinical syndromes (see Table 4.6):

- Silent carrier, which is asymptomatic
- β-thalassemia trait with mild anemia
- Thalassemia intermedia with moderate anemia and usually no transfusion requirement
- Thalassemia major with severe anemia and transfusion-dependent

4.4.3 Diagnostic Testing

Thalassemia testing can be confirmed with Hgb electrophoresis and family studies, or if necessary, DNA analysis can be used to make a definitive diagnosis. In

most states of the United States, screening for hemoglobinopathies is performed on newborn infants. Anemias in children who were not screened as newborns but present with hypochromic, microcytic anemias must be differentiated from iron deficiency (see formulas below).

Prenatal diagnosis of α-thalassemia may be done by testing the amniotic fluid or obtaining chorionic villus sampling if there is a suspicion for α-thal trait or a family history of hydrops fetalis. Differentiation between thalassemia trait and iron deficiency can be calculated based on the following formulas:

Formulas for differentiation of thalassemia trait from iron deficiency (adapted from Nathan and Orkin, 2003, p 881)

	Thalassemia trait	Iron deficiency
Mentzer index (655) MCV/RBC	<13	>13
Shine and Lal (665) (MCV)2 × MCH	<1,530	>1,530
England and Fraser (666) (MCV–RBC–[5 × Hb])–8.4	Negative values	Positive values

4.4.4 Treatment

Supportive therapy includes supplementation with folic acid, avoidance of oxidant drugs and iron salts, prompt treatment of infectious episodes, and judicious use of transfusions. β-thalassemia major patients require regular transfusions to sustain life. Thalassemia intermedia patients are able to maintain a Hgb concentration of 6–10 g/dl without transfusions except during periods of infection, surgery, or other stressors. Splenectomy may be considered in Hgb H, thalassemia intermedia, and β-thalassemia major if hypersplenism is present with leukopenia, thrombocytopenia, worsening anemia, or the development of increased requirement for transfusion (>200 ml PRBCs/kg/year). Splenectomy reduces the transfusion requirements by eliminating the organ causing the trapping of the RBCs. At least 2 weeks prior to splenectomy, polyvalent pneumococcal and meningococcal vaccines should be given. Following splenectomy, prophylactic penicillin 250 mg PO bid is implemented until adulthood. The importance of seeking medical assistance when the splenectomized patient is febrile is emphasized with parents and child to reduce the risk of developing overwhelming infection. Complications of ongoing transfusion therapy regimens are assessed (see section 4.2.7) including hemosiderosis.

4.4.5 Treatment of Hemosiderosis (Iron Overload)

Hemosiderosis is the accumulation of iron in organ tissues such as liver, pancreas, and joints as a result of chronic RBC transfusion therapy received by patients with β-thalassemia, Hgb H, sickle cell (i.e., those with a history of cerebrovascular accident, ACS, retractable vaso-occlusive crisis) or bone marrow failure syndromes (Olivieri, 1999; Beare, 2002). Hemosiderosis may also develop in the frequently transfused patient receiving myelosuppressive chemotherapy and/or radiation treatments. Chronic hemolysis and increased gut absorption of iron can also result in hemosiderosis. Exchange transfusion, phlebotomy, and chelation therapy are the only methods to manage transfusion-related iron overload at present.

4.4.6 Chelation Therapy

The objective of chelation therapy is to remove excess intracellular iron and bind free extracellular iron.

4.4.6.1 Initiation of Chelation Therapy

- Liver biopsy is the most accurate measurement of iron load, so if liver iron is 7 mg/g/dry weight or higher, then chelation should be started
- Ferritin level is helpful but not reliable because it is an acute phase reactant. Ferritin levels >1,000 µg/ml in steady state, then start chelation
- Cumulative transfusions of 120 ml or more PRBCs/kg/year promote hemosiderosis

4.4.6.2 Chelation Regimens

- Desferrioxamine is a complex hydroxylamine with a remarkable affinity to iron
- Desferrioxamine enters cells, chelates iron, returns iron to serum, and excretes the iron via kidney, liver, and skin
- Desferrioxamine 20–50 mg/kg/8–12 hours nightly × 5–6 days weekly
- Desferrioxamine by the IV route accelerates the rate of iron removal
- Supplemental oral ascorbic acid 100 mg daily PO enhances the urinary excretion of iron, particularly in vitamin C-deficient patients

4.4.6.3 Complications of Desferrioxamine

- Local erythema at the infusion site characterized by multiple subcutaneous nodules may be suppressed by including 5–10 mg hydrocortisone in the desferrioxamine solution
- Ototoxicity is a complication of desferrioxamine therefore a hearing test should be done every 6–12 months
- Ocular toxicity is a complication of desferrioxamine; therefore, the eyes should be examined every 6–12 months
- Noncompliance is an ongoing problem particularly with adolescent patients or parents who dread doing the desferrioxamine subcutaneous injections
- Do not administer desferrioxamine during infection or fever because the mobilization of iron aids in bacterial growth, particularly *Yersinia enterocolitica*

4.4.7 Clinical Advances (Hemosiderosis)

MRI of the liver is being studied to determine whether the imaging-measured iron content is comparable to a liver biopsy result, thereby providing a noninvasive means of measuring iron accumulation in the body. Another recent advance is an oral chelator known as deferiprone (L1 or 1,2-dimethyl-3-hydroxy) that has been used in Europe since 1999 in chelating iron in the thalassemia major patient. In July 2003, a new drug application was filed with the U.S. Food and Drug Administration for deferiprone. It is hoped that deferiprone will be available for use by the year 2005.

4.4.8 Prognosis

Bone marrow transplants from HLA-identified donors have been successfully performed worldwide on patients with severe β-thalassemia. A marked increase in survival to the fifth decade of life in the well-managed β-thalassemia patient is seen in developed countries.

4.4.9 Follow-up

All thalassemic β major patients should have 3-month interval appointments with the hematologist medical provider to manage therapies and side effects involving hemochromatosis, vision, hearing, enlarged organs, and dental side effects. Other thalassemic patients (β-intermedia, Hgb H) are usually seen every 6 months provided the patients have not developed any severe complications.

4.4.10 Future Perspectives

Institution of bone marrow transplantation with unrelated phenotypically matched donors and in utero transplantation are being investigated. Development of transduction methods and vectors to transfer genes and correct the genetic defect are being researched.

4.5 Hemolytic Anemia

Hemolytic anemias comprise a group of disorders that cause destruction of RBCs. The reduced RBCs survival may occur as result of intracorpuscular defects due to defective intracellular enzymes (i.e., glucose-6-phosphate dehydrogenase deficiency or pyruvate kinase deficiency) or abnormal membrane structural proteins as in hereditary spherocytosis (HS). The RBC survival is also affected by the extracorpuscular defect of autoimmune hemolytic anemia (AIHA).

4.5.1 Hereditary Spherocytosis (HS)

Hereditary spherocytosis (HS) is the most common congenital RBC membrane disorder. HS is characterized by a deficiency or abnormality of the RBC membrane protein spectrin, one of the major skeletal cell membrane proteins. The HS RBCs are repeatedly trapped by the splenic sinusoids, which causes damage and destruction to the spherocytes.

4.5.1.1 Epidemiology

HS is a common inherited hemolytic anemia, with an estimated incidence in Northern Europe of 1–2 in 5,000 individuals.

4.5.1.2 Etiology

Primary molecular defects in HS reside in membrane skeletal proteins and is a common inherited hemolytic anemia. Approximately 5–10 % of cases of HS are considered new mutations.

4.5.1.3 Molecular Genetics

Microscopically, HS cells show fewer spectrin filaments interconnecting spectrin/actin/protein to junctional complexes, but overall skeletal architecture is preserved except in the most severe forms of HS (Gallagher and Lux, 2003). Typically, HS is associated with approximately 70 % dominant and 20 % recessive inheritance. The membrane protein defects cause instability of the spectrin, which results in membrane instability, loss of surface area, and abnormal permeability, with the average lifespan of the red cell being 90 days.

4.5.1.4 Symptoms/Clinical Signs

A thorough history and physical may elicit a family history of neonatal hyperbilirubinemia, gallstones, splenomegaly or splenectomy, and intermittent jaundice that typically presents in infancy but may present at any age. Anemia is the most frequent presenting complaint, accompanied with reticulocytosis and manifested primarily by pallor, intermittent jaundice, and splenomegaly. Mild to marked jaundice may be present depending on the rate of hemolysis and the ability of the liver to conjugate and excrete indirect hyperbilirubinemia.

4.5.1.5 Diagnostic Testing

Spherocytes are dense, round, and hyperchromic, and lack central pallor on peripheral blood smear (see Fig. 4.1, plate 7). The laboratory findings of HS vary according to the severity and clinical classification. The trait may have a normal Hgb and normal to slightly elevated reticulocyte count (see Fig. 4.1, plate 5). Mild HS Hgb can be 11–15 g/dl, but with an elevated reticulocyte count can be 3–8 %. In moderate to moderately severe HS, the Hgb is 8–12 g/dl to 6–8 g/dl, respectively, with elevated reticulocyte counts above 8 %. Severe HS has a Hgb <6 mg/dl and a reticulocyte count >10. The majority of children with HS are classified as mild to moderate anemia.

Other laboratory findings include anemia (mild to severe) depending upon the HS classification, reticulocyte count, and increased osmotic fragility test (the most sensitive test for diagnosing HS). The spherocytes have a decreased surface area to volume ratio, and when placed in the hypotonic solution, the HS cells lose membrane surface area more readily because their membranes are leaky and unstable, resulting in an increase osmotic fragility test.

The MCV (mean corpuscular volume) is decreased except during reticulocytosis. The red cell distribution width (RDW) is elevated due to the presence of microspheres in proportion to the degree of hemolysis. The Coombs' test is negative, which excludes AIHA. Several other diagnostic tests used to detect HS include the acidified glycerol lysis test, hypertonic cryohemolysis test, and the autohemolysis test. HS must be differentiated from such disorders as AIHA, G-6PD, pyruvate kinase deficiency, elliptocytosis, and pyropoikilocytosis.

4.5.1.6 Treatment

- Because dietary intake of folic acid is inadequate for the increased needs of the erythroid HS bone marrow, the patient routinely receives folic acid 1 mg/day orally to prevent megaloblastic crisis

- The parents and child are instructed regarding signs and symptoms of hemolysis and hypersplenism, such as increased pallor, fatigue, abdominal pain, enlarging spleen, jaundice, and dark urine. The family and child are instructed to avoid trauma to the spleen area and are shown how to monitor spleen size
- If splenectomy becomes necessary, it is delayed until the child is 5 or 6 because the increased risk of postsplenic sepsis is very high in infancy and early childhood. The child should have pneumococcal and meningococcal vaccines at least 2 weeks prior to splenectomy. Prior to splenectomy, an abdominal ultrasonography should be done to determine spleen size and the presence of any accessory spleens and/or cholelithiasis
- After splenectomy, the child should receive prophylactic penicillin therapy 250 mg PO bid until adulthood

4.5.1.7 Prognosis

Splenectomy laparoscopically eliminates hemolysis but exposes the patient to life-long risk for lethal infections. Platelet counts tend to increase to $>1{,}000\times10^9$/l immediately after splenectomy but will usually decrease over several weeks without any intervention. Penicillin-resistant strains of *S. pneumoniae* have developed, but the use of prophylactic penicillin supersedes this complication because of the increase risk of life-threatening infections.

4.5.1.8 Follow-up

Yearly follow-up is needed for CBC and liver panel and to reinforce penicillin prophylaxis. The splenectomized HS patient should seek medical attention immediately for febrile illness. Healthcare providers should reinforce with the parents and patient that although the hemolysis is eradicated, the HS still exists.

4.5.1.9 Future Perspectives

Management of HS by subtotal splenectomy has shown beneficial results in a small cohort of patients by decreasing hemolysis and maintaining phagocytic function of the spleen (Baden-Meunier et al., 2001).

4.5.2 Autoimmune Hemolytic Anemia (AIHA)

A condition that develops from the interaction between erythrocytes and the immune system is known as autoimmune hemolytic anemia (AIHA). The most common types are AIHA that is composed of warm-reactive autoantibody, usually immunoglobulin (IgG), that binds with the erythrocyte antigen at 37 °C, or cold-reactive autoantibody, usually IgM, that binds to erythrocytes below 37 °C (Ware, 2003). These autoantibodies are recognized by the macrophages, which leads to intravascular destruction of the erythrocyte.

4.5.2.1 Epidemiology

AIHA is estimated to occur at an annual incidence of 1 in 80,000 persons of any age, race, or nationality.

4.5.2.2 Etiology

Children tend to develop AIHA after a recent viral illness or systemic illness because of the development of autoantibodies. The autoantibodies bind to the erythrocyte surface membrane, which results in premature red cell destruction, primarily in the spleen.

4.5.2.3 Molecular Genetics

The antierythrocyte antibodies that develop in most patients with AIHA represent a polyclonal B-lymphocyte response that is poorly understood. Case reports suggest there is an association between AIHA and certain immune response genes.

4.5.2.4 Symptoms/Clinical Signs

Many patients present with signs and symptoms of anemia, such as pallor, weakness, fatigue and lightheadedness, with a compensated cardiovascular aspect. Occasionally, the patient develops jaundice, due to accelerated erythrocyte destruction, and dark urine, reflecting intravascular hemolysis. A thorough history must be obtained, including questions regarding medications and the possibility of underlying systemic illness such as any history of newborn jaundice, gallstones, splenomegaly/splenectomy, or

episodes of dark urine or yellow sclera. The patient may have a palpable spleen and liver, with tachycardia or a systolic flow murmur manifested on physical exam.

4.5.2.5 Diagnostic Testing

Peripheral blood smear is very useful in establishing the diagnosis of AIHA. It contains numerous small spherocytes, occasional teardrop shapes or schistocytes, polychromasia (common finding), and reticulocytes (see Fig. 4.1, plates 4 and 5). Bone marrow aspiration is not mandatory but may be helpful to exclude a malignant process, myelodysplasia, or bone marrow failure syndrome. The bone marrow reveals erythroid hyperplasia with myeloid/erythroid ratio.

Elevated lactate dehydrogenase and aspirate aminotransferase levels reflect the release of intraerythrocyte enzymes; in contrast, other hepatic enzymes should not be elevated in AIHA. The serum haptoglobin level is typically low because it acts as a scavenger for free plasma Hgb, but haptoglobin is an acute phase reactant and is not synthesized well in infants. The unconjugated bilirubin is elevated and reflects accelerated erythrocyte destruction. The most useful laboratory test is the direct antiglobulin test (DAT or Coombs' test), which identifies antibodies and complement components on the surface of circulating erythrocytes.

The differential diagnosis includes hereditary spherocytosis, which may be excluded by performing the osmotic fragility test. Other rare disorders such as clostridial sepsis, Wilson's disease, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, transient erythroblastopenia of childhood, or acquired aplastic anemia are excluded by performing a DAT.

4.5.2.6 Treatment

If the patient has a severe anemia or a decreasing Hgb concentration, then therapy should be instituted. Therapy should begin with close observation, and corticosteroid therapy with the judicial use of erythrocyte transfusions. The corticosteroids are widely accepted first-line therapy. Corticosteroids inhibit the Fc receptor-mediated clearance of sensitized erythrocytes and also inhibit autoantibody synthesis. Corticosteroids, prescribed as 1–2 mg/kg of methylprednisolone IV q.6° × 24–72 hours, and then oral prednisone 2 mg/kg/day divided three times daily, are given until clinically stable. The prednisone is tapered over 1–3 months based on steroid concentration, reticulocyte count, and DAT.

The second line of therapy includes intravenous immunoglobulin therapy, with a systemic benefit at high doses of 5 g/kg/× 5 days, and may be accompanied by plasma exchange transfusion. Exchange transfusion is reasonable with the large IgM antibodies, which are removed by plasmapheresis, whereas the IgG autoantibodies in the extravascular spaces respond better to splenectomy. Transfusion of RBCs is difficult in the AIHA patient due to difficulty in obtaining compatible erythrocytes. The transfusion may result in severe hemolysis, so the transfusion is started at a slow rate, checking both plasma and urine for free Hgb. Other therapeutic modalities include cyclosporin A (suppresses cellular immunity), vinblastine (decrease autoantibody production), danazol (decreased IgG production), azathioprine, and cyclophosphamide (both interfere with autoantibody synthesis).

Splenectomy may be considered late in the disease; it removes the major site of autoantibody production, with a response in about 80 % of patients. These children should receive pneumococcal/meningococcal immunizations at least 2 weeks prior to splenectomy. Post-splenectomy patients should seek medical attention immediately if they develop fever >38.5 °C and should take penicillin or erythromycin (if allergic to penicillin) prophylaxis due to the possibility of sepsis.

4.5.2.7 Prognosis

There is a good prognosis for the majority of children who experience the acute self-limiting disease, with a mortality rate less than 10 %.

4.5.2.8 Future Perspectives

Rituximab appears to be a promising new treatment for refractory AIHA. Rituximab is a humanized murine monoclonal antibody directed against the human CD20 antigen, which is present only on B lymphocytes (Ware, 2003). A small study treated four chronic AIHA children with Rituximab even though two had prior splenectomies and all were dependent on high-dose steroids and refractory to other immunosuppressive therapy. All four patients became transfusion-independent and were weaned completely off prednisone after being treated with Rituximab, with few reactions.

4.5.3 Glucose-6-phosphate dehydrogenase deficiency (G-6PD)

G-6PD is the most common red cell enzyme deficiency. Because the gene for G-6PD is usually located on the X chromosome, males are either fully deficient or of normal phenotype (Perkins, 2001). However, females can be deficient fully, heterozygous (trait), or of normal phenotype (Lanzkowsky, 2000).

4.5.3.1 Epidemiology

G-6PD deficiency is a worldwide gender-linked red cell enzyme deficiency. The highest incidence is in Africans, African-Americans, Mediterraneans, Native Americans, Southeast Asians, and Sephardic Jews.

4.5.3.2 Etiology

G-6PD variants may be due to deletions or point mutations affecting transcription and processing or the primary structure. Therefore, G-6PD deficiency may not only be caused by mutations in the coding region and a decrease number of normal molecules but also by changes in the primary structure by affecting the catalytic function or by decreasing stability of the protein, or both (Luzzatto H, 2003).

4.5.3.3 Molecular Genetics

Since cloning of the G-6PD gene, nearly all the G-6PD variants possess a single amino acid replacement, which is caused by a single missense point mutation (Luzzatto, 2003). After exposure to an oxidative agent (see Table 4.7), the Hgb and other proteins are oxi-

Table 4.7. Hemolytic oxidants associated with g-6pd deficiency (adapted from Luzzatto, 2003)

Analgesics and antipyretics
Acetanilide
Acetylsalicylic acid (large doses)
Para-aminosalicylic acid
Acetophenetidin (phenacetin)
Nitrofurans
Nitrofurazone
Nitrofurantoin
Furaltadone
Furazolidone
Antimalarials
Pentaquine
Pamaquine
Primaquine
Quinocide
Chloroquine
Pyrimethamine
Plasmoquine
Sulfones
Thiazolsulfone
Diaminodiphenylsulfone
Sulfoxone sodium
Sulfonamides
Sulfanilamide
Sulfamethoxazole
Sulfacetamide
Sulfapyridine
Sulfadiazine
Sulfisoxazole
Sulfathiazole
Sulfacetamide
Miscellaneous
Naphthalene (mothballs)
Methylene blue
Chloramphenicol
Probenecid
Quinidine
Fava beans
Phenylhydrazine
Nalidixic acid
Infections
Diabetic acidosis

dized. The RBC destruction starts hemolyzing the oldest RBCs with the least G-6PD, and then progresses toward younger RBCs and the denatured Hgb precipitates, causing irreversible damage to the membrane, and the red cells lyse.

4.5.3.4 Symptoms/Clinical Signs

A thorough history must be obtained, including the possible precipitant of the acute event. A child with G-6PD deficiency is hematologically normal most of the time until hemolysis occurs secondary to an oxidant (see Table 4.7). Within 24–48 hours after exposure to an oxidant, the child may develop fever (38 °C), nausea, abdominal pain, diarrhea, dark-colored urine, jaundice, pallor, tachycardia, splenomegaly, and possibly hepatomegaly.

4.5.3.5 Diagnostic Testing

The peripheral smear shows moderate to severe normocytic, normochromic anemia, with marked anisocytosis, poikilocytosis, and reticulocytosis with inclusion bodies (Heinz bodies) (see Fig. 4.1, plates 4 and 5). The diagnosis is confirmed by quantitative enzyme assay in reticulocyte-poor red cells or by testing RBCs after reticulocytosis resolves. Other labs that support the G-6PD diagnosis include a reduced haptoglobin, elevated WBCs (predominance of granulocytes), elevated unconjugated bilirubin with normal liver enzymes. Urine is positive for blood (free Hgb).

Studies using polymerase chain reaction (PCR) may identify the abnormal gene as well as the biochemical abnormality (Perkins, 2001). Direct antiglobulin test will be negative in G-6PD and will exclude antibody-mediated red cell destruction. Other disorders to exclude from the differential include blackwater fever (malarial infection), paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria and mismatched blood transfusion (ABO mismatch).

4.5.3.6 Treatment

Treatment depends on the extent of the acute hemolysis. Supportive care during the acute event may require transfusion and must definitely include counseling regarding prevention of future events. Healthcare providers should reinforce to the parents and child the need to avoid the list of oxidants that can possibly trigger a hemolysis (see Table 4.7). For those individuals undergoing chronic hemolysis, dietary supplementation with folic acid (1 mg tab/day) is recommended (Hastings, 2002b).

4.5.3.7 Prognosis

The prognosis is good provided the patient avoids exposure to the oxidants.

4.6 Bone Marrow Failure Syndromes

Bone marrow failure syndromes are a reduction in the effective production of mature erythrocytes, granulocytes, and platelets by the bone marrow, causing pancytopenia. The bone marrow failure syndromes encompass aplastic anemia (AA), Fanconi's anemia, paroxysmal nocturnal hemoglobinuria, Shwachman-Diamond syndrome, dyskeratosis congenita, Diamond-Blackfan syndrome and many other disorders. This section will focus on AA, which is divided into acquired and inherited classifications.

4.6.1 Aplastic Anemia

Aplastic anemia (AA), a bone marrow failure disorder may be acquired or inherited. It is characterized by a reduced or absent production of blood cells in the bone marrow and peripheral blood, causing a decrease of two or more cell lines (i.e., RBCs, WBCs and platelets).

4.6.1.1 Acquired Aplastic Anemia

Aplastic anemia results from an immunologically mediated, tissue-specific, organ-destructive mechanism.

4.6.1.1.1 Epidemiology

An annual incidence of AA was established in European studies as 2 per million per year. The highest mortalities were in Japan, Thailand, and Northern Ireland, with an incidence two or three times higher than in European countries and the United States.

4.6.1.1.2 Etiology

Causative factors of acquired AA include toxins, medications, insecticides, immunologic disorders, irradiation, chemotherapy, and infections (i.e., HIV, CMV, parvovirus, hepatitis); however, most causes are unknown (70% idiopathic). Myelosuppressive drugs such as chemotherapy, antibiotics, insecticides, benzene compounds, and other medications cause dose-related marrow suppression by damaging the DNA and decreasing numbers of progenitors. Radiation injures DNA in the actively replicating progenitor cells, which also causes AA.

4.6.1.1.3 Molecular Genetics

Acquired AA is divided into severe and moderate aplastic anemia. Moderate aplastic anemia has normal to increased cellular marrow with at least two of the following present: granulocyte count >500/µl, platelet count >20 K/µl, and reticulocyte count >1%. Severe aplastic anemia has an aplastic marrow and at least two of the following present: granulocyte count <500/µl, platelet count <20 K/µl, and reticulocyte count <1%.

4.6.1.1.4 Symptoms/Clinical Signs

A detailed history, including medications, infections, radiation exposure, and any family history of aplastic anemia, should be obtained with a thorough physical examination. Thrombocytopenia and hemorrhagic manifestations are usually the first symptoms and are manifested by petechiae, ecchymoses, epistaxis, or oral mucosal bleeding. Neutropenia causes oral ulcerations, bacterial infections, and fever, which are rarely present early in AA. Erythropenia, manifested by pallor, fatigue, headache, and tachycardia, tends to be a late sign since red cells live approximately 120 days compared with platelets that live only 10 days and neutrophils that live 6–12 hours.

4.6.1.1.5 Diagnostic Testing

Blood counts are depressed, and blood smear displays a paucity of platelets, leukocytes, and normal to macrocytic red cells with decreased reticulocytes. Increased fetal Hgb (Hgb F) and red cell I antigen may be present secondary to stress hematopoiesis. Bone marrow examination must be done by obtaining an aspirate and biopsy, which demonstrates the conversion of red bone marrow to yellow fatty marrow. There are decreased numbers of blood and marrow progenitor cells due to a microenvironment that fails to support hematopoiesis.

Laboratory findings include the following:

- Normocytic, normochromic anemia with reticulocytopenia, leukopenia, and thrombocytopenia observed on smear
- Slightly to moderately elevated fetal Hgb noted on Hgb electrophoresis
- Bone marrow denotes marked depression or absence of hematopoietic cells and replacement by fatty tissue containing reticulum cells, lymphocytes, plasma cells, and usually tissue mast cells. Bone marrow biopsy is done to exclude granulomas, myelofibrosis, or leukemia, and a bone marrow chromosomal analysis is done to exclude Fanconi's anemia and myelodysplastic syndromes
- Diepoxybutane test (DEB) is performed on peripheral blood to exclude Fanconi's anemia
- Sugar-water test, Ham test and flow cytometry are done to exclude paroxysmal nocturnal hemoglobinuria (PNH)
- Liver function chemistries are done to exclude hepatitis
- Renal function chemistries are done to exclude renal disease
- Viral serology testing: hepatitis A,B,C antibody panel, Epstein-Barr virus antibody panel, parvovirus B19 IgG and IgM antibodies, varicella antibody titer, and cytomegalovirus antibody titer are done to determine etiology
- Quantitative immunoglobulins, C_3, C_4 and complement and antinuclear antibody (ANA), total hemolytic complement (CH50), and Coombs' test are done to exclude systemic diseases

- HLA typing of the patient and nuclear family is done to determine if bone marrow transplantation match is available
- Blood group typing is performed on the patient for possible transfusion
- Clotting profile including prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen is done to determine any clotting dysfunction

Differential diagnosis for pancytopenia is extensive and includes myelodysplastic syndromes, preleukemias, leukemias, paroxysmal nocturnal hemoglobinuria, myelofibrosis, and some lymphomas. Pancytopenia may occur secondary to systemic diseases such as systemic lupus erythematosus, hypersplenism, vitamin B_{12} or folate deficiencies, alcohol abuse, anorexia nervosa or starvation, and infections such as Sarcoidosis and Legionnaires' disease.

4.6.1.1.6 Treatment

Bone marrow transplant with HLA-matched sibling is the treatment of choice. If no HLA-matched sibling is available and the following indicators are present: bone marrow cellularity <30 % with at least two of the following findings: absolute neutrophil count <500/mm^3, platelet count <20 K/mm^3, reticulocyte count <1 %, then institute the following immunosuppressive therapy:

- Antilymphocyte globulin (ALG) or antithymocyte globulin (ATG), which are similar products from either horses or rabbits and mixed with human thoracic duct lymphocytes or thymocytes. ALG and ATG preparations contain mixtures of antibodies to lymphocytes and are immunosuppressive and cytotoxic (T-cell depletion). The recommended dose is 40 mg/kg/day × 4 days. The typical adverse reactions to ATG are thrombocytopenia, headache, myalgia, arthralgia, chills, fever, and serum sickness approximately 7–10 days following ATG administration
- Methylprednisolone given as IV boluses on days 1–4 at 10 mg/kg/day, then changed to an oral steroid such as prednisone 1 mg/kg/d until day 30 in order to prevent serum sickness. The toxicities associated with steroids are hypertension, hyperglycemia, increased susceptibility to fungal infection, potassium wasting, and fluid retention
- Cyclosporine is a specific T-cell inhibitor with a recommended oral dose of 15 mg/kg/day in children to maintain blood trough levels 100–250 µg/ml. Toxic effects from cyclosporine include hypertension, azotemia, hirsutism, gingival hypertrophy, and increased serum creatinine levels
- Hematopoietic growth factors (G-CSF) have shown promise in increasing neutrophil counts. G-CSF are administered subcutaneously at 5–10 µg/kg/day; side effects include fever, chills, headache, and bone pain
- Androgens (i.e., methyltestosterone, oxymetholone) no longer have a primary role in management of aplastic anemia unless the therapies discussed above are unsuccessful. The androgens increase erythropoietin production and stimulate erythroid stem cells. The oral dose is 2–5 mg/kg/day with side effects such as masculinization (hirsutism, deepening voice, genitalia enlargement), acne, nausea, weight gain, and liver dysfunction

4.6.1.1.7 Supportive Treatment

- Blood product support should be used sparingly while the family is HLA-typed
- Thrombocytopenic precautions should be implemented:
  - Promptly report signs and symptoms of bleeding (i.e., excessive bruising/petechiae, oral purpura, melena, prolonged epistaxis or gingival bleeding or hematuria)
  - Avoid contact sports or rough activities (i.e., football, soccer, wrestling, bicycle riding, skating, diving, tree climbing, trampolines)
  - Provide a safe environment to prevent trauma (use side rails, gates, helmets, and knee pads and avoid rectal manipulation, including with thermometers, suppositories, and enemas).
  - Avoid oral mucosa trauma (use soft toothbrushes and avoid dental floss, electric tooth brush and sharp food items)
  - Add stool softeners and increase fiber and fluids in the diet to prevent constipation

4.6.1.1.8 Prognosis

With immunosuppressive therapies or bone marrow transplant, the long-term survival for patients with aplastic anemia has improved to 80%. In the European International Marrow Unrelated Search and Transplant trial, the survival rate from an unrelated donor was about one-half after conventional transplantation, due to a high rate of graft rejection or failure.

4.6.1.2 Inherited Aplastic Anemia

The most common inherited aplastic anemia is Fanconi's anemia (FA) though several others are apart of the category (including Diamond-Blackfan anemia, dyskeratosis congenita, and Shwachman-Diamond syndrome). This section will discuss Fanconi's anemia.

4.6.1.2.1 Epidemiology

All races and ethnic groups have been reported, including American Caucasians, African-Americans, Asians, and Native Americans. The heterozygote frequency may be 1/300 in the United States and in Europe and 1/100 in South African (Alter, 2003).

4.6.1.2.2 Etiology

The incidence is difficult to ascertain. Approximately 25% of childhood aplastic anemia occurs in the presence of known marrow failure genes.

4.6.1.2.3 Molecular Genetics

FA is an autosomal recessive trait with about 10–20% of families having consanguineous marriages (Shende, 2000). There are limited data suggesting a defective gene in FA stem cells.

4.6.1.2.4 Symptoms/Clinical Signs

A detailed history should be obtained that includes toxin and radiation exposure, medications, and any family history of aplastic anemia, and a physical examination done that focuses on identification of any congenital anomalies. Hemorrhagic manifestations such as petechiae ecchymoses, epistaxis, and bleeding of oral mucosa are initially observed. Other signs and symptoms such as pallor, fatigue, headache, tachycardia, or infection are also seen.

Classic anomalies are seen in 75% of FA patients and include short stature, absent thumbs or radii, microcephaly, café au lait spots, skin hyperpigmentation, a broad nasal base, epicanthal folds, micrognathia, hyperreflexia, hypogenitalism, strabismus, ptosis, nystagmus, abnormalities of the ears, deafness, mental retardation, and renal and cardiac anomalies.

4.6.1.2.5 Diagnostic Testing

FBC/CBC with RBC indices, WBC count and differential, platelet count, and reticulocyte count should be obtained. Thrombocytopenia and leukopenia develop before pancytopenia, but severe aplastic anemia develops in most cases. Examination of blood smear shows macrocytic red cells with mild poikilocytosis, anisocytosis, decreased platelets and leukocytes. The bone marrow is a hypocellular fatty bone marrow with decreased myeloid and erythroid precursors and megakaryocytes. Prenatal diagnosis with chorionic villus biopsy and amniotic fluid cell cultures of FA can be made early in the pregnancy. The following labs and tests are usually obtained:

- ANA and DNA binding titer, Coombs' test, rheumatoid factor, liver function tests
- Viral serology: HIV; EBV; parvovirus; hepatitis A, B, C; PCR for virus
- Serum vitamin B_{12} and serum folate levels
- Bone marrow aspirate and biopsy
- Cytogenetic studies on blood lymphocytes (i.e., diepoxybutane (DEB) to diagnose FA)
- Cytogenetic studies on bone marrow to exclude FA
- Acid Ham test and sugar-water test to exclude PNH
- Skeletal x-rays, intravenous pyelogram, chest x-ray to determine congenital anomalies

FA may be differentiated between thrombocytopenia with absent radii (TAR), amegakaryocytic thrombocytopenic purpura, acquired aplastic anemia, and leukemia with a hypoplastic marrow by obtaining the above diagnostic test.

4.6.1.2.6 Treatment

Supportive care includes adherence to thrombocytopenic precautions (see section 4.6.1.1.7). Transfusion of PRBCs and/or platelets, growth factors (G-CSF) for neutropenia, erythropoietin, and e-aminocaproic acid (0.1 mg/kg/dose every 6 hours orally) may be instituted. Antibiotic and antifungal treatment should be used when clinically indicated. A patient without a matched sibling should be treated with androgens, usually oxymetholone 2–5 mg/kg/day. The side effects of androgens are listed in section 4.6.1.1.6. Blood counts, liver function tests, and periodic bone marrow biopsy (to monitor for the development of myelodysplastic syndrome and leukemia) are needed to monitor the patient.

4.6.1.2.7 Prognosis

The prognosis is poor, with projected survival between 20 and 30 years unless the patient receives HLA-matched nonaffected sibling bone marrow, which offers >70% survival. Almost 6% of FA patients develop myelodysplastic syndrome (dysmyelopoiesis and abnormal megakaryocytes), and almost 10% develop acute myeloid leukemia.

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Neutropenia

Cara Simon

Contents

5.1 Epidemiology

Neutropenia is a condition of inadequate numbers of granulocytes. The absolute neutrophil count (ANC) is calculated by multiplying the white blood cell (WBC) count by the total number of bands plus segmented (mature) neutrophils:

$$\text{ANC} = \text{WBC} \times \%\ \text{neutrophils (bands + segmented forms)}$$

Normal neutrophil counts vary by age and race. Newborn infants usually have an elevated ANC for the first few days of life (range 4.5–13.2 $\times 10^3/\text{mm}^3$). Certain populations of blacks and Yemenite Jews will have normally lower WBCs and ANC (men 3.36±1.55 $\times 10^3/\text{mm}^3$; women 3.13±1.47 $\times 10^3/\text{mm}^3$) (Baehner and Miller, 1995). Neutropenia is categorized as mild, moderate, or severe, based upon the level of the ANC (Table 5.1). The risk of infection increases as the ANC decreases. Patients with severe neutropenia, especially those with an ANC $<200/\text{mm}^3$, are at significant risk for infection.

Table 5.1. Categories of neutropenia

Category of neutropenia	ANC (mm^3)	Risk of infection
None	>1,500	None
Mild neutropenia	1,000–500	No significant risk of infection
Moderate neutropenia	500–1,000	Some risk of infection
Severe neutropenia	<500	Significant risk of infection

5.2 Etiology

Neutropenia results from four basic mechanisms: decreased production of granulocytes, ineffective granulopoiesis, a shift of circulating granulocytes to the vascular epithelium or tissue pools, or enhanced peripheral destruction. Confirmation of one of these mechanisms is difficult to obtain outside of the research laboratory. Therefore, classification of neutropenia is often based on whether the neutropenia is acquired or congenital.

The most common causes of acquired neutropenia are infection, drugs, and immune disorders. Neutropenia can result from bacterial (typhoid, paratyphoid, tuberculosis, brucellosis), viral (HIV, Epstein-Barr virus [EBV], hepatitis A and B, respiratory syncytial virus [RSV]), measles, rubella, varicella), and rickettsial infections. In most cases, neutropenia that results from infection, especially viral infections, is short-lived and rarely results in serious secondary infections. Congenital neutropenia is rare and may be associated with severe recurrent infections. Congenital neutropenia has been associated with mutations in the neutrophil elastase gene (Table 5.2).

Drug induced neutropenia is the second most common cause of neutropenia. The drugs at the highest risk of producing severe neutropenia are clozapine, the thionamides, and sulfasalazine (Table 5.3).

Table 5.2. Classification of neutropenias

	Infection
Acquired	Collagen vascular diseases Complement activation Drug-induced neutropenia Autoimmune Isoimmune neutropenia Transfusion reaction Chronic benign neutropenia Pure white cell aplasia Hypersplenism Nutritional deficiency Bone marrow disorders (neutropenia usually not isolated)
Congenital	Severe infantile agranulocytosis (Kostmann's syndrome) Shwachman-Diamond-Oski syndrome Myelokathexis/neutropenia with tetraploid leukocytes Cyclic neutropenia Chediak-Higashi syndrome Reticular dysgenesis Dyskeratosis congenita

Table 5.3. Common medications that cause neutropenia

Drug Group	Examples
Antibiotics	Chloramphenicol Cephalosporins Penicillins Sulfonamides Trimethoprim-sulfamethoxazole Macrolides Vancomycin
Anticonvulsants	Phenytoin Valproic acid Carbamazepine Ethosuximide
Anti-inflammatory agents	Sulfasalazine Nonsteroidal anti-inflammatory drugs Gold salts Phenylbutazone
Cardiovascular agents	Antiarrhythmic agents ACE inhibitors Propranolol Dipyridamole Digoxin Ticlopidine
Psychotropic agents	Clozapine Phenothiazines Tricyclic antidepressants Meprobamate
Antithyroid agents (thionamides)	Methimazole Carbimazole Propylthiouracil

5.3 Symptoms and Clinical Signs

Evaluation of the child with neutropenia should begin with a complete history and physical examination. The history should include the child's family history, drug or toxin exposure, recent illness, age, and ethnicity. Physical examination should pay particular attention to the presence of adenopathy, splenomegaly, evidence of chronic or underlying disease (chronic granulomatous disease [CGD], paroxysmal nocturnal hemoglobinuria, Fanconi's anemia, etc.), and stringent evaluation of the skin and mucous membranes for signs and symptoms of infection.

Recurrent infections are the most significant consequence of neutropenia. The infections can be serious or minor. The organisms responsible for the infection are usually pyogenic or enteric bacteria or certain fungi. The risk of infection is dependent upon the level and duration of neutropenia. Patients who have an ANC <500/mm^3 due to chemotherapy, bone marrow failure, or bone marrow exhaustion are at increased risk for overwhelming bacterial infection. In contrast, patients who have benign chronic neutropenia may have an ANC <200/mm^3 for prolonged periods of time but will not experience serious infections such as bacteremia or pneumonia.

Common sites of infection are the mouth, mucous membranes, skin, and perianal and genital areas. With persistent severe neutropenia, systemic infections can occur in the lungs, blood, and gastrointestinal tract. Common infectious organisms include *Staphylococcus aureus* from the skin and Gram-negative organisms from the gastrointestinal and urinary tracts, such as *Escherichia coli* and *Klebsiella Enterobacter*.

5.4 Diagnostic Testing

Diagnostic testing for neutropenia should start with the evaluation of the full/complete blood count (FBC/CBC) and examination of the peripheral smear. If the WBC differential has been generated by automatic counters, it should be repeated manually. If the child is asymptomatic and the neutropenia is of less than 6 weeks duration, a WBC count with differential should be done twice a week for 2 weeks to assess for cyclic neutropenia. If the neutropenia occurs after a viral illness or if the child is less than 12 months old, viral serologies should be drawn (i.e., cytomegalovirus [CMV], EBV, parvovirus B-19). A neutrophil antigen should be obtained in newborns (present in isoimmune neonatal neutropenia).

If the neutropenia persists longer than 8 weeks and the child remains asymptomatic, additional studies should include HIV antibody, quantitative immunoglobulins, C3, C4, CH50, antineutrophil antibody, ANA, anti-DNA, antiphospholipid panel, and a chest radiograph (to check for thymic shadow). A bone marrow aspiration and biopsy may be necessary to identify granulocyte precursors and defects in myeloid maturation. The bone marrow aspiration and biopsy is also helpful to exclude hematologic malignancies (e.g., leukemia), bone marrow infiltration, and fibrosis.

Suggested testing for the child with chronic neutropenia that lasts longer than 6 months includes quantitative T and B subsets, diepoxybutane (if the patient has dysmorphic features, to rule out Fanconi's anemia), B-12 level, folate level, copper level, radiographs of the long bones, exocrine pancreatic studies (if the patient has a history of diarrhea, short stature, or failure to thrive), CD55/CD59 (for paroxysmal nocturnal hemoglobinuria [PNH]), CBCs of family members, and a leukocyte function test to determine if patient has CGD (if the patient has a history of recurrent infections).

5.5 Treatment

Treatment of neutropenia is dependent upon many factors, including whether the neutropenia is acute or chronic, the severity of the neutropenia, and any underlying immune defects, illnesses, or malignancies. Patients with chronic neutropenia should receive regular dental care at least every 6 months to prevent chronic gingivitis and recurrent stomatitis. In the child with neutropenia, measures to prevent infection, such as good handwashing and protection against food-borne illness (washing and cooking

Table 5.4. Gram-positive and Gram-negative organisms and common antibiotic treatment

Bacteria	Common organisms	Common antibiotics
Gram-positive	Staphylocci (coagulase-negative, coagulase-positive) Streptococci (alpha-hemolytic; group D) *Corynebacterium* *Listeria* *Clostridium difficile*	Cefepime Oxacillin Ticarcillin and clavulanate Clindamycin Vancomycin Cefotaxime
Gram-negative	Enterobacteriaceae (*Escherichia coli, Klebsiella Enterobacter, Citrobacter*) Pseudomonads (multiresistant) Anaerobes (*Bacteroides* sp.)	Cefotaxime Cefepime Ceftriaxone Ticarcillin and clavulanate Amikacin Tobramycin

foods thoroughly) should be observed. The child with severe neutropenia (<500/mm^3) should have a monthly physical examination with careful attention to skin and mucous membranes and should observe social isolation (avoiding crowds and persons with infection).

Infections that occur in the child with neutropenia should be treated aggressively. Fever higher than 38 °C may be the only presenting sign of infection, and the child with fever and neutropenia should be treated immediately. The child with fever and an ANC <500/mm^3 should be managed as an inpatient. Following culture of blood and urine, the child with severe neutropenia and fever should receive broad-spectrum parenteral antibiotics for coverage of both Gram-positive and Gram-negative organisms (Table 5.4).

A combination of an aminoglycoside and a beta-lactam antibiotic is good for initial coverage. If the child becomes afebrile, the cultures remain negative, and the clinical course improves, antibiotics may be discontinued after 72 hours. Oral antibiotics are unnecessary if there is not a known source of infection, such as otitis media or pneumonia, and if all cultures remain negative after 72 hours. If fever persists, other therapies, especially antifungal therapies (e.g., fluconazole, flucytosine, or amphotericin B) should be initiated. Patients with fever and an ANC >1,000/mm^3 can generally be managed on an outpatient basis and treated with a beta-lactam antibiotic such as ceftriaxone and an oral cephalosporin such as Cefzil or Ceftin until all cultures are negative after 72 hours. The child who has fever and an ANC between 500/mm^3 and 1,000/mm^3 may be managed on either an inpatient or outpatient basis, depending upon other presenting signs and symptoms such as cough, chills, shortness of breath, or other signs of infection.

Myeloid growth factors, such as granulocyte-colony stimulating factor (G-CSF), can be used to correct neutropenia in patients with severe neutropenia. G-CSF is not indicated for all cases of neutropenia and is most effective when the neutropenia is associated with early myeloid arrest. The child with neutropenia and a serious life-threatening infection or sepsis should be started on G-CSF, 5 mcg/kg/day intravenously (IV) or subcutaneously (SQ), until the ANC is >5,000/mm^3 on two occasions. If there is no response after 72 hours, the dose of G-CSF can be increased to 10 mcg/kg/day IV or SQ.

The child with severe neutropenia (<500/mm^3) with recurrent symptoms or a past history of life-threatening infection should be started on G-CSF. G-CSF is usually started at a dose of 5 mcg/kg given SQ daily or every other day to maintain an ANC >1,000/mm^3. Potential side effects of G-CSF include nausea, bone pain, alopecia, diarrhea, low-grade fever, fatigue, anorexia, rash, and headache. Potential complications of G-CSF therapy include the de-

Table 5.5. Follow-up of acute vs. chronic neutropenia

Type of neutropenia	Interval of follow-up	Studies required
Acute neutropenia	3–4 weeks	FBC/CBC
Chronic neutropenia	Monthly Yearly	Physical examination, FBC/CBC Bone marrow (if on G-CSF)

velopment of a malignancy such as acute myeloid leukemia (AML) and an increased frequency of osteopenia and osteoporosis. It is unclear whether these are actually complications of G-CSF therapy or are complications of the underlying disease (now evident due to longer life expectancies of children with severe neutropenia). Therefore, the use of G-CSF should be reserved for the child with severe neutropenia who has recurrent symptoms or a past history of life-threatening illness. Patients on long-term therapy with G-CSF should have yearly bone marrow examinations, cytogenetic studies, and measurement of bone density.

Bone marrow transplant has been a successful treatment in some children with severe neutropenia (e.g., severe congenital neutropenia). It should be considered in the child who does not respond to G-CSF, if an appropriate HLA-matched donor is available.

5.6 Prognosis

The prognosis of the child with neutropenia depends on several factors, including the severity of the neutropenia and any underlying immune defects, illnesses, or malignancies. Prognosis also depends on the incidence, quick recognition, and treatment of life-threatening infections and/or sepsis, and is also affected by the potential development of a secondary malignancy due to the use of G-CSF.

5.7 Follow-up

Follow-up of the child with neutropenia is dependent upon many factors, including whether the neutropenia is acute or chronic, the cause of the neutropenia, the severity of the neutropenia, and any underlying immune defects, illnesses, or malignancies (Table 5.5). The child with chronic benign neutropenia of childhood who does not experience severe infections related to his neutropenia will require less follow-up than the child with severe neutropenia who requires G-CSF to prevent serious infections.

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Thrombocytopenia

Cara Simon

Contents

6.1 Epidemiology

A normal platelet count in adults and children ranges from 150,000/mm^3 to 450,000/mm^3. Thrombocytopenia is defined as a platelet count more than two standard deviations below the mean of the general population, or <150,000/mm^3. Thrombocytopenia is not usually detected clinically until the platelet count falls below 100,000/mm^3, and it is rarely associated with bleeding without trauma until the platelet count falls below 30,000/mm^3. A platelet count below 10,000/mm^3 can be associated with severe, often spontaneous, bleeding.

The most common cause of thrombocytopenia in children is immune thrombocytopenia purpura (ITP). The incidence of symptomatic ITP is approximately 3–8 per 100,000 children per year and may be acute or chronic. Acute ITP is defined as ITP that resolves within 6 months of diagnosis. It is more prevalent in children younger than 10 years of age and has a peak incidence at 2–5 years of age. In 80–85 % of patients with acute ITP, it will resolve spontaneously in 2–6 months. Acute ITP affects males and females equally. It is more prevalent during the late winter and spring months, and 50–80 % of cases are preceded by a viral illness within the previous 3 weeks. ITP has also been associated with live measles vaccination (Lanzowsky, 2000; Steuber, 2003).

Chronic ITP is defined as the persistence of ITP for longer than 6 months. It is more prevalent in adolescents than younger children and affects females more often than males. Up to one-third of patients with chronic ITP will have clinical and laboratory evidence of an underlying autoimmune disorder (Buchanan, 2000). Spontaneous remission of chronic

ITP after 1 year is uncommon but may occur after 4 or 5 years, with or without treatment (Lanzowsky, 2000; Buchanan, 2000).

Immune thrombocytopenia can occur in the newborn period as maternal ITP or as neonatal alloimmune thrombocytopenia (NATP). Both diseases are usually self-limiting and resolve within 6 weeks; however, there are significant differences between the two disorders. In maternal ITP the mother usually has a below-normal platelet count, whereas in NATP the mother usually has a normal platelet count. NATP occurs in approximately 1 in 5,000 newborns. The platelets of the infant contain different antigens than those of the mother; subsequent formation of maternal alloantibodies that cross the placenta result in platelet destruction. Subsequent siblings with NATP are usually more severely affected. NATP is a more serious disorder than maternal ITP and has a higher incidence of intracranial hemorrhage (10–30 % versus 1 %) (Fernandes, 2003).

6.2 Etiology

The etiology of thrombocytopenia includes disorders of impaired/decreased platelet production, enhanced platelet destruction, and dilutional or distributional thrombocytopenia (Table 6.1). Decreased platelet production occurs when platelet production by the bone marrow is suppressed or damaged, and it can be congenital or acquired. Thrombocytopenia can also occur when the bone marrow produces a normal number of platelets but there is enhanced platelet destruction, which can occur for various reasons. Dilutional or distributional thrombocytopenia occurs when circulating platelets are trapped or sequestered in the spleen.

6.3 Symptoms and Clinical Signs

Patients with thrombocytopenia may be asymptomatic; consequently, the low platelet count is detected on a routine blood test. The most common symptomatic presentation of thrombocytopenia is bleeding, usually mucosal and/or cutaneous (Table 6.2). Mucosal bleeding typically manifests as epistaxis, gingival bleeding, or wet purpura on the buccal mucosa. Cutaneous bleeding manifests as petechiae and ecchymoses. Menorrhagia can occur in adolescent females. Persons with thrombocytopenia may experience profuse bleeding from superficial cuts.

Postsurgical bleeding can be controlled with local measures, but oozing may occur for hours after small injuries such as a minor cut or knee scrape. Bleeding into the central nervous system occurs rarely but is the most common cause of death due to thrombocytopenia. Bleeding in patients with thrombocytopenia can be distinguished from bleeding in patients with coagulation disorders, as patients with coagulation disorders experience more deep bleeding, less bleeding after minor cuts, and tend not to develop petechiae.

A complete history and physical examination should be performed on the child with thrombocytopenia. The health practitioner should obtain a general history (including recent infection, recent immunizations, previously diagnosed hematologic disease, and family history), a bleeding history (both past and present), and a history of drug ingestion. The physical examination should include meticulous examination of the skin and examination for lymphadenopathy and hepatosplenomegaly.

Table 6.1. Differential diagnosis of thrombocytopenia

Etiology	Association	Diagnosis
Destructive thrombocytopenias	Immunologic	ITP Drug-induced Infection-induced Post-transfusion purpura Autoimmune disease Post-transplant Hyperthyroidism Lymphoproliferative disorders
	Nonimmunologic	Microangiopathic disease Hemolytic anemia and thrombocytopenia Hemolytic uremic syndrome Thrombotic thrombocytopenia purpura (TTP)
	Platelet consumption/destruction	Disseminated intravascular coagulation (DIC) Giant hemangiomas Cardiac (prosthetic heart valves, repair of intracardiac defects)
	Neonatal problems	Pulmonary hypertension Polycythemia Respiratory distress syndrome (RDS)/infection (viral, bacterial, protozoal, spirochetal) Sepsis/DIC Prematurity Meconium aspiration Giant hemangioma Neonatal alloimmune Neonatal autoimmune (maternal ITP) Erythroblastosis fetalis (Rh incompatibility)
Impaired production	Congenital and hereditary disorders	Thrombocytopenia-absent radii (TAR) syndrome Fanconi's anemia Bernard-Soulier syndrome Wiskott-Aldrich syndrome Glanzmann's thromboasthenia May-Hegglin anomaly Amegakaryocytosis (congenital) Rubella syndrome
	Associated with chromosomal defect	Trisomy 13 or 18
	Metabolic disorders	Marrow infiltration: malignancies, storage disease, myelofibrosis
	Acquired processes	Aplastic anemia Drug-induced Severe iron deficiency
Dilutional or distributional	Hypersplenism (portal hypertension, neoplastic, infectious, glycogen storage disease, cyanotic heart disease) Hypothermia	

Adapted from The Children's Hospital Oakland: Hematology/Oncology Handbook (2002)

Table 6.2. Clinical manifestations of thrombocytopenia

Mucosal bleeding	Epistaxis Gingival bleeding Wet purpura Menorrhagia
Cutaneous bleeding	Petechiae Ecchymoses (bruising)

6.4 Diagnostic Testing

Diagnostic testing for thrombocytopenia should start with the evaluation of the complete blood count (CBC) and examination of the peripheral smear. The peripheral smear is evaluated for estimation of platelet numbers, platelet morphology, and the presence or absence of platelet clumping, and is important to help determine the cause of the thrombocytopenia. Congenital disorders associated with thrombocytopenia can often be diagnosed by platelet morphology on the peripheral smear. Platelets that are of normal size (Fig. 6.1) or small suggest decreased platelet production or bone marrow failure. Large platelets (Fig. 6.2) suggest platelet destruction.

Table 6.3. Additional studies to be considered in thrombocytopenic patients

Viral serologies (EBV, CMV, Parvo)
HIV antibody
Antiplatelet antibody (PAIGG)
Lupus panel
Antiphospholipid antibody
Lupus anticoagulant
C3, C4
Lymphocyte panel
LDH
Direct Coombs
Quantitative immunoglobulins
DEB
PNH
Platelet EMs
X-ray radii
Family members' platelet counts

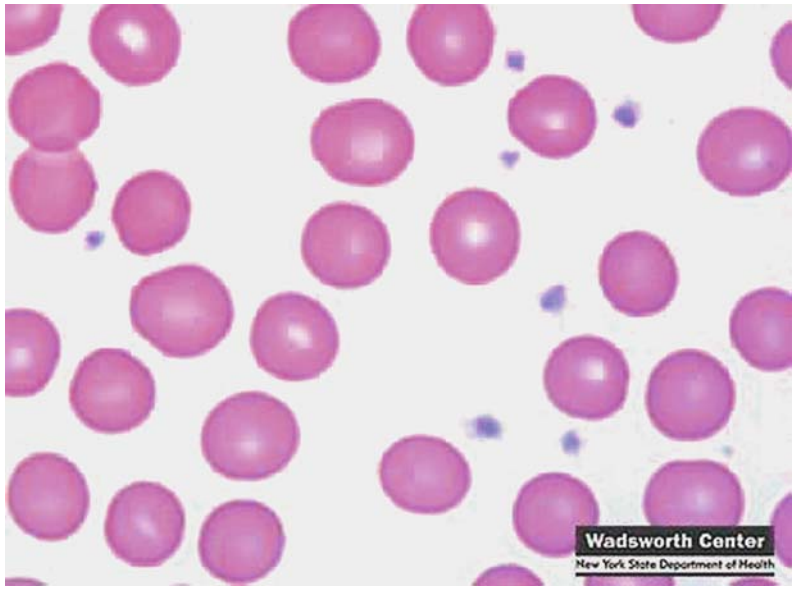

Figure 6.1
Normal platelets. Reprinted with permission from http://www.wadsworth.org/chemheme/heme/microscope/platelets.htm

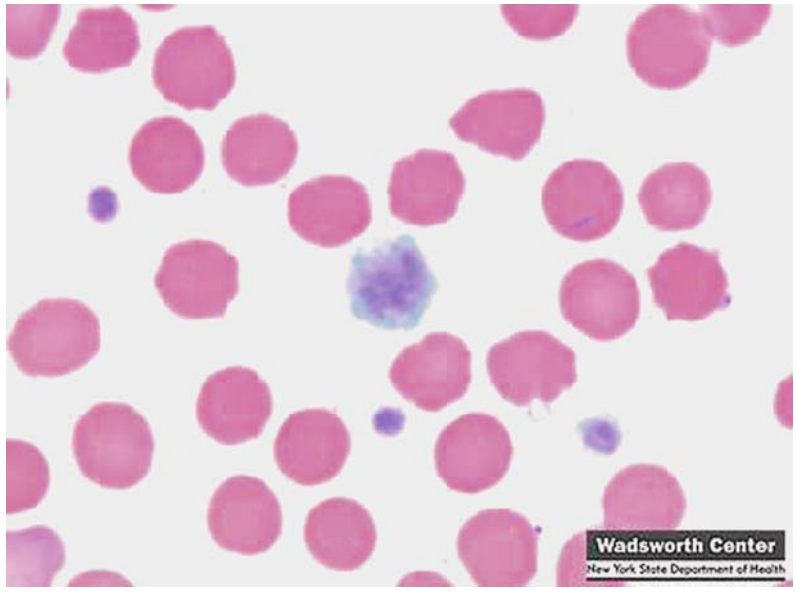

Figure 6.2
Giant platelets. Reprinted with permission from http://www.wadsworth.org/chemheme/heme/microscope/giantplatelet.htm

Bone marrow aspiration and biopsy is indicated in patients with unexplained thrombocytopenia. The presence of normal to increased numbers of megakaryocytes in the bone marrow is indicative of increased peripheral destruction of platelets; absent or decreased megakaryocytes in the bone marrow indicate decreased platelet production. In a hypercellular marrow, dysplastic changes are indicative of a myelodysplastic disorder. Bone marrow aspiration may also show the presence of infiltration with malignant cells.

Patients with isolated thrombocytopenia who have a normal physical examination and whose peripheral smear does not suggest other etiologies are diagnosed as having ITP and do not need a bone marrow aspiration and biopsy. However, if ITP persists longer than 6 months, a bone marrow exam may be warranted (Table 6.3).

6.5 Treatment

Treatment depends upon the cause of the thrombocytopenia. Thrombocytopenia that results from decreased platelet production by the bone marrow is treated by platelet transfusion. Platelet transfusion is utilized to correct episodes of bleeding. Bone marrow transplant can be used to treat some disorders of congenital thrombocytopenia, such as Wiskott-Aldrich syndrome and Fanconi's anemia.

Thrombocytopenia that results from increased platelet destruction cannot be treated by platelet transfusion because the immune system will destroy the transfused platelets as well as the patient's own platelets. Treatments for acute ITP include intravenous immune globulin (IVIG), corticosteroids, and anti-Rho(D) immune globulin (Table 6.4). All three of these treatments have advantages and disadvantages. None is curative but will increase the platelet count as the body recovers.

Treatment for ITP does not need to be continued to maintain a normal platelet count, but rather to decrease bleeding complications. Patients with chronic ITP who demonstrate persistent significant episodes of bleeding despite frequent and repeated interventions may require splenectomy. Splenectomy is effective in improving the platelet count in 60–90% of children with chronic ITP. It is recommended that it not be performed until a child is at least 5 years old, and should not be performed in a child less than 2 years of age if possible. Prior to splenectomy, immunizations should be up to date, including Pneu-

Table 6.4. Comparison of ITP treatments

Treatment	Dose	Advantages	Disadvantages	Side effects
IVIG	400 mg/kg IV per day for 5 days, or 1 gm/kg IV per day for 1–2 days	Faster recovery of platelet count	Cost (can be as much as 70 times more expensive than corticosteroids)	Nausea, vomiting, headache, fever, chills Rare: anaphylaxis
Corticosteroids	4 mg/kg/day PO for 4 days (with or without a taper) or 2 mg/kg/day PO for 2–3 weeks, then tapered over 1 week	Easy to administer Relatively inexpensive	Sharp decrease in platelet count after discontinuation	Weight gain, hypertension, Cushing's syndrome, mood changes
Anti-Rho(D) immune globulin	50–75 mcg/kg/day IV; may be divided and given over 2 days	Infusion time less than for IVIG Inexpensive	Must be Rh+ 1–1.5 g/dl or greater fall in hemoglobin as a result of hemolysis (occurs 1–2 weeks after administration)	Fever, chills, headache, anemia Rare: anaphylaxis

movax 23 and Meningovax. The benefit of splenectomy needs to be carefully weighed against the risk of overwhelming post-splenectomy infection that can be life-threatening.

Patients with thrombocytopenia should be instructed on thrombocytopenia precautions. These patients should be discouraged from participating in contact sports, such as football and wrestling, or activities at high altitudes when there is a chance of falling and sustaining a head injury. Children with thrombocytopenia should be instructed to avoid aspirin, ibuprofen, and other aspirin-containing medications that may interfere with platelet function.

The treatment for autoimmune and alloimmune thrombocytopenia in newborns is similar. Both can be treated with IVIG, steroids, platelet transfusions, and exchange transfusions. Platelets should be transfused if the platelet count is $<20{,}000/mm^3$, but if the infant is premature or ill, they should be given if the platelet count is $<50{,}000/mm^3$. An adequate platelet count should be maintained for the first 72–96 hours to prevent intracranial hemorrhage. An important distinction is that patients with NATP should be transfused with plasmapheresed or washed platelets from the mother because they lack the alloantigen responsible for the formation of the antiplatelet antibodies. In contrast, infants born to mothers with ITP should not receive platelets from the mother because they contain the antigens responsible for forming platelet autoantibodies.

6.6 Prognosis

The prognosis of the child with thrombocytopenia depends upon several factors, including the severity and underlying cause of the thrombocytopenia, the response to treatment, and the frequency and severity of bleeding complications. Prognosis also depends on the incidence, quick recognition, and treatment of life-threatening bleeding complications such as intracranial hemorrhage.

6.7 Follow-up

Follow-up of the child with thrombocytopenia is determined by the cause and degree of thrombocytopenia, the frequency and severity of bleeding complications, and the response to treatment. The child with chronic ITP with few bleeding complications may be followed in clinic every 3–6 months, whereas the child with congenital thrombocytopenia who requires frequent platelet transfusions to treat bleeding complications may require more frequent follow-up. At each clinic visit or with bleeding episodes, a FBC/CBC should be collected to check the platelet count.

6.8 Future Perspectives

Some medications that are currently being researched for the use of chronic ITP include Rituximab, vinca alkaloids, danazol, cyclophosphamide, and alpha interferon. Cytokines to stimulate platelet production are being studied and include interleukin-3 (IL-3), stem cell factor, IL-6, IL-11, and thrombopoietin.

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Bleeding Disorders

Nicole M. Sevier

Contents

7.1 Hemophilia

7.1.1 Epidemiology

Hemophilia is a condition characterized by a clotting factor deficiency of the intrinsic or plasma pathway of the coagulation cascade. Over 80 % of all individuals with hemophilia have a deficiency in factor VIII, also known as hemophilia A, which occurs in one in every 10,000 men. Hemophilia B (previously called Christmas disease), or a deficiency of factor IX, comprises approximately 20 % of those with hemophilia and occurs in one in every 34,000 live male births. A deficiency in either of these coagulation factors results in the delayed formation of fibrin and a consequent tendency to hemorrhage. A factor VIII or IX assay of 0–2 %, compared with a normal assay of approximately 50–150 %, is classified as severe disease, and these patients can have frequent and significant symptoms. Moderate hemophilia is generally noted as a factor level of 2–5 %, and these patients have intermittent symptoms. Mild hemophilia indicates a factor assay of greater than 5 %; correspondingly, these patients have less frequent bleeding complications. Hemophilia is reported in all races and ethnicities. Other factor deficiencies are possible and infrequent, but some are associated with bleeding symptoms.

7.1.2 Etiology

Factors VIII and IX are integral parts of the intrinsic coagulation pathway that assists in the formation of a fibrin clot. Decreased functional amounts of factor VIII or IX hamper clot formation and hemostasis. Deficiencies of factor VIII or IX are inherited X-

linked diseases; the genetic aspects of hemophilia will be reviewed in the upcoming section. It is now recognized that women, who are generally thought of as carriers of hemophilia, can have significantly low factor assays and be symptomatic due to the effects of lyonization.

7.1.3 Genetics

Hemophilia is a sex-linked recessive disease. The genes for both factor VIII and factor IX are located on the long arm of the X chromosome. Heterozygous women are typically asymptomatic, but can transmit the disease to 50% of their sons and can transmit the carrier state to 50% of their daughters. Random new mutation is possible, although infrequent, and can result in a carrier state in females or a disease state in males. Affected hemizygous males will transmit the gene to all their daughters, making them carriers. It is possible for a woman to have the disease, or symptoms, by either lyonization of the carrier state, by new mutation, or as a product of the combination of an affected male and a carrier female.

7.1.4 Symptoms and Clinical Signs

There is no distinguishing clinical difference between hemophilia A and B. Presentation of a patient with hemophilia varies, depending on known family history and severity of disease. Obviously, if family history is significant for hemophilia, then the patient's diagnosis is typically made prior to any untoward events. Otherwise, patients with severe hemophilia often present within the first year of life. Approximately 5% of these patients present with perinatal intracranial or subgaleal bleeding. Use of forceps, suctioning, or traumatic birth may be associated with intracranial hemorrhage. Prolonged bleeding after circumcision is also a common presenting symptom. Otherwise, infants and children with severe hemophilia typically present with significant and excessive ecchymosis with little or no trauma; abnormal bleeding, especially of the mucous membranes; or hemarthrosis (Figs. 7.1, 7.2). There may be no associated injury to produce bleeding in these patients, as hemorrhage can be spontaneous.

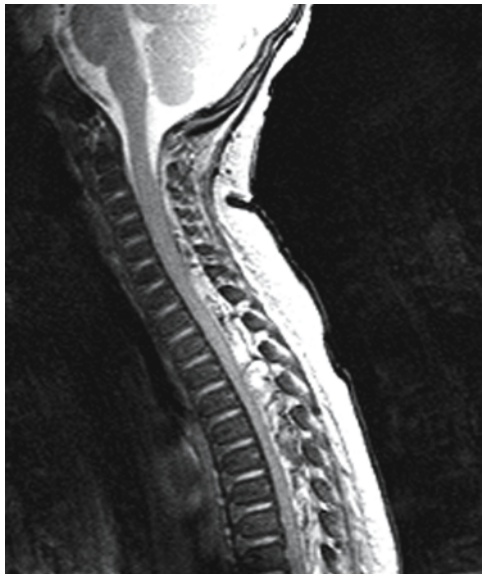

Figure 7.1

CT imaging of a cervical intraspinal epidural hemorrhage in an 8-month-old male with hemophilia A

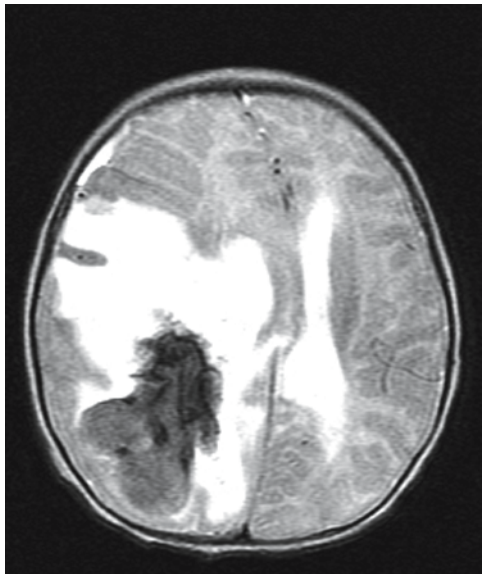

Figure 7.2

CT imaging of a right temporal subdural hemorrhage in a 9-month-old male with hemophilia A

Moderate to mild hemophilia can be associated with bleeding symptoms in later childhood or possibly adulthood. These finding are usually bleeding or bruising thought to be excessive with normal activities or due to some trauma, and hemarthrosis is possible with a significant injuring event. The disease can be so mild that it may not be detected until an adult has an invasive procedure or surgery. It is important to remember that disease genotype does not always accurately correlate with phenotype.

Specific sites of bleeding that are noteworthy include the following:

1. CNS – Intracranial hemorrhage can occur spontaneously in those with severe hemophilia, and is possible with injury or trauma in all classes of hemophilia. Typically, presentation includes symptoms of lethargy, headache, and vomiting. Silent hemorrhage is also possible, however. Head or spinal injury is considered a medical emergency; therefore, factor replacement should occur prior to any diagnostic testing. A CT of the brain is typically performed as it is more immediately available than MRI, but MRI alone may detect some silent intracranial hemorrhages.
2. Head and neck – Epitasis and mouth bleeding after tooth loss, eruption, or trauma is not uncommon in hemophilia. The fibrinolytic activity in mucous membrane areas makes stabilization of clot formation difficult, and prolonged bleeding can occur. Retropharyngeal bleeding, considered a medical emergency because of the possibility of airway obstruction, can be caused by pharyngitis, coughing, vomiting, or trauma to the neck area.
3. Musculoskeletal system – Hematoma development within the muscle causes pain, swelling, and possible decreased muscle function. When bleeding occurs in an extremity, compartment syndrome is possible, and consequent damage to peripheral nerves, vasculature, and tissue can be permanent. Pseudotumor, or encapsulated hematoma, can occur when a muscle hematoma is left untreated, and once developed it is difficult to treat and often recurs. Bleeding into a joint area, or hemarthrosis, is more common in patients with severe disease, but can occur in any patient. Joint swelling, warmth, pain, stiffness, and limp or limited movement are common symptoms of this event. Irritability and refusal to use the affected area may be the only symptoms in infants and small children. Recurrent hemarthrosis to a target joint can culminate in significant chronic arthropathy.
4. Genitourinary system – Hematuria can be spontaneous in severe hemophilia or due to trauma in all types of hemophilia. The patient most often has no symptoms other than the noted hematuria, but pain can indicate clotting in the ureter or renal pelvis. Other diagnoses must be ruled out. Hematoma to the penis can result in urinary obstruction, and testicular hematoma is significant as this may lead to infertility.
5. Post-traumatic bleeding – Most patients, whether with severe or mild disease, will not have significant bleeding after venipuncture. Bleeding post-trauma is related to the trauma itself and the severity of hemophilia. Bleeding can be delayed, occurring hours after the injury or procedure.

Other complications that may occur in a patient with hemophilia include infections due to exposure to blood products or factor replacement and the development of inhibitors.

Unfortunately, prior to 1990 a number of individuals receiving factor products did become infected with hepatitis C and/or HIV. Infections are extremely rare now due to the advent of virucidal treatments such as pasteurization and solvent-detergents and to current screening techniques. Despite treatments and screening, it is still possible for parvovirus B19 to be transmitted, and the newest concern is the possible transmission of Creutzfeldt-Jakob disease (CJD), a transmissible spongiform encephalopathy. There have been no known transmissions of CJD, but there are no current screening tests or treatments for this disease.

The development of inhibitors, or antibodies, to factor VIII or IX is a significant complication that occurs in approximately 25% of those with severe hemophilia A and up to 5% of those with severe hemophilia B. Inhibitor development in mild or moderate disease states is possible, but not common. Routine

testing for the presence of inhibitors is recommended in all patients with hemophilia who have received factor replacement; testing should be annual or semi-annual, or more frequently in high-titer patients. The inhibitor, measured in Bethesda units (BU), removes infused factor replacement at a rate directly proportional to the level of the inhibitor, thus making bleeding episodes difficult to treat. A low-titer inhibitor, or low responder, is usually classified as less than 5 BU, and a high-titer inhibitor, or high responder, as greater than 5 BU. It may be possible to overwhelm a low-titer inhibitor with a high dose of factor replacement, but this is not usually possible with high titers. There is a significant risk, as high as 26%, that those with hemophilia B who develop inhibitors will have anaphylactic reactions to factor IX replacement.

7.1.5 Diagnostic Testing

Initial evaluation should include a platelet count, prothrombin time (PT), and activated partial prothrombin time (aPTT). The aPTT, as a test of the intrinsic clotting pathway, will be prolonged in most patients with hemophilia (with the exception of some patients with mild factor IX deficiency). The PT and platelet count should be within normal limits. Factor VIII or IX assays will indicate the deficiency state. Several types of factor assays are available. The one-stage clotting assays are commonly used, but two-stage assays are less influenced by variables; the chromogenic assay is very specific but technically complicated. Factor VIII levels can be low in several types of von Willebrand disease, and therefore it is important to distinguish between the two diseases. A von Willebrand panel, to include the ristocetin cofactor assay, von Willebrand factor antigen assay, and multimer analysis, should be done. In addition, type 2N (Normandy) von Willebrand testing, or factor VIII binding assay, should be considered, as in this disease the factor VIII assay is low, but the von Willebrand panel may be normal.

7.1.6 Treatment

There are several options for Factor VIII replacement. The product of choice is typically recombinant factor VIII, a genetically engineered product, as this has the least known risk of viral contamination, but these products are among the most costly treatments available. First-generation recombinant products contain human albumin, which is used to stabilize the factor VIII protein, but the second-generation products have little or no albumin and are stabilized in sucrose. Plasma-derived factor VIII products are less expensive than recombinant products and are most commonly used by those who have previously been exposed to this type of product, or when cost or availability are issues. One unit of factor VIII, either recombinant or plasma-derived, is equal to 2% of factor activity in vitro. The half-life of plasma-derived or recombinant factor VIII is between 8 and 12 hours. Dosing is reviewed in Table 7.1.

Recombinant factor IX is available for factor IX replacement and is a DNA-synthesized product. This product has no added albumin, is thought to have a very limited risk of viral contamination, and is generally the treatment of choice for this diagnosis. Plasma-derived factor IX is less expensive that recombinant factor IX but carries some risk of viral contamination. Factor IX is dosed in units per kg of body weight; one unit of plasma-derived factor IX is equal to 1% factor IX activity in vitro, but one unit of recombinant factor IX is equal to about 0.8% activity in vitro. The half-life of plasma-derived or recombinant factor IX is approximately 16 hours. There is some evidence that if an individual develops an inhibitor, he will likely have an anaphylactic reaction when exposed to factor IX. Because of this risk it is recommended that the first 10–20 infusions of factor IX be done in the clinic or hospital setting (Jadhav and Warrier, 2000).

Table 7.1. Intravenous treatment guidelines for factor VIII and IX deficiency

	Hemophilia A treatment with factor VIII (% activity)	Hemophilia B treatment with factor IX (% activity)	Comments
Hemarthrosis, any joint	40–50 units/kg ×1 (80–100), followed by 25–50 units/kg (50–100) q12–24h for 2–5 days	25–50 units/kg ×1 (25–50), followed by 25–50 units/kg (25–50) q24h for 1–3 days	Apply ice/cold pack, immobilize ×48h, then light ambulation; increase dose prn worsening symptoms; consider prednisone 1–2 mg/kg/day
Hematoma, soft tissue	25–35 units/kg ×1 (50–70), followed by 25 units/kg (50) qd ×2	20–30 units/kg ×1 (20–30), followed by 30 units/kg (30) qd ×2	Ice/cold pack
Hematuria	35 units/kg ×1 (70), followed by 25 units/kg (50) q12–24h ×2–7 days	25–50 units/kg ×1 (25–50), followed by 30 units/kg (30) q24h ×2–7 days	Hydration is helpful; may use prednisone 1–2 mg/kg/day ×7–14 days; consider differential diagnosis; do not use antifibrinolytic (risk of thrombosis)
Gastrointestinal	35–50 units/kg ×1 (70–100), followed by 35 units/kg (70) q12h ×2–7 days	50–100 units/kg ×1 (50–100), followed by 50–100 units/kg (50–100) qd ×2–7 days	Determine cause/extent; monitor CBC; potentially life-threatening
Mucosal	35–50 units/kg ×1 (70–100), followed by 25–35 units/kg (50–70) q24h ×1–2 days	25–50 units/kg ×1 (25–50), followed by 25–50 units/kg (25–50) q12–24h ×1–2 days	Ice/ cold pack; use antifibrinolytic
Head trauma	50 units/kg ×1 (100), followed by 35 units/kg (70) q12h ×7–10 days	100 units/kg ×1 (100), followed by 50–100 units/kg (50–100) q12h ×7–10 days	First dose to be given immediately, then CT, etc; maintain trough >50% activity
Major surgery	50 units/kg ×1 (100), followed by 35 units/kg (70) q12h ×3–8 days	50–100 units/kg ×1 (50–100), followed by 50–100 units/kg (50–100) q24h ×7–10 days	Monitor factor activity, trough >50%
Dental extraction	50 units /kg ×1(100), followed by 35 units/kg (70) q12h ×3 days	25–50 units/kg ×1 (25–50), followed by 25–50 units/kg (25–50) q24h × 2–7 days	Use antifibrinolytic
Prophylaxis	25–35 units/kg (50–70) three times per week	25–40 units /kg twice per week	
Immune tolerance	50–100 units/kg q24–48h	Risk of anaphylaxis	

Table 7.2. Desmopressin challenge

DDAVP IV or SQ	.3 μg/kg in 50 ml of normal saline IV over ~20 min, or same dose for SQ injection
Stimate (150 μg/ml)	<50 kg; one puff intranasally or >50 kg two puffs intranasally, q12–24h

DDAVP IV may elicit a stronger response than intranasal dosing. An increase in factor VIII levels can be expected in ~30 min
Challenge instructions: Draw factor VIII assay just before dose is given, and repeat 1 hour after dose. A three-fold increase is considered a good response

Table 7.3. Antifibrinolytic medications

Aminocaproic acid (Amicar)	50–100 mg/kg/dose q6h (maximum 3–4 doses) IV or PO
Tranexamic acid (Cyklokapron)	25 mg/kg/dose q6–8h IV or PO

These drugs cannot be used with PCCs or APCC replacement products

In emergency situations when factor replacement is not available, fresh frozen plasma can be used for those with hemophilia A or B. Cryoprecipitate can be used for factor VIII-deficient patients. Both of these products are typically available through local blood banks, and although the risk is small, possible viral contamination is always a concern for patients and families. For dosing recommendations, see Chapter 28.

Prophylaxis is used in hemophilia A and B to decrease the risk of bleeding and involves a strategy of routine administration of factor replacement. Primary prophylaxis refers to the initiation of prophylaxis during the first few years of life, and several studies have shown that this reduces the risk of chronic arthropathy in the future (Panicker et al., 2003; Shapiro, 2003). It is generally recommended that those with severe hemophilia can reap significant benefit from primary prophylaxis. Secondary prophylaxis, which is introduced after the patient has demonstrated frequent bleeding episodes, can minimize joint damage.

Several therapies other than factor replacement can be utilized for adjuvant therapy for bleeding in the patient with hemophilia. Desmopressin, or DDAVP, is a synthetic antidiuretic hormone and can increase available factor VIII levels for 12 and up to 24 hours by stimulating release of factor VIII from storage sites in the endothelial cells. This is typically effective only in those with mild factor VIII deficiency, but it does not work on each individual; therefore, a trial dose (DDAVP challenge) should be given to determine efficacy (Table 7.2). This medication is available in IV form or as a nasal formulation, Stimate (150 μg/ml). Common side effects include flushing, tachycardia, and headache, and uncommonly, hyper- or hypotension. A decreased infusion rate may diminish these effects. Overuse of DDAVP can lead to the antidiuretic effects of this medication, including fluid retention and sodium depletion. Giving more than three doses of DDAVP requires fluid restriction and sodium monitoring. Repeated doses will lead to depletion of stored factor VIII and decreased drug efficacy.

Antifibrinolytic therapies are available for mucous membrane bleeding. Aminocaproic acid (Amicar) and tranexamic acid (Cyklokapron) inhibit the action of fibrinolysis that occurs at mucous membrane sites. Both of these medications stabilize clot formation and are typically used in conjunction with factor replacement, but they may be effective when used alone for minor bleeding in a patient with mild hemophilia. To avoid thrombotic risk, these drugs should not be used concomitantly with prothrombin complex concentrate (Table 7.3). Fibrin glue is being used for wound and tissue sealing with some success in individuals with hemophilia (Kavakli, 1999).

The patient with factor inhibitors presents a significant treatment challenge. The inhibitor may be bypassed by using activated prothrombin complex concentrates (APCCs) for factor VIII inhibitors, and

Table 7.4. Treatment for acute bleeding in patients with factor inhibitors

FEIBA (factor eight inhibitor bypass activity) or Autoplex	Effective for factor VIII inhibitors	75–100 units/kg IV q12–24h	Monitor fibrinogen and D-dimers after 3rd dose due to thrombosis risk; not to be used with antifibrinolytic drugs
Recombinant factor VIIa (NovoSeven)	Effective for factor VIII or factor IX inhibitors	~90 µg/kg IV q2h, weaning to larger intervals as bleeding stabilizes; larger doses may be necessary in some patients	

recombinant factor VIIa for factor VIII or IX inhibitors. Large doses of APCCs are associated with some risk of thrombosis, and there is no in vitro assay to monitor efficacy of APCCs. Porcine factor VIII concentrate can be used to bypass the factor VIII inhibitor and is typically a treatment option for those with high-titer inhibitors. There is the possibility of cross-reactivity between porcine and human factor inhibitor development; therefore, a porcine factor VIII inhibitor assay must be evaluated prior to any treatment with this product. Hypersensitivity is also an issue with porcine factor VIII.

Immune tolerance (IT) strategies or desensitization is used to overwhelm factor inhibitor production in hopes of eliminating the inhibitor. Studies report that this works best if the inhibitor is at low titer levels at the initiation of IT. IT with use of factor IX in the patient with hemophilia B can be complicated by the concomitant development of anaphylactic reaction to factor IX (Jadhav and Warrier, 2000). Additionally, IT is less successful in hemophilia B (~30% success rate) than in hemophilia A (~70% success rate) and is associated with steroid-resistant nephrotic syndrome. Plasmapheresis is used to help rapidly decrease inhibitor levels, such as when the patient requires a surgical procedure, and is usually followed by some combination of IT (Barnes et al., 2000; Jansen et al., 2001). Newer strategies for IT still under investigation include disruption of T-helper cell function, inhibition of antibody receptors, and immunization of anti-idiopathic antibodies.

The therapeutic management of hemophilias A and B are similar and will be reviewed together. Tables 7.1 and 7.4 provide general guidelines for treatment of typical bleeding. Each patient's plan of care must be individualized to reflect any special circumstances or conditions that may require more or less intervention. The patient's dose should be rounded to the nearest vial whenever possible. It is important to note that doses of recombinant factor IX must by adjusted upward by a factor of 1.2 (1 unit = 0.8% activity) to achieve the desired factor IX in vitro percent activity goal.

Supportive treatments are beneficial and include application of an ice or cold pack to the injured area when possible, pressure (local pressure or Ace wrap, if applicable), elevation of the extremity, and rest or immobilization of the affected extremity. Use of nonsteroidal anti-inflammatory drugs should be avoided because they typically diminish platelet function.

7.1.7 Prognosis

Hemophilia is a genetic condition, and as such is a lifelong, chronic condition. Currently there is no cure. In countries where treatment is readily available, individuals with hemophilia typically have normal lifespans, with heart disease as the leading cause of death. Dangers of morbidity and mortality are more significant in those with severe hemophilia.

7.1.8 Follow-Up

The chronicity and multisystem effects of hemophilia lend themselves well to the care provided at a multidisciplinary comprehensive center. Routine surveillance visits to a hemophilia specialist are recommended every 3–6 months for more severe disease

and annually for mild hemophilia. Prevention of complications is the key to the care of the individual with hemophilia, and prompt treatment when bleeding or injury occurs is paramount. Management of disease complications and health maintenance are additional aspects of care.

Home care for these patients is an integral aspect of care, as prompt treatment can be given in the home. Additionally, home care can help facilitate the goal of self-infusion, which is especially important in the patient with severe disease. Routine immunizations are necessary; the deep subcutaneous injection route is preferred to intramuscular injections. Hepatitis A and B vaccinations are advised because these viruses are possible contaminates of factor concentrates. Routine surveillance of blood-borne infections should be done in those exposed to factor concentrates. Regular dental care is important, with a focus on preventing caries, infection, and extraction. Dental procedures should be discussed in advance with the treatment team because extraction and, in some cases, cleaning can cause bleeding that would require treatment. Physical therapy evaluation and treatment are required for those with affected joints or musculoskeletal complications. Certainly, education regarding hemophilia, treatment options, and safety precautions must be provided to the patient and family. Exercise is encouraged, but contact sports should be avoided. Genetic counseling should be offered to all parents and patients.

7.1.9 Future Perspectives

The search for a cure for hemophilia continues, and there are several human phase 1 trials ongoing in the United States. The goal of gene therapy is to convert severe factor deficiency to mild, or greater than 5% activity, but one of the difficulties has been how to incorporate the normal gene. Lentiviruses appear promising for future research, as it has been possible to remove the virulent factors and because these viruses infect both nondividing and dividing cells (Lusher, 2002).

7.2 Von Willebrand Disease

7.2.1 Epidemiology

Von Willebrand factor (vWF) is an important component of the clotting system because it acts as a carrier and stabilizer for factor VIII and adhesively binds platelets to subendothelial cells at the site of injury. Von Willebrand disease (vWD) is a group of bleeding diatheses in which there is a quantitative deficiency or qualitative defect in one of the functions of vWF. vWD is thought to be the most common bleeding disorder worldwide, affecting up to 1% of the population. Spread over a continuum of mild to severe disease manifestations, vWD classification includes type 1, type 2 (with several variants), type 3, and pseudo platelet-type. Type 1 vWD is the most common variant; the frequencies of the other types are identified in Table 7.5. This is typically a relatively mild bleeding disorder, and can be so mild as to go undiagnosed until late in life. In a few patients vWD is severe, leading to symptoms comparable to those of severe hemophilia. This is a genetic condition passed on through inheritance, but random mutation is possible. vWD affects males and females equally and is not associated with a specific ethnicity.

7.2.2 Etiology

vWF is a high-molecular-weight adhesive protein (or multimer) that is produced in the endothelial cells of the vasculature and in small amounts in the megakaryocytes. Disease classification is based on the qualitative and/or quantitative defect present in the vWF (Table 7.5).

vWF is an acute phase reactant; therefore, vWF levels rise in individuals during stress, inflammatory processes, pregnancy, exercise, and adrenergic stimulation.

Acquired vWD is possible and is associated with several diseases. Most frequently, acquired vWD occurs in those individuals with clonal lymphoproliferative or autoimmune diseases who have formed an

Table 7.5. Classifications of von Willebrand disease (*hwm* high-weight multimers)

Type	Pathology	Frequency
Type 1	Partial quantitative deficiency of vWF	70–80%
Type 2A	Absence of hwm and associated decrease in platelet binding functions	10–12%
Type 2B	Increased affinity for platelet complex	3– 5%
Type 2M	Decrease in platelet binding functions	<1%
Type 2N	Significantly decreased affinity for factor VIII	<1%
Type 3	Almost complete absence of vWF	<1%
Pseudo platelet-type	Intrinsic abnormality of the platelets, leading to loss of hwm	<1%

Table 7.6. Signs and symptoms of von Willebrand disease

Easy bruising or hematomas	Recurrent epistaxis
Mouth or gum bleeding	Excessive bleeding post-dental extractions
Menorrhagia	Hematuria
Gastrointestinal bleeding (10% of patients)	Bleeding with IM injections
Hemarthrosis	Mild thrombocytopenia
Prolonged oozing from minor wound	Postoperative hemorrhage

antibody to vWF. Other associated causes include absorption of vWF into tumor cells (e.g., Wilms' tumor), destruction by proteolytic enzymes during accelerated fibrinolysis (e.g., pancreatitis), reduced production in hypothyroidism, and associated decreases with certain pharmacological agents (e.g., valproic acid, dextrans, hetastarch).

7.2.3 Genetics

The genetic code for vWF is located on the short arm of chromosome 12 and is a complex single-copy gene. This gene has been sequenced and, more recently, most mutations have been identified. Most types of vWD are autosomal dominant; however, type 2A can be either dominant or recessive, and type 2N and type 3 are autosomal recessive.

7.2.4 Symptoms and Clinical Signs

Logically, symptoms of vWD vary depending on severity of disease. The most common symptoms overall are easy bruising and mucous membrane bleeding. However, the patient with type 1 vWD may have no symptoms at all until an untoward event causes significant injury or until surgery is required. Symptoms of bleeding early in life, hemarthrosis, and significant bruising with normal activities or minor trauma can occur with type 3 vWD. Patients with type 2N vWD can also exhibit more serious bleeding difficulties, such as soft tissue and urinary bleeding, as it is associated with low factor VIII levels and can mimic hemophilia (Schneppenheim et al., 1996) (Table 7.6).

7.2.5 Diagnostic Testing

Diagnostic testing should be done in those who present with clinical symptoms suspicious for a bleeding disorder. The following laboratory tests are common screening tests for vWD: activated partial thromboplastin time (aPTT); a von Willebrand panel, including vWF antigen (vWf:Ag), vWF ristocetin cofactor (vWF activity or functional assay; vWf:RCo), vWF multimers; and factor VIII assay. During screening for bleeding disorders, a prothrombin time (PT) is often done, the results of which should be normal in the patient with vWD. The aPTT, part of the routine screening for bleeding disorders, serves as a measure of the intrinsic pathway. It may be prolonged in an individual with vWD, but if the disease is quite mild, it may be normal. Some centers use a bleeding time (BT) to assist with screening, but this test has fallen out of favor due to variable results and poor correlation with disease. The platelet function analyzer assay, or PFA 100, is a relatively new screening test that identifies patients with poor platelet aggregation, which if noted would place a high index of suspicion on vWD. The PFA 100 appears to be replacing the BT as a screening test. A platelet count is also routinely done and may be abnormally low in those with type 2B, type 2M, type 3, and pseudo platelet-type vWD.

The acute phase reactant qualities of vWF make laboratory evaluation challenging, and repeated testing is commonly necessary, especially in those with mild vWD or type 1. Should repeat von Willebrand panel testing be needed, the tests should be separated by 4 weeks or more. Blood type should be evaluated because those with type O blood have vWF levels approximately 25–30% lower than those with other blood types. Therefore, in those patients with type O blood and no significant personal or family history of bleeding, and with low normal von Willebrand panel assay results, vWD can likely be excluded. Also confounding laboratory evaluation is the issue of vWF (both antigen and ristocetin cofactor) as an acute phase reactant. Consequently, physical stressors such as illness and exercise, and even emotional stressors, can elevate vWF levels; a low normal von Willebrand panel may indeed indicate that disease is present but not demonstrated on that particular day. Estrogen therapy can increase vWF levels, making it another complicating factor, as women sent for evaluation of a bleeding diathesis often have symptoms of menorrhagia and are being treated with oral contraceptives to control menses (Cordoni, 2000).

Ristocetin platelet aggregation (RIPA) testing is typically used to determine subtypes of vWD after initial von Willebrand panel testing has been abnormal. vWD type 2B and platelet-type vWD both have increased sensitivity to low doses of ristocetin; a low-dose RIPA is performed if either type of vWD is suspected (Table 7.7).

In emergency situations when vWF replacement is not available, cryoprecipitate can be used. Platelet transfusions are the appropriate treatment for pseudo platelet-type vWD. Both of these products are typically available through local blood banks, and although the risk is small, possible viral contamination is always a concern for patients and families. For dosing recommendations, see Chapter 28.

Factors beyond laboratory testing should assist in determining diagnosis. The personal and family history has significant relevance in the patient being evaluated for a bleeding disorder. Patients with vWD may experience easy bruising; bleeding or oozing of blood after dental or surgical procedures, especially tonsillectomy; menorrhagia; or epistaxis. Family history is often remarkable for the same complaints or events. Some female relatives may have undergone hysterectomy for uncontrolled uterine bleeding but were never diagnosed with vWD. Of course, any history of family members as being “free bleeders” or even as having hemophilia should alert the provider to the possibility of vWD. The individual’s personal and family history is utilized in conjunction with laboratory reports to determine diagnosis. Should family and personal history be unremarkable, the possibility of acquired vWD should be considered.

7.2.6 Treatment

Treatment of vWD is based on the pathophysiology of the specific variant or type of vWD. Several treatment strategies are available to control bleeding events. Desmopressin, or DDAVP, is a synthetic antidiuretic hormone and can increase available vWF lev-

Table 7.7. Diagnostic testing for von Willebrand disease (*hwm* high-weight multimers, *iwm* intermediate-weight multimers, *lwm* low-weight multimers)

Test	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3	Platelet-type pseudo
vW ristocetin factor	Normal or decreased	Decreased	Normal or decreased	Normal or decreased	Normal	Decreased or absent	Normal
vWF antigen	Normal or decreased	Decreased	Normal or decreased	Decreased	Normal	Decreased or absent	Normal
Multimer	Normal	Absent hwm and iwm, increased lwm	Absent hwm	Normal	Normal	Absent	Absent hwm
Factor VIII	Normal or decreased	Normal or decreased	Normal or decreased	Normal or decreased	Decreased	Decreased or absent	Normal
Ristocetin-induced platelet aggregation	Poor	Poor	Poor			Poor	Hyper-responsive at low dose
Platelet Count	Normal	Normal	Decreased	Decreased	Normal	Decreased	Decreased

els for 12 and up to 24 hours by stimulating release of vWF from storage sites in the endothelial cells. Desmopressin is usually most effective in those with type 1 vWD and is somewhat effective in types 2A, 2M, and 2N, but it does not work on every individual; therefore, a trial dose should be given to determine efficacy (DDAVP challenge, Table 7.8). DDAVP should not be used in those with type 2B VWD, as the vWF high-molecular-weight multimers have an increased affinity for platelets; thus, increasing the endogenous vWF may cause thrombocytopenia and possibly worsen bleeding.

Once the degree of efficacy is established, DDAVP can be used for minor bleeding events, and for those who respond very well, it may be used for some of the more serious events (epistaxis, menorrhagia, etc). DDAVP should be used in conjunction with vWF replacement therapy for life-threatening injury or when repeated dosing is likely. This medication is available in IV or subcutaneous form or as Stimate, a nasal formulation (150 µg/ml). A lower-concentration nasal spray and pill forms are also available but are not useful for this diagnosis. Common side effects include flushing, tachycardia, and headache, and uncommonly, hyper- or hypotension. A decreased infusion rate may diminish these effects. Overuse of DDAVP can lead to the antidiuretic effects of this medication, including fluid retention and sodium depletion. Giving more than three doses of DDAVP requires fluid restriction and sodium monitoring. Repeated doses of desmopressin will lead to tachyphylaxis (Table 7.8).

Table 7.8. Desmopressin dosing guidelines

DDAVP IV or SQ	.3 µg/kg in 50 ml of normal saline IV over ~20 min, or same dose for SQ injection
Stimate (150 µg/ml)	<50 kg; one puff intranasally or >50 kg two puffs intranasally, q12–24h

DDAVP IV may elicit a stronger response than intranasal dosing. Increase in vWF levels can be expected in ~30 min
Challenge instructions: Draw factor VIII assay, ristocetin cofactor, and vWF antigen just before dose is given, and repeat 1 hour after dose. A three-fold increase is considered a good response

Humate-P is considered replacement therapy for vWD, as it contains plasma-derived vWF. This is a pasteurized, solvent-treated product, and the risk of

Table 7.9. Humate-P dosing guidelines

Type	Event	Dosage (IU vWf:RCo/kg)
Type 1	Serious event: Severe epistaxis GI bleeding CNS trauma Traumatic hemorrhage	Loading dose 40–60 units/kg Then 40–50 units/kg q8–12h for 3 days to keep nadir >50% Then 40–50 units/kg QD for ~7 days of treatment
Mild		
Moderate to severe	Minor event: Mucous membrane bleeding Menorrhagia	40–50 units/kg, 1–2 doses
	Serious event: Severe epistaxis GI bleeding CNS trauma Traumatic hemorrhage	Loading dose 50–75 units/kg Then 40–60 units/kg q8–12h for 3 days to keep nadir >50% Then 40–60 units/kg QD for ~7 days of treatment
Type 2 (all variants) and 3	Minor event: Mucous membrane bleeding Menorrhagia	40–50 units/kg, 1–2 doses
	Serious event: Severe epistaxis GI bleeding CNS trauma Traumatic hemorrhage	Loading dose 60–80 units /kg Then 40–60 units/kg q8–12h for 3 days to keep nadir >50% Then 40–60 units/kg qd for ~7 days of treatment

viral transmission is considered low. It is typically dosed in ristocetin cofactor units; dosing recommendations and indications are outlined in Table 7.9 (Aventis Behring, 2000). These recommendations are general guidelines for treatment of typical bleeding. Each patient's plan of care must be individualized to reflect any special circumstances or conditions that may require more or less intervention. The patient's dose should be rounded to the nearest vial whenever possible.

Other similar products are available in the United Kingdom and Europe. Recombinant vWF has been developed and is currently being tested but is not yet available for use in humans.

Antifibrinolytic therapies are available for mucous membrane bleeding. Aminocaproic acid (Amicar) and tranexamic acid (Cyklokapron) inhibit the action of fibrinolysis that occurs at mucous membrane sites. Antifibrinolytics do appear to be effective for menorrhagia and are also used to prepare for dental procedures and oral surgery. Both of these medications stabilize clot formation and are typically used in conjunction with factor replacement, but may also be effective when used alone for minor bleeding in a patient with mild or type 1 vWD (Table 7.10).

Table 7.10. Antifibrinolytic medications

Aminocaproic acid (Amicar)	50–100 mg/kg/dose q6h (maximum 3–4 doses) IV or PO
Tranexamic acid (Cyklokapron)	25 mg/kg/dose q6–8h IV or PO

These drugs work best if continued for an additional 3–4 days after bleeding stops

Supportive treatments are beneficial and include application of an ice or cold pack to the injured area when possible, pressure (e.g., local pressure or Ace wrap) if needed, elevation of the extremity, and rest or immobilization of the affected extremity. Use of nonsteroidal anti-inflammatory drugs should be avoided because they typically diminish platelet function.

7.2.7 Prognosis

The prognosis for the patient with vWD is excellent. Most patients have very mild symptoms except at times of significant trauma or surgery. Those with type 3 vWD can have more serious symptoms and sequelae, similar to the patient with moderate to severe hemophilia.

7.2.8 Follow-up

Individuals with vWD should be seen at regular intervals by a hematologist who is familiar with vWD management. Routine surveillance visits are recommended every 6–12 months or more frequently for severe disease. Prevention of complications depends on prevention prior to anticipated bleeding events and to prompt treatment when bleeding or injury does occur. Routine immunizations are necessary; in those with more severe types of vWD, the deep subcutaneous injection route is preferred to intramuscular injections. Hepatitis A and B vaccinations are advised because these viruses are possible contaminates of factor concentrates. Routine surveillance of blood-borne infections should be done in those exposed to factor concentrates. Regular dental care is important, with a focus on preventing caries, infection, and extraction. Dental procedures should be discussed in advance with the treatment team because extraction and, in some cases, cleaning can cause bleeding that would require treatment. Home care may be useful for patients with more severe variants, as prompt treatment with Humate-P can be given in the home. Physical therapy evaluation and treatment are required for those with severe disease and those with affected joints or musculoskeletal complications. Certainly, education regarding vWD, treatment options, and safety precautions must be provided to the patient and family. Exercise is encouraged, but contact sports should be avoided. Genetic counseling should be offered to all parents and patients (Cordoni, 2000).

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PART III

Chemotherapy

Christine Chordas

Contents

8.1 Introduction

In the 1940s chemotherapy was introduced as part of standard therapy for childhood cancer. Prior to this time, surgery and radiation therapy were the only treatments available. Following the discovery of nitrogen mustard after World War I, rapid drug development occurred and continues into the 21st century, with novel drug development at the forefront of clinical investigations. Since the introduction of chemotherapy, overall 5-year survival rates for childhood cancers have increased from near 0% to nearly 75%. However, current therapies fail to cure approximately 30% of all children with malignancies (Bernstein et al., 2001), necessitating ongoing investigation of new agents as well as continued improvement of old agents. Today the hallmark approach to treating most childhood cancers is with multimodality treatment that includes some combination of chemotherapy, surgery, and radiation.

8.2 Chemotherapy Principles

The goal of chemotherapy is to eradicate all cancer cells, but chemotherapy is also used for palliation to control disease when cure is not likely and for myeloablation in preparation for stem cell transplant. Chemotherapy agents kill malignant and nonmalignant cells as they move through the five phases of the reproductive cell cycle (Fig. 8.1). Most chemotherapy agents kill cells in the active phases of the cycle (G1, S, G2, M). Malignant and nonmalignant cells in the resting phase (G0) are not dividing and are more resistant to the effects of chemotherapy. Nonmalignant cells that undergo rapid division (e.g., hematopoietic, mucosal, and gastrointestinal cells) are not spared, as demonstrated by some of the side effects exhibited (e.g., bone marrow suppression, mucositis).

Tumors initially grow exponentially, with a high growth fraction and short doubling time (Table 8.1), making them most susceptible to chemotherapy agents. Once in the resting phase, damaged tumor cells may die, become resistant to the particular

Figure 8.1
The reproductive cell cycle

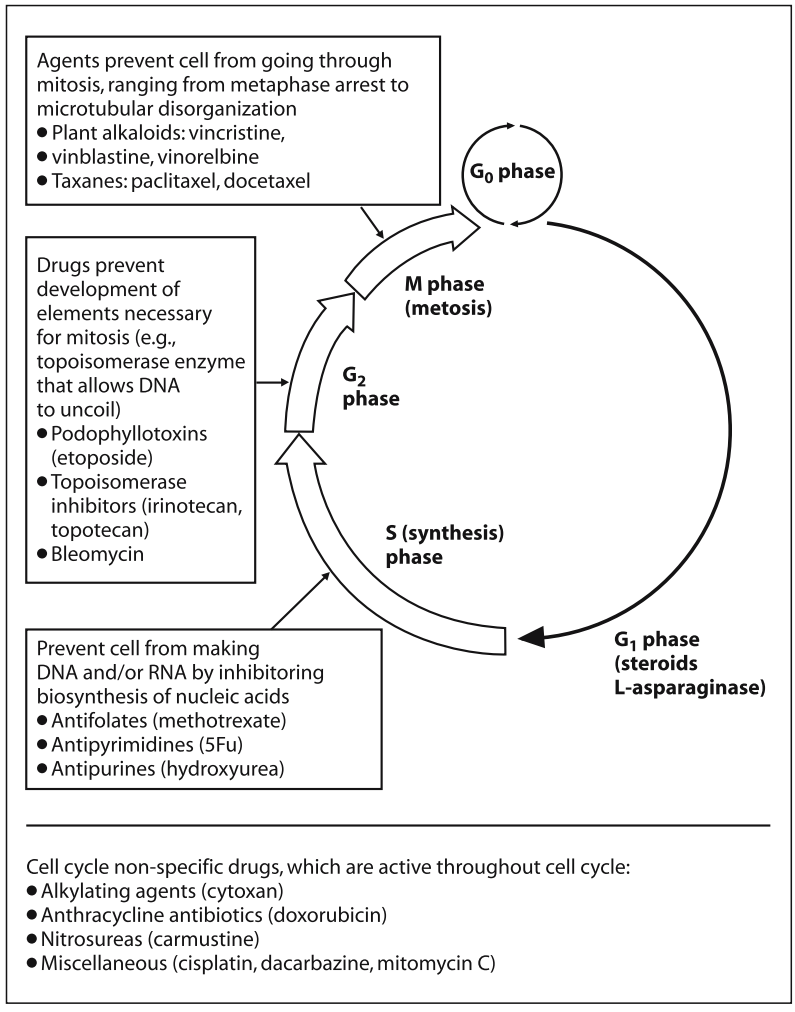

Table 8.1. Key terms related to the tumor kinetics

Term	Definition
Apoptosis	Programmed cell death
High growth fraction	High percentage of cells in active phases of the cell cycle
Low growth fraction	Few percentage of cells in active phases of the cell cycle
Doubling time	Time for any given number of cells to double

agent, or repair and reenter the proliferation process, whereas nonmalignant cells have a programmed number of cell divisions before apoptosis. To achieve maximum cell kill, a combination of chemotherapy agents with different mechanisms of action to target the various phases of cellular reproduction is given (Table 8.2).

Table 8.2. Classification of agents

Cell cycle phase-specific agents (CCPSA)	Cell cycle phase-non-specific agents (CCPNSA)
Antimetabolites	Alkylating agents
Plant derivatives	Antitumor antibiotics
	Corticosteroids
	Miscellaneous agents

8.2.1 Cell Cycle Phase-Specific Agents

- Kill actively dividing cells only during a specific reproductive phase.
- Most effective in tumors with a high growth fraction.
- Typical administration is in small divided doses given at repeated intervals or by continuous infusion to target cells during active phases of reproduction.

8.2.2 Cell Cycle Phase-Nonspecific Agents

- Kill cells actively dividing during any phase of the reproductive cycle.
- Disrupt DNA synthesis, causing cells to die.
- Most effective in tumors with a low growth fraction.
- Typical administration is via single intravenous (IV) bolus dose.

Some malignant cells demonstrate resistance to chemotherapeutic agents. The mechanisms of drug resistance (Ettinger et al., 2002) include the following:

- Decreased drug uptake by the cell.
- Increased efflux of drug out of the cell.
- Detoxification of drugs in the cell secondary to metabolic changes.
- Increased DNA repair.
- Alterations in the structure of drug receptor sites or targets.
- Decreased sensitivity to apoptosis.

Table 8.3. Key terms related to tumor pharmacokinetics and pharmacodynamics

Term	Definition
Absorption (bioavailability)	Rate and extent of absorption of a drug
Biotransformation	Metabolism of a drug
Clearance	Rate of drug elimination
Half-life	Time to reduce a drug's concentration by 50%
Area under the curve (AUC)	Exposure to drug over time
Excretion	How drug is eliminated from body

- Multidrug resistance gene from genetic mutation following exposure to particular chemotherapeutic agents.

To overcome resistance, most chemotherapeutic agents are administered at the maximum tolerated dose intensity and at consistent intervals. The use of multiple combinations of agents may provide a synergistic effect against the tumor cells. Agents with different toxicity profiles and cell cycle effects are typically part of a treatment regimen to enhance cell kill with minimal side effects.

Other principles used to optimize drug dose and scheduling to achieve maximum cell kill include pharmacokinetics (how the body processes the agent) and pharmacodynamics (how the agent affects the body) (Table 8.3). Physiologic and cellular factors, including concomitant agents, side effects, the child's weight and nutritional status, and organ dysfunction, may alter the agent's pharmacokinetics and pharmacodynamics.

Table 8.4. Types of antimetabolites and indications

Folate analogs	Purine analogs	Purine analogs
Methotrexate (amethopterin, MTX)	Mercaptopurine (Purinethol, 6-MP)	Cytarabine (ARA-C, cytosine arabinoside, cytosar-U)
	Thioguanine (6-thioguanine, 6-TG)	Fluorouracil (5FU, Adrucil)

8.3 Clinical Trials

Regulation of therapeutic products is mandated for all clinical research (Bernstein et. al, 2001). After agents are initially tested in vitro, preclinical studies are then performed in animals to determine toxic effects and safe doses to start clinical trials in human subjects. Before general use, investigational new drugs (INDs) are next given to adult subjects in three phases of clinical trials. Pediatric phase I studies usually follow adult phase I studies, starting at 80% of the adult maximum tolerated dosage (MTD).

8.3.1 Phase I Clinical Trials

- Establish the MTD by administering increasing dosages of the agent until unacceptable side effects are observed. The MTD is the highest dose able to be given without unacceptable side effects.
- Define dose-limiting toxicities as scored by the common toxicity criteria (CTC) scoring system defined by the National Cancer Institute.
- Characterize pharmacokinetics by determining how the agent is metabolized.
- Begin to define antitumor activity.

8.3.2 Phase II Clinical Trials

- Determine efficacy of an agent in a particular type of cancer.
- Further define the safety and toxicity profile of the agent.

8.3.3 Phase III Clinical Trials

- Determine effectiveness of the new treatment compared with existing standard treatment via randomized clinical trials.

8.3.4 Phase IV Clinical Trials

- Evaluate the agent's therapeutic profile following FDA approval for use.

8.4 Types of Chemotherapy Agents

8.4.1 Antimetabolites

8.4.1.1 Mechanism of Action

Antimetabolites are similar in structure (analogs) to normal cellular metabolites. They inhibit essential enzymes from binding in the DNA or RNA pathways, causing nucleic acids to produce the wrong codes (Table 8.4).

Methotrexate is the most widely used antimetabolite for treating childhood cancers. It is used in the treatment of acute lymphocytic leukemia (ALL), non-Hodgkin's lymphoma (NHL), the histiocytoses, and osteosarcoma.

Mercaptopurine is used in the treatment of ALL, chronic myeloid leukemia (CML), and histiocytosis. Thioguanine is used in gliomas. Cytarabine is often used in combination treatment for ALL and lymphoma. Fluorouracil is typically not used for the treatment of common childhood cancers.

Table 8.5. Alkylating agents

Nitrogen mustards	Nitrosoureas	Metal salts	Other
Mechlorethamine (nitrogen mustard)	Lomustine (CeeNU, CCNU)	Cisplatin (Platinol, CDDP)	Dacarbazine (DTIC)
Oxazaphosphorines: Cyclophosphamide (Cytoxan, CTX); ifosfamide (IFOS)	Carmustine (BiCNU, BCNU)	Carboplatin (CBDCA)	Procarbazine (Matulane)
Melphalan (Alkeran)			Busulfan (Myleran)

8.4.1.2 Side Effects

Myelosuppression, mucositis, nausea, and vomiting are the most common side effects following administration of antimetabolites. Other rare effects include dermatitis (characterized by erythema and desquamation), allergic reactions, acute pneumonitis, osteopathy, and neurotoxicity. A syndrome of high fever, malaise, myalgias, joint or bone pain, rash, conjunctivitis, and chest pain has been reported with standard doses of cytarabine.

8.4.2 Alkylating Agents

8.4.2.1 Mechanism of Action

The nitrogen mustards were the first class of alkylating agents used to treat cancer in the 1940s. These antitumor agents act through the bonding of saturated carbon atoms to cellular molecules, causing intracellular alkylation resulting in DNA damage and ultimately cell death (Table 8.5).

Several of the alkylating agents are widely used today as part of multiagent regimens for the treatment of childhood cancer. Cyclophosphamide is used in acute leukemia, a variety of solid tumors, and as part of a preparative regimen before bone marrow or peripheral stem cell transplantation. Phase II trials have demonstrated the activity of ifosfamide alone or in combination with etoposide in sarcomas, lymphoma, germ cell tumors, Wilms' tumor, and neuroblastoma. Melphalan appears to be active against rhabdomyosarcoma. The administration of bone marrow ablative doses of melphalan followed by rescue with autologous bone marrow transplant has resulted in high response rates in children with neuroblastoma, Ewing's sarcoma, and acute leukemia. The nitrosoureas have been used primarily to treat patients with brain tumors or lymphomas, and high-dose carmustine has been incorporated into transplant preparative regimens.

8.4.2.2 Side Effects

Myelosuppression is the primary dose-limiting side effect for most of the alkylating agents. Other common toxicities include nausea, vomiting, alopecia, allergic and cutaneous reactions, and gastrointestinal and neurological toxicity. Hemorrhagic cystitis is a toxicity that is unique to the oxazaphosphorines. It can range from mild dysuria and frequency to severe hemorrhage due to bladder epithelial damage. The reported incidence is 5–10% for cyclophosphamide and 20–40% for ifosfamide. The oxazaphosphorines are also nephrotoxic and can result in water retention, proximal tubular damage resembling Fanconi's syndrome, decreased glomerular filtration rate, and distal tubular damage. Cumulative doses exceeding 70–80 g/m^2 appear to be the primary risk factor. Neurotoxicity related to oxazaphosphorines is greater in children who previously received high cumulative doses of cisplatin. Cardiac toxicity has been reported with high doses of cyclophosphamide (doses >100–200 mg/kg). Ifosfamide has also been implicated as a cause of cardiomyopathy and arrhythmias at doses of 10–18 g/m^2 in patients undergoing transplant. Interstitial pneumonitis is associated with cyclophosphamide and ifosfamide.

Mechlorethamine exerts an anticholinergic effect that can lead to diaphoresis, lacrimation, and diarrhea. It also is a potent vesicant. With cumulative doses of the nitrosoureas of >1,500 mg/m^2, progressive renal atrophy has been reported. Cumulative doses of carmustine (>=1,500 mg/m^2) are associated with progressive, and frequently fatal, pulmonary toxicity. High-dose carmustine (300–750 mg/m^2 can produce hypotension, tachycardia, flushing, and confusion. High-dose busulfan (600 mg/m^2) has a high incidence of severe and persistent ovarian failure.

Busulfan is associated with hepatic venous occlusive disease (VOD) and seizures.

8.4.2.3 Long-Term Effects

Most alkylating agents are carcinogenic, mutagenic, and teratogenic. Gonadal atrophy that permanently affects reproductive function can occur. Nitrogen mustards and nitrosoureas have been linked to pulmonary fibrosis. Nephrotoxicity occurring after treatment with nitrosoureas, cisplatin, and ifosfamide can permanently damage renal function. Secondary leukemia is associated with the administration of melphalan.

8.4.3 Antitumor Antibiotics

8.4.3.1 Mechanism of Action

Antitumor antibiotics interfere with cellular metabolism via various mechanisms to inhibit synthesis of DNA, RNA, or both (Table 8.6). The anthracyclines form free radicals and inhibit topoisomerase II by blocking the rejoining of DNA strands. These agents are used in the treatment of ALL, lymphomas, sarcomas of soft tissue and bone, Wilms' tumor, neuroblastoma, and hepatoblastoma. Acute toxicities include myelosuppression, mucositis, nausea, vomiting, and diarrhea. Cardiomyopathy is a late toxicity associated with cumulative drug doses.

Table 8.6. Types of antitumor antibiotic and indications

Anthracyclines	Chromomycins	Miscellaneous
Daunorubicin	Dactinomycin (actinomycin-D)	Bleomycin
Doxorubicin		Mitomycin
Idarubicin		
Mitoxantrone		

Bleomycin chelates metals and binds to DNA to produce DNA breaks. Primary side effects are manifested in pulmonary (e.g., interstitial pneumonitis, pulmonary fibrosis) and skin (e.g., hyperpigmentation) toxicities. Dactinomycin is less widely used today.

8.4.4 Plant Derivatives

8.4.4.1 Mechanism of Action

Plant derivatives are obtained from plant material or manufactured from plant extracts. They interfere with normal microtubule formation and function, causing arrest during mitosis (Table 8.7). Vinca alkaloids extracted from the leaves of vinca plants (e.g., periwinkle) primarily arrest cells during mitosis (M phase) by interfering with microtubule formation and function. Vincristine is used to treat ALL, Hodgkin's and non-Hodgkin's lymphomas, rhab-

Table 8.7. Types of plant derivatives and indications

Vinca Alkaloids	Taxanes	Epipodophyllotoxins	Camptothecins
Vincristine	Paclitaxel	Etoposide	Topotecan
Vinblastine		Tenoposide	Irinotecan
Vinorelbine			
Vindesine			

domyosarcoma, Ewing's sarcoma, Wilms' tumor, brain tumors, and neuroblastoma, and vinblastine is used to treat histiocytosis, testicular cancer, and Hodgkin's disease. Neurotoxicity is the primary dose-limiting toxicity for vincristine. A single dose maximum is 2 mg. The dose-limiting toxicity for vinblastine is myelosuppression.

The epipodophyllotoxins inhibit topoisomerase II, producing DNA breaks during the S and G phases of cellular reproduction. They are used to treat ALL, Hodgkin's and non-Hodgkin's lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, germ cell tumors, and brain tumors. The primary dose-limiting toxicity is myelosuppression. Secondary leukemia has been reported with use of the epipodophyllotoxins.

The camptothecin analogs are extracts containing camptothecin. This agent was first isolated more than 50 years ago from a native Chinese tree, *Camptotheca acuminate*. Two camptothecin analogs, topotecan and irinotecan, have been approved by the FDA for clinical investigation. These agents target the intranuclear enzyme topoisomerase I and are often referred to as topoisomerase I inhibitors. During cellular reproduction as the DNA helix unwinds, camptothecin analogs cause a single strand of DNA to break. DNA damage occurs during the S-phase of cellular reproduction. Topotecan appears to be active against neuroblastoma and rhabdomyosarcoma. It is currently being investigated in phase III clinical trials. Both agents have demonstrated activity against gliomas and medulloblastomas.

Myelosuppression and diarrhea are the most common toxicities of the camptothecin analogs. Other toxicities include nausea, vomiting, alopecia, mucositis, elevated hepatic transaminases, and rash. Malaise and electrolyte abnormalities have been observed with irinotecan.

Table 8.8. Antiangiogenic agents

Angiostatin
Endostatin
Thalidomide (Thalomid)

8.4.5 Antiangiogenic Agents

8.4.5.1 Mechanism of Action

Antiangiogenic agents are a newer classification of agents that limit tumor growth and development by interfering with proliferating microvessels, a process called angiogenesis. Unlike the classical chemotherapy agents, antiangiogenic agents are not cytotoxic but can be used to limit further tumor growth and metastases (Table 8.8).

The resurgence of thalidomide following its initial use as a sedative in the early 1960s and its quick withdrawal from the market secondary to severe birth defects is due to its therapeutic benefit in the treatment of recurrent myeloma. To avoid birth defects, Celgene Corporation has developed a program called STEPS ("system for thalidomide education and prescribing safety") for controlling and monitoring access to thalidomide (Tariman, 2003). Other side effects include constipation, somnolence, fatigue, skin rash, deep vein thrombosis, peripheral neuropathy, and bradycardia.

8.4.6 Miscellaneous Agents

Miscellaneous agents include those with a wide range of actions that do not fit into a particular class. Miscellaneous agents include corticosteroids, asparaginase, and hydroxyurea.

8.4.7 Corticosteroids

8.4.7.1 Mechanism of Action

Corticosteroids modify the transcription of DNA by interfering with protein synthesis and cellular metabolism. Corticosteroids primarily used in pediatrics include prednisone and dexamethasone. These agents induce cell death by changing the expression of genes by binding to glucocorticoid receptors in the cell, and have a role in treatment regimens for ALL, lymphoma, Hodgkin's disease, histiocytoses, and brain tumors. They may also be used to control side effects (e.g., nausea, vomiting, increased intracranial pressure, anorexia) of other chemotherapeutic agents.

8.4.7.2 Common Side Effects

Common side effects include increased appetite, centripetal obesity, immunosuppression, myopathy, osteoporosis, avascular necrosis, peptic ulceration, pancreatitis, psychiatric disorders, cataracts, hypertension, precipitation of diabetes, growth failure, amenorrhea, impaired wound healing, atrophy of subcutaneous tissue, and osteoporosis.

8.4.8 Asparaginase/Peg-asparaginase

8.4.8.1 Mechanism of Action

A bacterial enzyme derived from *Escherichia coli* or *Erwinia carotovora*, asparaginase depletes asparagine by converting it to the nonessential products aspartic acid and ammonia, inhibiting DNA, RNA, and protein synthesis. Peg-asparaginase is a modified form of L-asparaginase. These agents are used in treatment regimens for ALL, depriving the leukemia cells of amino acids that are essential for survival and replication.

8.4.8.2 Common Side Effects

Allergic reactions occur in 20–30% of patients. Elevated liver enzymes, hepatic toxicity, and coagulopathies can lead to clotting and hemorrhagic complications. General malaise and changes in mental status may occur.

8.4.9 Hydroxyurea

8.4.9.1 Mechanism of Action

Hydroxyurea inhibits DNA synthesis by interfering with the ribonucleotide reductase enzyme system and is administered in the chronic phase of chronic myeloid leukemia (CML). Myelosuppression is a known side effect.

8.5 Administration of Chemotherapy Agents

Chemotherapy can be administered by the oral, intravenous, intramuscular, subcutaneous, and intrathecal routes (Table 8.9). Intraperitoneal and intraarterial routes are rarely used in administering chemotherapy agents to children. Assessment and education of the patient and family are essential before giving any chemotherapeutic agent. Nurses are responsible for giving the patient and family specific information about the treatment's side effects and interventions that can help minimize those effects. Patient education guidelines should consist of four parts: preparation, planning, presentation, and follow-up (Goodman, 2000).

8.5.1 Preparation

- Be available when treatment is explained to better reinforce the information that the physician has given.
- Identify learning needs and give written information regarding medications and prevention of side effects.
- Provide patients and families with self-care guidelines.
- Note the family's primary language and provide for an interpreter if needed.
- Identify any barriers to learning (e.g., anxiety, illiteracy).

Table 8.9. Chemotherapy agents and administration

Bleomycin (Blenoxane)	A test dose of 1–2 units of bleomycin should be given for the first two doses. Monitor vital signs every 15 minutes; wait a minimum of 1 hour before administering remainder of dose Administer IV slowly over at least 10 minutes (no greater than 1 unit/minute) at a concentration not to exceed 3 units/ml Bleomycin for IV continuous infusion can be further diluted in normal saline or dextrose water (D_5W) Administration by continuous infusion may produce less severe pulmonary toxicity Primary route of elimination is via renal excretion
Carboplatin (Paraplatin)	Administer by IV intermittent infusion over 15 minutes to 1 hour or by continuous infusion Compatible with ondansetron Injection site irritation and erythema can occur with infiltration but no ulceration or necrosis Needle or IV administration sets containing aluminum parts should not be used in the administration or preparation of carboplatin. Aluminum can interact with carboplatin, resulting in precipitate formation and loss of potency Maintain adequate hydration to minimize renal toxicity Route of elimination is via renal excretion
Carmustine (BiCNU)	Infusion may burn as it goes in and should be monitored closely Lower the IV rate and apply heat packs to relieve pain along the vein during administration Administer in 100–500 ml D_5W or NS as a 1–2-hour infusion Hypotension can occur if the infusion is given rapidly Avoid contact with skin; a brown stain may result Facial flushing and dizziness occurs infrequently Incompatible with polyvinylchloride infusion bags and sodium bicarbonate Administer by fresh stick if using a peripheral vein. Flush with 5–10 ml NS before and after administration to check vein patency Route of elimination is via renal and biotransformation
Cisplatin (Platinol)	Administer after appropriate hydration with mannitol Do not use sets that contain aluminum parts should not be used for administration of the drug due to loss of drug potency Keep urine output high with adequate hydration and diuresis Monitor hearing loss with audiograms At concentrations greater than 0.5 mg/ml, may act as a vesicant Primary route of elimination is via renal excretion Administer with caution in patients receiving other potentially nephrotoxic drugs
Cyclophosphamide (Cytoxan)	Encourage hydration and frequent voiding or the addition of mesna to help prevent hemorrhagic cystitis Administer IV dose slowly to prevent nasal congestion, headache, and dizziness When taking oral doses, encourage patient to take all pills before 5 pm while oral intake is adequate to minimize bladder contact with toxic metabolites
Cytarabine (Cytosine arabinoside)	Can be administered IM, IVP, IV infusion, or SQ at a concentration not to exceed 100 mg/ml High dose concentrations are usually administered by IV infusion over 1–3 hours or as IV. Continuous infusion For IT use, reconstitute with preservative-free saline or preservative-free lactated Ringer's solution Rotate sites for SQ injections

Table 8.9. (Continued)

Dacarbazine (DTIC)	Irritant; avoid extravasation Could be painful; administer slowly in 50–500 ml of solution over 30–60 minutes. A warm compress applied to the vein may decrease discomfort during infusion Protect drug from the light because it may turn a pinkish color Hypersensitivity reaction can occur with high-dose therapy
Dactinomycin (Actinomycin D)	Vesicant – use extravasation precautions
Daunorubicin (daunomycin)	Vesicant – use extravasation precautions Incompatible with heparin, 5-FU, and dexamethasone Irreversible myocardial toxicity may occur as total dosage approaches 300 mg/m^2 in children older than 2 years or 10 mg/kg in children less than 2 years; 550 mg/m^2 in adults; 400 mg/m^2 if the patient is receiving chest radiation
Dexamethasone	Greater than 80 % of oral form is absorbed Hepatic metabolism is primary method of elimination. Small amount via renal clearance Drug interactions include ketoconazole, estrogen-containing oral contraceptives, phenytoin, rifampicin, carbamazepam, barbiturates
Docetaxel (Taxotere)	Monitor liver functions carefully Avoid infiltration – irritant that may cause tissue damage depending upon the concentration
Doxorubicin (Adriamycin)	Vesicant – use extravasation precautions Incompatible with heparin, dexamethasone, furosemide, aminophylline, 5-FU Turns urine reddish-orange for 8–10 hours after administration Local erythematous streaking along the vein and or facial flushing may indicate too rapid a rate of administration Has a similar name and color to daunorubicin. Check to ensure that correct drug given to correct patient
Doxorubicin hydrochloride liposomal injection (Doxil)	Irritant – use extravasation precautions Total cumulative dose to decrease risk of irreversible cardiac toxicity
5-Fluorouracil (5-FU, Adrucil)	Administer in early morning on an empty stomach Patient should not eat for 2 hours before and after administration Wash hands immediately after topical application
Ifosfamide (Ifex)	Irritant – use extravasation precautions Administer over at least 15–30 minutes with aggressive hydration to reduce the incidence of hemorrhagic cystitis Compatible with mesna and may be infused concurrently when high-dose ifosfamide is given
Irinotecan (CPT-110)	Local irritant Stable for 4 hours at room temperature Refer to hospital protocols for treatment of irinotecan-associated diarrhea Instruct patient and parents to expect diarrhea, nausea, and vomiting Give medications for diarrhea
L-Asparaginase (Elspar)	Observe patient for 1 hour after IM injection for signs and symptoms of hypersensitivity reaction Intramuscular route more commonly used because of its lower risk of severe allergic reactions Consider test dose prior to administration Review standing orders for management of anaphylaxis Teach patient and family symptoms about reactions Route of elimination is via biotransformation Do not infuse through a filter Do not use if solution is cloudy For IV administration, give slow IVP over 30 minutes. Observe for hypersensitivity reaction

Table 8.9. (Continued)

Mechlorethamine hydrochloride (nitrogen mustard)	Avoid extravasation, inhalation of vapors, or contact with skin, mucous membranes, and eyes Potent vesicant, give with extreme caution Must be given within 5 minutes of preparation Administer via IVP via freely running IV line to avoid venous thrombosis and pain
Melphalan (Alkeran)	Administer oral meds on an empty stomach Ensure adequate patient hydration Irritant
Mercaptopurine (6-MP, Purinethol)	Oral administration concurrent with allopurinol results in a five-fold increase in bioavailability, increasing risk for severe hematologic toxicity Do not administer with meals as food decreases bioavailability
Methotrexate (MTX, Mexate)	Lower doses are usually given IVP without leucovorin rescue For high dose methotrexate (>100 mg/m^2) give leucovorin rescue, adequate hydration, and alkalinization. Maintain urine pH >6.5 and <9.0 Timing of leucovorin rescue is critical. Use for all doses >100 mg/m^2 and consider in any case of delayed excretion
Mitomycin (mitomycin C)	Vesicant – use extravasation precautions Skin ulceration may occur at sites distant from the site of drug administration
Mitoxantrone (Novantrone)	Irritant with a low potential for ulceration Extravasation may result in a blue discoloration of the skin Discolors serum and urine green for about 24 hours after administration Dark blue solution in vials. Sclera may turn blue Incompatible with heparin Administer IV over at least 5 minutes
Paclitaxel (Taxol)	Give premedications prior to infusion Irritant with a low potential for ulceration Administer in IV glass bottle or non-PVC IV bag; use non-PVC tubing and filter When administering with doxorubicin, cisplatin, or carboplatin, the doxorubicin, cisplatin, or carboplatin is given first to avoid disruption in elimination of the platinum compound
Teniposide (Vunom, VM-6)	Administer over at least 45 minutes to avoid hypotension Avoid extravasation; local phlebitis may occur Watch for hypersensitivity reactions: hypotension, bronchospasm, tachycardia, urticaria, facial flushing, diaphoresis, periorbital edema, vomiting, fever
Thalidomide (Thalomid)	Oral dosage form Absolute contraindication is pregnancy
Thiotepa (Thioplex)	A 1 mg/ml solution is considered isotonic, not a vesicant May cause local irritation
Topotecan (Hycamptin)	Typically administered daily for 5 days Continuous infusion schedules have been studied Intrathecal investigational use in neoplastic meningitis and recurrent CNS leukemia Synergistic effect if administered simultaneously with cyclophosphamide
Vinblastine (Velban)	Vesicant – use extravasation precautions Maintain adequate hydration Allopurinol may be helpful in preventing uric acid nephropathy Give stool softeners to help prevent constipation
Vincristine (Oncovin)	Vesicant – use extravasation precautions Dose range: 1.0–2.0 mg/m^2 with maximum dose 2 mg Dose by body weight in infants less than1 year of age: 0.03–0.05 mg/kg Administer over 1 minute at a concentration of 1 mg/ml

Table 8.9. (Continued)

Vinorelbine tartrate (Navelbine)	Venous irritation occurs in about 5% of patients; symptoms include erythema and pain at the site Administer over 6–10 minutes through a freely-running IV Local tissue damage, necrosis, or phlebitis may occur if the drug infiltrates Pain at tumor site may occur during administration

8.5.2 Planning

- Know the basics about the child's plan of care by reviewing the chart, the protocol, and the information regarding the antineoplastic agents to be given.
- Educate the patient and family about the medications before the treatment is given, and continue to educate with each treatment. Calendars, prescriptions, handouts, and drug information sheets may be useful visual tools to aid with education.

8.5.3 Presentation

- Introduce yourself and explain your role.
- Identify any questions or concerns before proceeding.
- Discuss the treatment process with the parents and give the patient age-appropriate information about the treatment, including the name of the medication, its purpose, the procedure for administering it, the length of the treatment, immediate events, expected follow-up, the medication's side effects, and home care after treatment.
- Describe potential side effects during and after administration, and offer interventions to minimize these effects. Include specific information: what to look for, how to take a temperature, when to call the doctor, how to do mouth care, and other pertinent information related to specific side effects.
- Give written instructions about activity, diet, hygiene, and medications.
- Describe any changes that may occur (e.g., urine color changes, ringing in ears) and identify appropriate interventions.

8.5.4 Follow-up

- Document the encounter and the patient's and family's responses to the teaching.
- Question the patient and parents regarding their understanding.
- Give the patient and family necessary phone numbers for follow-up, including emergency contacts, nurse, physician, home infusion companies, ambulatory clinic, pharmacy, and infusion company.

8.5.5 Nursing Preparation

- Review your institution's policies and procedures for chemotherapy administration.
- Assess response from previous treatments and current lab values.
- Review previous courses for any reactions.
- Assess the patient's prior experience with chemotherapy in order to provide additional medications with this course if needed. Note any monitoring parameters and any premedications that the patient may need.
- Review the treatment plan and orders.
- Compare written orders to formal drug protocol.
- Calculate drug dosages. Review the patient's height and weight and double-check the body surface area (BSA). The BSA is determined by a BSA calculator or nomogram or by calculating the square root of the height (cm) multiplied by weight (kg) divided by 3,600. In obese patients, some institutions use the ideal body weight (IBW) to calculate the BSA. Know your institution's policy regarding the administration of chemotherapy to obese patients. Ascites or edema may affect a patient's weight. Evaluate the prefluid retention weight as a possible basis for dosage calculations. The area under the curve (AUC) is used in patients receiving carboplatin. This dose is calculated based on the glomerular filtration rate (GFR) or the creatinine clearance.

- Review the cytotoxic agents that will be administered and any side effects. Note the emetogenic potential, any premedications needed, or any fluids needed prior to administration.
- Assess the records for any dose modifications. Doses are reduced if there has been severe toxicity with prior treatments. Many protocols or treatment regimens outline how the dose reduction is to be done. Patients may have an increase in the medication if they have tolerated treatment very well. These adjustments will be outlined in the treatment protocols.

8.5.6 Infusion Preparation

- Verify drug order and recheck doses and BSA calculations.
- Obtain agent and double-check for accuracy.
- Obtain supplies and equipment for safe drug administration (e.g., extravasation kit, infusion pump).
- Wash hands and don appropriate protective clothing.
- Assess the child's developmental level and coping mechanisms (Table 8.10).

8.6 Routes of Administration and Practice Considerations

8.6.1 Topical

- Instruct patient and/or parent on the application to the affected area.
- Avoid mucous membranes.
- Use safe chemotherapy handling procedures.
- Observe for adverse reactions (e.g., severe burning or rashes).

8.6.2 Oral

- When preparing oral medications, select the most accurate method to measure medications.
- Give milk or food with oral medications that are irritating to the gastrointestinal mucosa. (e.g., prednisone). Make sure milk products or acidic juices do not interfere with absorption (e.g., 6-MP).
- If the child vomits within 10 minutes of taking the medication, the dose should be repeated (Table 8.11).
- Provide calendars or pill boxes to help patients take the medication on schedule.
- It may be necessary to watch the child take medications.
- During adolescence, teenagers develop more independence and are highly influenced by peers. If the side effects of the medication are unpleasant, the teen may not be compliant.

8.6.3 Intramuscular

- Follow your institutional policy regarding administration of intramuscular (IM) injections.
- Consider appropriate syringe size for small volumes.
- Infants have very few IM injection sites. Usually, 1 ml is the maximum volume that should be injected in a single site for infants and children. The muscles of a small infant may not tolerate more than 0.5 ml.
- The general preferred site for IM injections in an infant is the vastus lateralis.
- The preferred site for IM injections in children of all ages is the ventrogluteal site (Wilson and Perry, 1999).
- The recommendation for using the dorsogluteal site is to wait until after the child has been walking at least 1 year.
- Alternate the injection sites. Repeated use of a single site is associated with fibrosis of the muscle and subsequent muscle contractures. Injections close to large nerves (e.g., the sciatic nerve) may cause permanent disability.
- Use safety precautions in administration, including positive patient identification and confirmation that the medication is not a vesicant.
- Decrease pain by using ethyl chloride or a topical anesthetic (e.g., EMLA) at the injection site. Change the needle if it pierced the rubber stopper on the medication vial, warm medications to room temperature, and use distraction techniques.
- Never give a sleeping child an injection.

Table 8.10. Developmental issues related to the administration of chemotherapy

Ages	Developmental milestones	Nursing interventions
Birth – 1 month	– Reaches toward mouth; strong reflex to grasp objects – Poor head control – Tongue movement may force items out of infant's mouth – Strong suck reflex – Responds to tactile stimuli – Stops sucking when full – Goes from sitting to crawling to walking – Tongue may protrude when swallowing – Responds to tactile stimuli	– Tape lines (central lines, IV lines) out of reach of infants. They like to grasp objects and could pull on lines – Place liquid in an empty nipple, place the nipple in the infant's mouth, and allow the child to suck – Draw medication up into a syringe, place the syringe along the inside of the child's cheek, and administer medication slowly. Infants will suck medicine from a needleless syringe or dropper in small increments (0.5 ml) at a time – Use a nipple or special pacifier with a reservoir for the drug. (e.g., Medibottle) – Raise the child's head slightly during administration to avoid aspiration
1 – 30 months	– Walking to running – Feeds self – Uses cup – Development of 2nd molars – Expresses feelings; may throw temper tantrums – Follows simple directions – Responds to and participates in activities of daily living	– Consider putting medications in a cup rather than a syringe – Secure IV lines – Explain all procedures in age-appropriate language – Use distraction when frustration increases; direct the child to other, less frustrating activities; and reward the child's positive response
30 months – 6 years	– Knows name – Enjoys making decisions – Has fantasies and fears mutilation – More coordinated – Loses teeth	– Explain all procedures in age appropriate language – Allow to have decision-making opportunities – Explain procedures in age-appropriate language – Offer bandages with needle sticks
6 – 12 years	– Strives for independence – Concerned with body image – Tells time – Peer support and interaction are important – Has concern for body mutilation	– Offer praise when they handle a stressful situation – Allow to express feelings – Give the child something to concentrate on during painful procedures – Have the child assist with care
12+ years	– Strives for independence – Understands abstract theory – Reasons are influenced by peers – Questions authority figures – Concerned with sex and sexuality	– Give choices in care – Explain procedures and allow them to ask questions – Provide reasons for medications

Table 8.11. Special tips for giving oral chemotherapy to children (from Meeske and Ruccione, 1987)

Problems administering	Tips and notes
Oral medications to a child who cannot swallow	The ability to swallow pills depends more on the child's past experiences than on age Do not use a medication that has an unpleasant taste to teach the child how to swallow a tablet Teach child to swallow by starting with small candies (e.g., Tic Tacs or M&Ms) When teaching the child to swallow, have him place the tablet on the tongue and concentrate on swallowing the liquid instead of the pill Consult child-life or behavioral medicine if available to help the child with swallowing tablets Do not crush unpleasant meds and try to administer. Give to patient whole or crush and place in gelatin capsule
Tablets	Tablets may be chewed if palatable Do not crush sustained-release tablets If a tablet is appropriate for crushing, crush it into a fine powder and mix with a small amount (about 1 teaspoon) of a sweet substance, such as honey (except in infants, due to the risk of botulism), flavored syrups, jam, fruit, pudding, flavored yogurt, sherbet, or ice cream. Make sure food or milk does not interfere with absorption (e.g., 6-Mercaptupurine) Avoid using the child's favorite foods to disguise medications
Capsules	Open capsules (e.g., lomustine, procarbazine, hydroxyurea) and sprinkle contents into food Not all capsules should be opened; consult with a pharmacist
Medications with an unpleasant taste (e.g. prednisone)	Give a chaser of water, juice, soft drink, or flavored juice after the drug Discourage the chewing of tablets Mix crushed tablet in juice or food with a strong taste (e.g., peanut butter, maple syrup, fruit-flavored syrup) Mix crushed tablet with a small amount of juice or food. Remember that the child must take all to receive the entire dose Crush pills and place in a gelatin capsule Do not mix tablet powder with essential food items because avoidance may develop through conditioned association When the medication has un unpleasant taste, have the child pinch his nose and drink the medicine through a straw (much of what we taste is associated with smell)
Partial doses	Break scored tablets only Pharmacy may crush tablets and dispense in unit-dose packages If a tablet is appropriate for crushing, crush under BSC hood and put the prescribed in a small amount of juice acceptable to the child
Compliance at home	Negotiation, partnership, empowerment and timing Evening administration of 6mp may be easier for families to remember

8.6.4 Subcutaneous Injection

- Some medications (e.g., gCSF, monoclonal antibody) are given daily via subcutaneous (SQ) injection.
- Parents may need to learn injection techniques to administer these medications at home. Begin educating patients and families as early as possible to maximize the amount of practice time.
- Recommendations include offering techniques to decrease the perception of pain, demonstrating the angle for SQ injection, and demonstrating common sites of administration, including the abdomen, the center third of the lateral aspect of the upper arm, and the center third of the anterior thigh.

- It is important to monitor the platelet count. If it is <50,000, additional pressure will need to be maintained at the injection site.

8.6.5 Intravenous

- There are several different ways to administer intravenous chemotherapy: peripheral IVs, PICC lines, and central venous catheters.
- For ease of administration, central lines are commonly used in children receiving chemotherapy.

8.6.6 Peripheral IV Administration

- Prepare the child and parents for the procedure. Medical play is an excellent stress reduction technique and can be used when explaining to a patient what is about to occur. If child life is available at your facility, consult for highly anxious patients and families.
- Arrange for a quiet, private setting for the child during the IV insertion, but avoid safe places such as the child's hospital room, the playroom, or the activity room.
- Provide distraction activities that allow the child to "assist" (e.g., holding the supplies, cleaning the site with alcohol, and assisting with taping).
- Assess whether the child has had an IV inserted before. Some children have never had the experience of an IV catheter, whereas many others will remember the experience quite vividly. If the child has had many IVs, ask the parents or the child which site usually works best.
- Select an appropriate IV site. There are many things to consider regarding peripheral IV insertion sites. Follow institutional guidelines related to starting an IV. Whenever possible, avoid using the child's dominant hand. Foot veins should be avoided in children who are learning to walk or are already walking. Choose a site that restricts movement as little as possible. For veins in the extremities, it is best to start with the most distal site. Avoid using veins in the antecubital fossa for chemotherapy administration. Scalp veins in an infant less than 1 month old can be used as IV sites; however, do not administer a vesicant into a scalp vein.
- A warm pack may be used to distend the veins.
- Maintain the integrity of the vein. In young children the needle or catheter should be firmly secured with tape and protected with a commercial shield. This protects the IV site from any playing and tugging at the IV site that the child may do. This intervention may not be necessary with older children or adolescents. When working with children, padding the undersides of the butterfly wings of the access needle may be necessary if the needle does not lie securely on the skin. Maintain visualization of the site so that infiltration can be identified early.
- Assess for blood return and patency.
- Certain institutional policies state that if a vesicant is to be given, a new IV site must be accessed.
- Pharmacologic interventions: Consider use of an anesthetic for pain during IV insertion. However, it is not advisable to use a topical anesthetic cream (e.g., EMLA) for PIV insertion when a vesicant is to be administered because the cream may leave the patient unable to feel the sensation associated with an extravasation.

8.6.7 Intrathecal/Intraventricular

- For intrathecal or intraventricular administration, the child may require conscious sedation or general anesthesia. Consult your institution's guidelines.
- Have the child lie flat for 30 minutes to an hour after intrathecal administration to facilitate drug distribution throughout the central nervous system and to potentially minimize headache.
- Keep intrathecal medications separate from intravenous medications to reduce the risk of giving the wrong medication intrathecally. Accidental administration of the wrong drug could be fatal.

8.6.8 Post-administration Guidelines

Post-administration documentation should include the following:

- Patient's name, date, and time.
- Site, needle gauge, and length or type of central line.
- Site assessment prior to infusion.

- Presence of blood return before, during, and after the infusion.
- Amount and type of flush used.
- Chemotherapy agent, route, dose, and duration of infusion.
- Patient's response to infusion.
- Patient education.
- Follow-up care required.

8.6.9 Professional Guidelines to Minimize the Risk of Medication Errors

8.6.9.1 Prescribing Errors

- Only a healthcare provider responsible for the care of the patient and most familiar with the chemotherapy regimen should write the orders.
- Use preprinted order sheets, or if these are not available, the generic drug name should be written clearly and in its entirety.
- Avoid using abbreviations.
- The name of the agent, the dose in mg/m^2, the dose to be given, the total daily dose, and the total number of days that the dose is to be given must be indicated on the order sheet.
- Avoid using ".0" to avoid ten-fold dosing errors.
- The original orders should be sent to the pharmacy. Do not transcribe or rewrite the order before sending it to the pharmacy.

8.6.9.2 Compounding

- Compounding should be performed by a well-trained pharmacist.
- In most settings, computer-generated labels are used. Make sure all information is contained on the label: the child's name, name of medication, amount of drug, and the amount and type of solution the drug is mixed in.
- Label medications with warning labels as needed; for example, "Do not give intrathecally," "Chemotherapy – Handle with care," or "For oral use only."

8.6.9.3 Dispensing

- Dispense medication on trays or in plastic zip-locked bags large enough to hold all the drugs given to one patient.
- Do not combine more than one patient's drugs in the bags or on the tray.

8.6.9.4 Administration

- Administer in a safe, nonhurried environment.
- Chemotherapy should only be administered by a chemocompetent nurse.
- Double-check the treatment plan, medication, and orders prior to administration.

8.7 Safe Practice Considerations

"Safety in the workplace is the prevention of injury by control of the environment and the use of proper work methods" (Harrison, 1996, p. 906). The Occupational Safety and Health Administration (OSHA) requires that healthcare institutions provide safe working conditions for those under their employment. Institutions should develop policies based on OSHA's guidelines for the safe handling of cytotoxic agents. These guidelines are to assist healthcare personnel who may be exposed to cytotoxic drugs through inhalation, skin absorption, or trauma (Table 8.12). The guidelines listed are based upon OSHA recommendations.

8.7.1 Mixing Chemotherapeutic Agents

- In large oncology centers chemotherapy is usually prepared by pharmacy personnel, but in some hospitals and small physicians' offices, chemotherapy may be prepared by physicians and nursing staff. If this is the case, OSHA has guidelines to aid in mixing chemotherapy (OSHA, 2002).
- Chemotherapy should be prepared under a biological safety cabinet (BSC). Even if care is taken, there may be opportunity for absorption through inhalation in areas that are not well ventilated. The blower on the vertical airflow hood should be on at

Table 8.12. Toxic effects of exposure to cytotoxic agents

Dermatologic effects	Nitrogen mustard is a potent irritant. May cause chemical burns. Inhalation of vapors can cause irritation of nasal and bronchial mucous membranes and the eyes BCNU causes inflammation and hyperpigmentation of skin following exposure during administration Doxorubicin causes contact dermatitis 5 FU is a topical irritant
Ocular effects	Doxorubicin may cause intraocular damage after accidental instillation during mixing. Burning and lacrimation, edema of upper lid, conjunctival injection, photophobia, and foreign body sensation may occur 5-FU may cause tear-duct fibrosis ARA-C may cause reversible corneal toxicity Vinblastine causes serious corneal injury
Systemic effects	Symptoms can include lightheadedness, dizziness, nausea, vomiting, flu-like symptoms, headache, cough, wheezing, urticaria rashes. Long-term exposure may cause liver disease

all times. Venting to the outside is preferable if feasible. BSC units should be recertified by a qualified technician every 6 months or any time the cabinet is moved. Technicians servicing these cabinets or changing high-efficiency particulate air (HEPA) filters should be warned of the nature of the cytotoxic agents and should use the same personal protective equipment as an employee dealing with a large spill. The cabinet should be cleaned daily with 70% alcohol and decontaminated weekly, whenever spills occur, or when the cabinet requires service or certification.

- Personal protective equipment should be worn, and hands should be washed prior to donning equipment. Surgical latex gloves should be worn. New research indicates that surgical latex gloves are less permeable to many cytotoxic drugs than the polyvinylchloride gloves previously recommended. A double layer of gloves is substantially less permeable and should be used if double-gloving does not interfere with technique. Gloves should be changed immediately if they are torn or punctured. A protective gown made of lint-free low-permeability fabric with a closed front, long sleeves, and elastic cuffs must be worn. Surgical masks do not protect against the breathing of aerosolized agents. If used in place of a BSC cabinet, a plastic face shield or splash goggles complying with ANSI criteria should also be worn. An eyewash fountain should be made available. All used gowns, gloves, and disposable materials used in preparation should be disposed of according to the institution's toxic waste procedures.
- Cytotoxic agents should be prepared in one centralized area, and the work areas should be provided with a closable, puncture-resistant, shatterproof container for disposing of contaminated sharps and breakable materials.
- Proper aseptic techniques are essential for worker protection.
- Use the appropriate technique when opening ampules.
- Syringe bottles and IV bottles should be labeled with the patient's name and room number (if applicable), drug name and quantity per total volume, route of administration, date and time prepared, dose, expiration date, and storage requirements (if the drug is not to be transported immediately). All syringes, IV bags, and bottles containing cytotoxic drugs should be labeled with a distinctive warning label such as "Chemotherapy – handle with gloves – dispose of properly."
- Using large-bore needles, #18 or #20, will avoid high-pressure syringing of the solutions.
- Wash hands immediately after handling cytotoxic agents.
- If oral medications are to be crushed, that needs to be done under the BSC cabinet.

- IV tubing should have Luer-Lock connections with the connection sites taped. IV tubing should be primed under a BSC cabinet.
- There should be no eating, drinking, smoking, chewing of gum or tobacco, application of cosmetics, or food storage in areas where antineoplastic agents are used.

8.7.2 Transporting Cytotoxic Agents

- Drugs should be securely capped or sealed and packaged in impervious packing materials for transport.
- Personnel involved in transporting should be cautioned and trained in the necessary procedures should a spill occur.
- All drugs should be labeled with a warning label and clearly identified as a cytotoxic agent.
- Transport methods that produce stress on contents (e.g., pneumatic tubes) should not be used.

8.7.3 Safe Handling After Chemotherapy

- Institute universal precautions when handling the blood, emesis, excreta, or linen soiled with bodily fluids of a patient who has received chemotherapy within 48 hours.
- For children who are incontinent of urine, clean the skin well with each diaper change. Apply a barrier ointment so the patient will not develop chemical burns from contact with contaminated urine. Change diapers frequently.
- Have the patient flush the toilet with the lid down at least twice with each void for 48 hours after receiving chemotherapy.
- Bed linens at home that become contaminated should be washed twice in hot water in a washing machine. No other household garments should be washed with the bed linens.
- Bed linens in the hospital should be placed into a plastic contamination bag. These items need to be prewashed before being washed with other hospital linens.
- Personal protective equipment should be used in handling all linens soiled by someone on chemotherapy.
- If a patient expires within 24 hours of receiving a cytotoxic agent, the mortuary staff needs to be informed of the potential for exposure to chemotherapy (Harrison, 1996).

8.7.4 Disposal of Cytotoxic Materials

- In the hospital, locate and review institutional policies before handling cytotoxic agents.
- Place chemotherapy in a sealable leak-proof plastic bag.
- Use puncture-proof containers for sharps and breakable items.
- Do not break or recap needles.
- Wear gloves when disconnecting the chemotherapy.
- Dispose of the chemotherapy bag and tubing as an intact unit. Capping the end of the infusion tubing after disconnecting it from the patient can decrease the chance of chemotherapy getting onto the skin.
- Only housekeeping personnel who have received instructions regarding the safe handling of hazardous materials should be allowed to handle the containers filled with cytotoxic agents.

8.7.5 Spill Management

- Spill kits should be available in all admixing and administration areas.
- Prior to giving chemotherapy, review the institution's policy regarding spills. Everyone who works with cytotoxic drugs should be trained in spill management (Harrison, 1996); this includes shipment-receiving personnel, physicians, nurses, pharmacists, housekeepers, and employees involved in transporting or storing the drugs. These individuals should receive orientation regarding the known risks of relevant techniques and procedures for spills, for the handling of and proper use of protective equipment, and for medical procedures of cytotoxic drugs.
- In the event of a chemotherapy spill, notify the institutional safety officer and post a sign or have a person available to warn others of the spill. Don protective clothing including heavy-duty gloves, gown, NIOSH respirator, and eye protection.

- In the event of a chemotherapy spill, use the items in the spill kit to prevent the spill from contaminating other areas. Absorb the spill with chemical spill pillows, gauze pads, or absorbent towels. Decontaminate the area if a neutralizing agent is available. Seal and double-bag all contaminated materials for disposal. Broken glass should only be handled with heavy-duty gloves and a disposable scoop. Clean the spill according to the type of spill and the location. A dry powder should be covered with a generous supply of water-dampened absorbent towel or gauze (Harrison, 1996). On hard surfaces, wipe up liquids using absorbent pads. On carpeted surfaces, use absorbent powder to absorb the spill and a vacuum specifically for hazardous clean-up to remove the powder (Oncology Nursing Society, 2001).
- Report and document spill according to institutional policy. Include in documentation the name of the agent and the volume spilled, how the spill occurred and how it was managed, and the names of personnel, patients, and others exposed to the agent.

8.7.6 Procedures Following Accidental Exposure

- If direct skin exposure occurs, rinse immediately with water (Table 8.11). An emergency eyewash or shower should be available.
- For eye exposure, rinse with an eye wash solution for at least 15 minutes (Table 8.11).
- Report all episodes of exposure to employee health.

8.7.7 Storage

- Store chemotherapy drug containers in a location that permits appropriate temperature and safety regulation.
- Label all drug containers to indicate hazardous materials.
- Provide instructions on what to do in case of accidental exposure (e.g., Material Safety Data Sheets).
- Ensure that packaging is intact before removing chemotherapy drug containers.

8.7.8 Medical Management

- Employees who are pregnant or planning to become pregnant, who are breastfeeding, or who have a reason to limit exposure to cytotoxic agents (e.g., hypersensitivity reactions) should be offered work in areas where exposure is not likely.

8.8 Administration of Chemotherapy in the Home

The home care industry is the fastest growing segment of the healthcare industry. Home health agencies provide a wide range of services and can be extremely effective. They can provide intravenous hydration, administer some chemotherapeutic agents, and administer other symptom management drugs. The administration of chemotherapy in the home provides an alternative to hospitalizations and numerous outpatient visits for the pediatric oncology patient.

Studies have shown that home chemotherapy can have a positive impact on patient outcomes, family satisfaction, and the provision of cost-effective care (Close et al., 1995). The frequent hospitalizations and clinic visits required for the treatment of children with cancer disrupt the patterns and flow of family life and the education and socialization of children. Administration of select chemotherapy at home results in lower billed charges, reduced expenses, reduced loss of income for parents, and improved patient and family satisfaction.

The technological advances in equipment and supportive measures (Table 8.13) over the last 20 years have attributed to the increased use of home health agencies.

The National Association of Children's Hospitals and Related Institutions (NACHRI) conducted a patient care oncology focus group. The group developed specific recommendations for home care requirements for children and adolescents with cancer (NACHRI, 2000), and the Association of Pediatric Oncology Nurses reviewed and endorsed these recommendations. A summary of the recommendations follows:

Table 8.13. Functions and equipment provided by home health agencies

Provide central venous access education and care
Administer chemotherapy regimens and antiemetic support
Administer continuous IV infusions, IV hydration, and IV antimicrobial and antifungal treatment
Provide nutritional support
Provide pain management
Provide programmed infusion pumps

- Pediatric health care providers, the payor, and the family must collaborate to select the most appropriate healthcare delivery setting based on assessment of the child and family.
- Families must be given the option to interview and select a home healthcare agency based on the child's specific needs and the agency's expertise (e.g., skilled care requirements, durable medical equipment).
- Home care agencies offering oncology services to children must ensure access to home care nurses and pharmacists with documented competency in pediatrics and oncology.
- Mechanisms must be established to ensure adequate and timely communication between the home care agency, payor, primary care provider, and pediatric oncology specialist about the child's long-term treatment.

8.8.1 Eligibility Guidelines for Home Chemotherapy

The following criteria should be considered before implementing a home treatment plan:

- The medical, nursing, and psychosocial staff should evaluate, with the family, the appropriateness for home chemotherapy
- A comprehensive discharge plan that incorporates all aspects of home health care and supportive services is necessary.
- The child's medical condition should be stable and easily managed in the home by family caregivers partnered with home care professionals.
- Agents that have previously caused an adverse reaction in the patient should not be administered at home.
- Any therapy with a high affinity for anaphylaxis should not be given at home (e.g., L-asparaginase).
- A central venous access device may be required for continuous infusions, vesicants, and parenteral nutrition.
- Prior authorization from the insurance company is necessary for all home administration.
- The best supportive care regimen to prevent and minimize side effects of the therapy in the home should be established.
- The home environment must include general cleanliness, electricity, telephone, refrigeration, plumbing, and heating and cooling systems.
- The caregiver and parent must be physically present in the home during infusions and must demonstrate their ability to operate the infusion pumps and lines.

8.8.2 Home Care Agency Chemotherapy Safety Guidelines

The following are guidelines and criteria to consider for patients and families participating in home chemotherapy:

- The agency should be accredited and licensed by state regulatory agencies.
- There should be a competency program for pharmacists, compounding technicians, and pediatric nurses demonstrating skill with central venous access devices.
- Chemotherapy certification should be required, including safe administration of vesicants and management of side effects.
- Written policies and procedures that address the handling and safe administration of chemotherapy must be in place.
- A system for documentation of double-checking chemotherapy orders must be in place.

8.8.3 Management of Home Chemotherapy Guidelines

- All home care providers must be notified of the planned discharge and start of home therapy. A chemotherapy plan should be sent to the provider.
- The pharmacist must receive the orders the day before discharge in order to process the order safely and communicate questions to the oncology team.
- A visit in the house by the home care nurse should be set up as soon as possible after discharge.
- A chemotherapy spill kit must be available in the home that includes gloves, goggles, a respirator mask, absorbent materials, large plastic disposal bags, and toxic waste labels (Table 8.14).
- Appropriate extravasation interventions and policies must be available.
- Approved laboratory services must be available.
- Family and caregiver education regarding the chemotherapy agent, the treatment schedule, and the method of administration should be ongoing (Table 8.15).
- Patient handbooks, contact numbers, and educational materials should be provided.

Table 8.14. Contents of a home care chemotherapy kit

IV start kit	Normal saline vials
CVL dressing kit	Heparin flush
Implanted catheter access kit	100-cc bag NS
IV tubing	Chemotherapy spill kit
Extension tubing	Oral airway
3-cc syringes	Cold pack and warm pack
5-cc syringes	
10-cc syringes	
Injection cap	
Alcohol preps	Anaphylaxis kit:
Tourniquet	IV diphenhydramine
Latex gloves	IV epinephrine 1:1,000
Mask	IV hydrocortisone
Sharps container	
Gauze	
Bandages	

Table 8.15. Family/caregiver education and information needs for administration of home chemotherapy

Names and indications of all prescribed drugs	Care of the central venous access device
Common side effects of all drugs	Preparation of equipment and working area for giving chemotherapy and medications
Action to take in the event of an allergic reaction	Drug administration procedure
Action to take if child becomes febrile	Technique for taking child's temperature
Safe storage and disposal of drugs and sharps in the home	Monitoring of intake and output
Importance of compliance with prescribed medication	Understanding of how to observe for and report any problems
Details of planned home visit and/or follow-up	Treatment plan, medication record, and allergy sheet in a notebook or folder for ready reference
Knowledge of where to seek advice, with 24-hour contact numbers	Equipment troubleshooting
Handling of antineoplastic agents in the home	Emergency contact numbers (should be displayed near telephones in the home)

Table 8.16. Vesicant (*V*) and irritant (*I*) antineoplastic agents

Alkylating agents	Antitumor antibiotics	Plant alkaloids
Nitrogen mustard (V)	Doxorubicin (V)	Vincristine (V)
Cisplatin (V)	Daunomycin (V)	Vinblastine (V)
Carboplatin (I)	Dactinomycin (V)	Vinorelbine (V)
Ifosfamide (I)	Mitomycin C (V)	Etoposide(I)
		Teniposide (I)

Table 8.17. Key terms related to extravasation

Extravasation	Leakage of a drug into subcutaneous tissue, potentially causing local inflammation, hyperpigmentation, induration, ulceration, pain, sloughing of tissue, damage to nerves and tendons, necrosis
Irritant	Agent that can cause aching, tightness, or phlebitis at the injection site or along the vein (with or without an inflammatory reaction)
Vesicant	Agent that can cause tissue destruction
Delayed extravasation	Extravasation in which symptoms occur 48 hours or more after drug is given
Flare	Local allergic reaction without pain that is usually accompanied by red blotches along the vein. Symptoms subside within 30 minutes with or without treatment

8.8.4 Evaluation of Home Administration of Chemotherapy

Continuous collaboration among the pediatric oncology treatment team, the home care agency, and the family is essential throughout treatment. The treatment team must have a mechanism for evaluating family and treatment center satisfaction with the home care services. Children with cancer should be ensured access to appropriate services for their care.

8.8.5 Immediate Complications of Chemotherapy Administration

Although most immediate complications from chemotherapy are rare, it is important that the pediatric oncology nurse be knowledgeable on how to recognize and manage adverse events. Recognizing side effects that can be potentially damaging or life-threatening is an important skill that at times may be difficult due to the fact that infants and children have difficulty communicating symptoms.

8.9 Extravasation

An extravasation that occurs in a child may lead to an increased risk for injury because of the patient's inability to verbalize pain or changes in sensation during vesicant administration (Tables 8.16, 8.17). Rates of occurrence range from 0.5–6%. Consequences of extravasation can include significant tissue damage, altered limb function, and pain (Table 8.16) and can impact quality of life for long-term survivors (Kassner, 2000).

8.9.1 Pathophysiology of Extravasation

Two major mechanisms are believed to cause tissue damage. Some agents (e.g., anthracyclines) are absorbed by local cells in the tissue and bind to DNA, causing cell death. The vesicant agent is then released into the surrounding tissue, causing further cell death. Healing is inhibited when the process repeats itself and the drug is absorbed by other cells. Dox-

orubicin at significant levels has been found in surrounding tissues for weeks to months after an extravasation (Albanell and Baselga, 2000).

Other agents (e.g., vinca alkaloids) do not bind to cellular DNA. Local tissue damage is more easily neutralized than damage to surrounding tissues.

8.9.2 Risk Factors of Peripheral Extravasation

Peripheral administration of vesicant agents in children is challenging. Children may be at risk for serious injury due to the difficult access of peripheral veins. Other risk factors include the following:

- Anatomic issues, including site of venous access, venous integrity, vessel size, and blood flow (Kassner, 2000)
- Duration of tissue exposure and the amount of infiltrate (Kassner, 2000)
- Types of intravenous catheters; for instance, steel needles are associated with increased risk of extravasation (Kassner, 2000)
- Smaller-gauge catheters, which allow easier blood flow around the catheter (Beason, 1990)
- Inability of the child to communicate pain or change in sensation during the infusion (Kassner, 2000)

8.9.3 Risk Factors of Extravasation with Central Venous Access Devices

Although the use of central venous access devices (CVADs) in the pediatric oncology population has improved the ease and safety of chemotherapy administration, especially for continuous infusions of vesicants, the risk for extravasation still exists. These factors include the following:

- Needle dislodgement, incorrect needle length, and incomplete or improper needle access technique (Schulmeister and Camp-Sorrell, 2000)
- Increased activity or sleeping on the side of the port-a-catheter (Kassner, 2000)
- Rupture or tear in the catheter or port septum (Kassner, 2000)
- Migration of the catheter tip (Oncology Nursing Society, 2002)
- Fibrin sheath formation at the catheter tip (Oncology Nursing Society, 2002)
- Persistent withdrawal occlusion (e.g., inability to draw blood but able to flush the line without difficulty) or "positional blood draws" (Kassner, 2000)
- Tugging or improper securing of IV tubing

8.9.4 Administration Techniques That May Help Prevent Extravasation

8.9.4.1 Peripheral Administration

- Only nurses who are skilled at venipuncture techniques and know how to assess and intervene in case of extravasation should administer vesicant agents. Competency should be reviewed yearly (Camp-Sorrell, 1998).
- It is recommended that a new peripheral site be used versus an existing IV site, if possible (Camp-Sorrell, 1998).
- Large veins in the nondominant upper extremity should be used whenever possible. The forearm is recommended because this area has more fleshy soft tissue and a decreased risk of physical impairment if extravasation does occur (Kassner, 2000).
- Repeated attempts to place the catheter below the original IV site should be avoided for 24 hours to allow the vein wall to heal (Kassner, 2000).
- Avoid the dorsum of the hand and foot and the antecubital fossa as these areas present an increased risk for serious functional damage because of the proximity of tendons and nerves (Kassner, 2000).
- Select a catheter that is appropriate for the length and rate of the infusion. Small-gauge catheters (0–3 gauge) are recommended by the Intravenous Nursing Society because they cause less trauma to the vein and promote greater blood flow around the needle (Kassner, 2000).
- Short, single-dose infusions can be safely administered through a butterfly catheter, whereas longer infusions should be administered through polyethylene or Teflon catheters (Kassner, 2000).
- Use the two-syringe method, using one syringe to inject the vesicant and the other syringe to check for blood return and patency.

- The vesicant should be given over less than 3 minutes, with blood return being checked after every 1–2 ml of drug administered (San Angel, 1995).
- Avoid using syringe pumps because of the high flow pressure that can increase the risk for extravasation (Kassner, 2000)

8.9.5 Central Venous Access Device Administration

Extravasation into the upper neck or torso can cause serious tissue damage that may require extensive reconstructive surgery. Therefore, administration into a CVAD should be done very carefully.

- CVADs should be used for all continuous infusions of vesicant agents.
- An appropriate size, non-coring needle should be used in patients with a port-a-catheter (Schulmeister and Camp-Sorrell, 2000).
- The nurse's competency to access the port-a-catheter should be reviewed annually.
- A brisk blood return should be noted from the CVAD before starting the administration of a vesicant agent.
- If persistent withdrawal occlusion occurs, alteplase should be administered per institutional policy (Schulmeister and Camp-Sorrell, 2000; Deitcher et al., 2002a).
- For lines that do not clear with alteplase, radiographic studies should be used to determine correct placement of the CVAD before administering a vesicant agent (Schulmeister and Camp-Sorrell, 2000).
- For IV push administration, blood return should be checked every 1–2 ml.
- For continuous infusions into a CVAD, blood return should be assessed every 1 hour (Camp-Sorrell, 1998).
- A clear, occlusive dressing should be placed over the CVAD site, and the tubing should be securely taped (Kassner, 2000).
- Instruct the patient to immediately report any tugging or pulling on the tubing.
- Monitor active children to prevent needle or catheter dislodgement.
- Instruct the child with a port-a-catheter to try to sleep on the opposite side from the needle.

8.9.6 Assessment and Treatment of Extravasation

8.9.6.1 Signs and Symptoms of Extravasation

It is important that anyone who administers vesicant agents be aware of the signs and symptoms of extravasation (Table 8.18) so that quick and appropriate intervention can be done to limit tissue damage. Many of these signs and symptoms are noticeable immediately after the event, but some may occur over several weeks or months. Continued monitoring of the affected site is necessary. Necrosis of tissue may occur up to 6 months after the extravasation and may lead to loss of function in the affected area (Oncology Nursing Society, 2002).

Signs of extravasation include

- Pain at the infusion site
- Any reports of burning or stinging
- Crying or inconsolability in nonverbal children
- Hyperpigmentation
- Induration
- Vesicle formation or ulceration
- Sloughing of skin at injection site

8.9.6.2 Treatment for Extravasation

Knowledge and understanding of the appropriate actions to take in the event of an extravasation may limit its long-term effects (Table 8.19).

8.9.6.3 Peripheral Access

- Stop infusion of vesicant at the first sign of infiltration.
- Notify the physician or nurse practitioner.
- Remove syringe with vesicant agent from tubing, but leave the IV in place.
- Use a 1–3-cc syringe to aspirate any residual drug from the butterfly or catheter.
- Administer the appropriate antidote.
- Instill the appropriate volume into the catheter and discontinue the IV.

Table 8.18. Nursing assessment of extravasation and other reactions

Assessment parameter	Extravasation signs (immediate)	Extravasation signs (delayed)	Vein irritation	Flare reaction
Pain	Severe pain or burning that lasts minutes or hours and eventually subsides; usually occurs while the drug is being given around the needle site	Occurs at least 48 hours post-infusion	Aching and tightness along the vein	No pain
Redness	Blotchy redness around the needle site; not always present at time of extravasation	Occurs 24–48 hours post-infusion	The full length of the vein may be reddened or darkened	Immediate blotches or streaks along the vein, which usually subside within 30 minutes or without treatment
Ulceration	Develops insidiously; usually occurs 48–96 hours later	Occurs late	Not usually	Not usually
Swelling	Usually occurs immediately; is severe		Not usually	Not usually
Blood return	Inability to obtain	Good return during drug administration	Usually present	Usually present
Other		Local tingling and sensory deficits		Urticaria

- Avoid excessive pressure on the site.
- For subcutaneous administration of the antidote, discontinue the IV catheter without putting excess pressure on the site. Use a 25-gauge needle to inject the antidote into the surrounding subcutaneous tissue. Apply heat or cold to the site as appropriate (Oncology Nursing Society, 2001).
- Instruct the patient and family to rest the affected site for 48 hours.
- If blisters appear, instruct the patient and family not to break them.

8.9.6.4 Central Venous Access

- Stop infusion at first report of pain, burning, swelling, color change, change in sensation, or lack of blood return.
- Notify the physician or nurse practitioner.
- If patient has a port, assess for proper needle placement.
- Aspirate residual drug.
- Administer the appropriate antidote and nursing interventions.
- Avoid excess pressure on the site.
- Assess need for radiographic study of the CVAD.

Documentation of extravasation should be very specific and include

- Date and time of occurrence
- Size and type of needle/type of CVAD
- Needle insertion site
- Number of previous venipuncture attempts and sites
- Sequence of chemotherapy agent administration
- Drug administration technique
- Patient complaints/statements/activities
- Appearance of site
- Approximate amount of drug administered
- Physician or nurse practitioner notification
- Nursing interventions at time of the incident
- Follow-up measures
- Patient education provided

Table 8.19. Antidotes for extravasations

Drug	Antidotes	Local care	Comments
Anthracyclines Daunorubicin (Daunomycin) without ice Doxorubicin (Adriamycin) Epirubicin Idarubicin (Idamycin)	Dimethylsulfoxide 50% (DMSO); apply topically and allow to air dry every 3 hours. After first 4 hours if extravasation area is stable, switch DMSO to every 6 hours After 48 hours, may use DMSO every 6 hours only	Apply ice for 15 minutes on and 15 minutes off for first 4 hours as tolerated. After 4 hours, ice every 3 hours. Elevate extremity and do not use for several days	Doxorubicin produces severe prolonged tissue necrosis because of the slow release of the tissue-bound drug. Lesions may need surgical consult
Alkylating agents Mechlorethamine (nitrogen mustard) Cisplatin (Treat cisplatin extravasation only if volume of infiltrate >0 ml and concentration of >0.5 mg/ml)	Sodium thiosulfate Mix 4 ml 10% sodium thiosulfate with 8.4 ml sterile water. Inject 1–4 ml through existing IV line or SQ at extravasation site	Apply cool packs for 3 days	
Vinca alkaloids Vincristine Vinblastine Vinorelbine	None known	Apply warm compresses for 15–20 minutes four times a day for 1–2 days	Heat increases local blood flow, which enhances absorption and removal of the drug from the site Topical cooling is NOT recommended
Dactinomycin (Actinomycin D) for 48 hours		None known	Elevate and apply ice packs
Mitomycin C (Mutamycin)	Dimethylsulfoxide (DMSO); apply topically and allow to air-dry. Repeat every 4–6 hours for 14 days	Apply ice packs for 24 hours	Protect from sunlight or heat.

8.9.6.5 Follow-Up Guidelines

- Site should be monitored 24 hours after the incident, and then 1 week after the incident, and then 2 weeks after.
- Following up with photographs is recommended.
- Elevate the involved extremity.
- Keep the area clean and dry.
- Do not rupture blisters.
- Consultation with a plastic surgeon may be required depending on the extent of tissue damage or/and functional limitation.

8.9.6.6 Patient Education

- Before administering vesicant agents, educate the patient and family about the possibility of extravasation.
- Instruct the patient to report any symptoms during or after the infusion.
- Provide written instructions on care of the site.

8.10 Acute Hypersensitivity Reactions to Chemotherapy

Although hypersensitivity reactions (HSRs) to chemotherapy are relatively rare, it is important for the pediatric oncology nurse to recognize agents that may have a higher incidence of causing them. Hypersensitivity reactions to chemotherapeutic agents range from a localized immune response that is mild and short, to anaphylaxis, which is a systemic response, severe in nature, and may lead to shock and death. Assessing for the signs and symptoms of an acute HSR and being knowledgeable about the appropriate treatment is imperative.

Hypersensitivity, flare reactions, and anaphylaxis are mediated IgE (Oncology Nursing Society, 2001). These types of reactions can be triggered by four factors (Labovich, 1999): route of entry, amount of antigen received, rate at which the antigen is absorbed, and the individual's degree of hypersensitivity. The clinical manifestations of HSR and anaphylaxis may include

- Urticaria (hives).
- Localized or generalized itching.
- Shortness of breath, with or without wheezing.
- Uneasiness or agitation.
- Periorbital edema or facial edema.
- Lightheadedness or dizziness.
- Tightness in the chest.
- Abdominal cramping or nausea.
- Chills.
- Hypotension.

8.10.1 Risk Factors for Hypersensitivity, Flare Reactions, or Anaphylaxis

- History of allergies, particularly drug allergies.
- Receiving a drug known to cause hypersensitivity reaction (see section 8.9.9).
- Previous exposure to the agent.
- Failure to receive known effective prophylactic premedications.
- Previous exposure to metals (Ciesielski-Carlucci et al., 1997).
- Agent was injected versus being ingested (Labovich, 1999).

8.10.2 Chemotherapy Agents That Can Cause HSRs

8.10.2.1 L-Asparaginase (*E. coli, Erwinia,* Pegaspargase)

- One of the agents *most likely* to cause HSRs (principal side effect that limits treatment).
- Occur in up to 25% of patients (Weiss, 1997).
- Prior exposure to the agent.
- Intravenous route of administration increases.
- Patients that react to *Erwinia* may be switched to PEG-asparaginase without further clinical hypersensitivity (Bryant, 2001).

8.10.2.2 Etoposide/Teniposide

- Approximately 6% of patients will experience a HSR (Carr and Burke, 2001).
- Reactions may occur with any dose (Carr and Burke, 2001).

- Signs and symptoms of an HSR include dyspnea, wheezing, hypotension, hypertension, urticaria, pruritus, angioedema, facial flushing, and rash (Carr and Burke, 2001).

8.10.2.3 Taxanes (Paclitaxel/Docetaxel)

- If given without premedication, paclitaxel administration has been associated with a rate of HSR as high as 16 % (Carr and Burke, 2001).
- Mandatory use of premedications has reduced the incidence of HSR to 1–3 %, and at the same time has reduced severity of the reaction (Carr and Burke, 2001).
- Suggested premedications before administration of paclitaxel include dexamethasone, diphenhydramine, and an H_2-receptor antagonist such as ranitidine. Oral dexamethasone should be administered at 12 and 6 hours before the first and second infusions (Carr and Burke, 2001).
- HSRs with paclitaxel usually occur within the first 10 minutes of the infusion (Carr and Burke, 2001).
- Reactions to docetaxel may also occur within minutes of starting the first or second infusion (Carr and Burke, 2001).
- Common reactions include generalized pruritus, bronchospasm, generalized urticaria, severe hypotension, angioedema, and fluid retention (Carr and Burke, 2001).
- Premedications are also required before docetaxel infusions. Dexamethasone may be given orally 3 days prior to starting the infusion.

8.10.2.4 Carboplatin

- Allergic reactions may occur in 2–30 % of children (Yu et al., 2001).
- Reason for allergic reaction is unclear. May be IgE-mediated (Yu et al., 2001).
- Increased risk for HSR with multiple doses, but risk is not correlated with a single dose (Yu et al., 2001; Schiavetti et al., 1999).
- Weekly dosing schedule is major risk for HSR (Yu et al., 2001; Schiavetti et al., 1999).
- Children with low-grade gliomas treated with carboplatin are at increased risk for HSR (Yu et al., 2001).
- Consider the use of a desensitization protocol in patients with history of HSR to carboplatin.

8.10.3 Recommended Steps to Prevent HSRs

- Obtain baseline vital signs.
- Review patient's allergy and hypersensitivity history.
- Review with parents if any premedications were given prior to arriving for therapy; if so, document when they were given.
- Administer premedications as ordered.
- Be familiar with the location of emergency equipment and medications.
- Obtain orders for anaphylaxis prior to drug administration (Table 8.18).
- Educate the patient and family on signs and symptoms of HSR.
- If patient has high likelihood of hypersensitivity, perform a scratch test or intradermal skin test or administer a test dose before giving the initial dose of the drug. Patient should be observed for any local or systemic reaction for 1 hour or more after the test is performed. If no sign of hypersensitivity, proceed with initial dosing.
- If administering an IV bolus dose of a drug that is associated with hypersensitivity, infuse the drug slowly and observe the patient for signs and symptoms of hypersensitivity.
- Consider medication desensitization. Premedicate with antihistamines and/or corticosteroids. Dilute the drug with additional solution. Increase the infusion time.

Any chemotherapy drugs that are known agents for HSR should only be administered in a controlled setting with appropriate medications and equipment available, not in the home (Bryant, 2001).

8.10.4 Emergency Management of HSR/Anaphylaxis

- HSRs usually occur within the first 15 minutes of the drug's administration.
- Stop the chemotherapy infusion immediately.
- Stay with the patient; call for help.
- Assess airway, breathing, and circulation.

Table 8.20. Emergency drugs for use in case of hypersensitivity or anaphylactic reaction

Drug	Strength	Usage
Epinephrine	0.01 mg/kg IV or SQ or 0.1 mg-0.3 mg q10–15 min for maximum of three doses Epi-pen JR 0.15 mg IM for children </= 15 kg Epi-pen 0.3 mg IM for children >15 kg	Anaphylaxis or allergic reaction
Diphenhydramine hydrochloride	1 mg/kg IV (maximum 50 mg)	Administer IV
Steroids		
Solu-Medrol	0.3–0.5 mg/kg IV	Administer IV
Solu-Cortef (hydrocortisone)	4–8 mg/kg IV (max. 50 mg)	
Dexamethasone	0.1–0. mg/kg IV	
Dopamine	5–0 mcg/kg/min IV	Administer IV; adjust to patient's response

- Maintain an IV line with normal saline or other appropriate solution.
- Place patient in supine position.
- Monitor vital signs every 2 minutes until stable, then every 5 minutes for 30 minutes, then every 15 minutes.
- Administer emergency medications (Table 8.20).
- Provide emotional support for the patient and family.
- Document all treatments and patient's response (Oncology Nursing Society, 2001).

8.10.5 Patient and Family Education

- Explain the importance of being knowledgeable about the patient's history of allergies to medications and remind the family to inform healthcare providers before starting any therapy.
- Explain all side effects of medications and review signs and symptoms of HSRs.
- Instruct family that a delayed reaction to certain medications can occur, and provide them with instructions on how to notify the healthcare team.

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Radiation Therapy

Joan M. O'Brien · Deborah Tomlinson

Contents

Radiotherapy has had a role in malignancies for the last century. X-rays were discovered by Von Roentgen in 1895 and were used diagnostically. The element radium was isolated by Marie and Pierre Curie in 1898. The first therapeutic report of a patient cures by radiation therapy was in 1899.

However it has a diminishing role in childhood malignancies due to more effective chemotherapy regimens and the recognition of late effects of radiation treatment. Children will often be assessed on an individual level regarding the need of radiotherapy. However it is still required for around 20% of children and young people with cancer.

Focus in radiation therapy (XRT) has been on methods of delivery that will minimize injury to normal tissues, to try to avoid long-term negative sequalae.

9.1 Principles of treatment

Radiotherapy causes damage to cells in a localised area. Ionising radiation both causes and treats cancer. Damage is caused by breaking strands of DNA; either double or single strands. This inhibits cell division. It may harm normal cells in the area they pass through or in the area around tumor.

Radiation treatment has three main roles in the treatment of childhood and young person's cancer:

- Radical: Treatment with curative intent
- Adjuvant: "Added on" treatment
- Palliative: Treatment aimed at symptom control.

Radiation is frequently used as part of a bone marrow ablative regimen. At times radiation may be used to ameliorate side effects from tumors that are threaten

life or organ function; to quickly reduce the size of a mass that is impinging on the airway, or to relieve pressure on the spinal cord to decrease or prevent paralysis.

Palliative radiotherapy is given to relieve pain in progressive or metastatic disease. It provides shrinkage of tumor to relieve pain and/or obstructions interfering with quality of life. The dose is monitored to ensure minimal toxicities.

9.2 Description of treatment

All radiation emits radiant energy; either in waves and particle form.

- Electrons are electromagnetic and produced from a linear accelerator. They can provide treatment to superficial tumors and have increased absorption to bone. (X-rays are electromagnetic radiation that is produced extranuclearly; electrons are accelerated to high energy and then stopped abruptly at a tungsten target (Farah and Weichselbaum 1994)).
- Gamma rays are electromagnetic radiation produced intranuclearly from a radioactive source. They provide local and wide-field radiation, and are skin sparing. Gamma rays require lead or concrete to absorb them.
- Protons are high energy atoms, emitted from a machine, for the treatment of tumours needing specific dose localization. They are delivered by stereotaxis (a form of radiation that delivers the beam in an extremely precise manner).

9.2.1 Cell radiosensitivity

Factors that contribute to cell radiosensitivity include:

- Phase of cell cycle that cell is in: Studies have shown that cells are most radiosensitive in the M and G2 phases and most resistant in late S phase (Farah and Weichselbaum 1994). Between dose fractions, cells may move through the cell cycle to more sensitive phases. This process is called "reassortment". This allows for a greater cell kill.
- Rate of division: Rapidly dividing cells are more likely to be in the dividing phase of the cell cycle; therefore they are more radiosensitive.
- Oxygenation: Hypoxic cells tend to be radioresistant and only a small quantity of oxygen is required for radiosensitisation. During the course of treatment, oxygenated cells are killed, tumours become smaller, and hypoxic cells move to the well-oxygenated compartments (Farah and Weichselbaum 1994). This is termed reoxygenation. A patient's haemoglobin should be maintained at a minimum of 10 gms/dl.
- Degree of differentiation of cell type: Poorly differentiated cells are more radiosensitive.
- Use of radiosensitizers: Certain chemotherapeutic agents have been known to increase tumor cells' sensitivity to radiation and are often used in combination with radiation to optimize cell kill (Tarbell and Kooy, 2002). These agents include dactinomycin, doxorubicin, etoposide and methotrexate.

9.2.2 Units of radiation

The unit of absorbed radiation dose is a Gray (Gy). A centigray (cGy) is a small fraction (1/100) of a Gy. Prior to the 1990's that unit of energy was referred to as a "rad".

9.3 Methods of delivery

9.3.1 External Beam/Teletherapy (*Tele* comes from the Greek for "far")

- Two-dimensional (2-D) external beam radiation is the most common form. Linear accelerators have mainly replaced cobalt-60 machines in most radiotherapy centers. Linear accelerators generate beams of photons and electrons and can emit megavoltage radiation. Cobalt-60 machines also deliver megavoltage radiation but the machines contain the radioactive material and require to be in thick concreted-walled rooms. Delivery of radiation is faster using a linear accelerator and therefore has obvious advantages in pediatrics.

- Three-dimensional (3-D) conformal and image modulated radiation therapy (IMRT), which allows visualization of radiation in three dimensions. Beams are focused from multiple areas to penetrate the tumor, making the actual radiation field smaller with less "scatter" and damage to normal tissues.
- Stereotactic radiosugery and stereotactic radiation: Stereotactic radiation can be performed as radiosurgery, where multiple beams converge at a point to deliver high dose of radiation to a small area of tumour. This is done as a one time treatment and produces a high degree of tumour necrosis. Tumours must be well circumscribed, < 4 cm in size, and not involve critical structures, such as the brain stem. This type may be carried out using either a linear accelerator or a system frequently referred to as a "Gamma knife" procedure (Swift 2002). For brain tumors, a fixed head frame is secured to the head to ensure precise delivery of the radiation beam. Stereotactic radiotherapy is similar to radiosurgery, but is carried out over multiple fractions and can treat larger tumor volumes. Again, a removable head frame is used to ensure precision of treatment.
- Intraoperative radiation is performed in a fashion similar to radiosurgery, except it is done when the tumour bed is exposed during surgery. It allows a precise treatment field, a higher dose, and potentially less side effects.

9.3.1.1 Fractionation

Fractionation is the process of radiotherapy delivery that divides the total dose into daily doses. The total dose determines the length of treatment. Treatment is normally given Monday to Friday. Fractionation provides better tumor control for a given level or normal tissue toxicity than a single large dose.

Fractionation spares normal tissues because of:

1. the repair of sublethal damage between fractions
2. cellular repopulation.

The normal 2 day rest each week provides time for normal cells to recover.

Tumour damage is increased because of:

1. reoxygenation
2. reassortment of cells within the cell cycle.

However, protracted courses of small doses of radiation may allow for malignant cell re-growth, as they have been given time to repair.

Hyperfractionation is further dividing the daily dose into 2 doses, usually with 6-8 hours between the 2 treatments. Theoretically higher doses may be given with less toxicity and greater tumor cell kill. This technique has been studied for several years and for some tumors, such as brain stem gliomas, no benefit has been found (Mandell et al 1999; Neider et al 1999). Research continues using this technique.

9.3.1.2 Total Body Irradiation (TBI)

The purpose of TBI is to cause bone marrow aplasia, that is to empty out the marrow cavity to allow for new stem cell growth. This is often the preparation for stem cell transplant. It is the aim that TBI will also eradicate malignant cells in sanctuary sites and/or minimal residual disease i.e. it has an antileukemic/antitumor effect.

After TBI, the patient would die of overwhelming infection if stem cells were not given. All organ systems at risk for side effects. TBI is usually given in fractionated doses twice a day for 4 to 5 days.

9.3.2 Interstitial implants/brachytherapy (Sealed source) (*brachy* comes from the Greek for "short distance")

Interstitial implants are isotopes provided as individually customised "seeds or pellets" that are inserted directly into a body cavity, either close or in contact with the target tissue. They provide a high dose of radiation to a very localised area, while having minimal damage to normal tissue. They may be placed for several days or left permanently in place. Most common uses are for gynecological cancers and supratentorial brain tumors in adults. In children, interstitial implants may be used in retinoblastoma lesions within the eye and removed 72 hours later. Also, in pelvic rhabdomyosarcomas, external beam radiation would

have to travel through growing bones and intestines of the child. This could result in major growth retardation. Brachytherapy can minimize the dose delivered to surrounding normal tissue.

9.3.3 Unsealed source of radioisotope

A radioactive isotope is attached to a metabolite or an antigen-specific antibody, for example: iodine-131 – metaiodobenzylguanidine (^{131}I-MIBG). An MIBG scan, using a dye which is taken up by catechoanergic cells, is also useful for diagnostic purposes in children with neuroblastoma in identifying metastases, but this is not available at all centres. I-MIBG is a norepinephrine analog that concentrates in adrenergic tissue and therefore holds promise for cell-specific treatment of neuroblastoma. The MIBG can be labelled with radioactive isotopes of iodine, suitable either for diagnostic imaging or therapy. This is targeted radiotherapy.

9.3.4 Treatment planning

In the delivery of external beam radiotherapy there must be assured accuracy of:

- Dose
- Intensity
- Direction of beam
- Target area.

This will ensure that there is maximum damage to tumour cells with minimal damage to normal, surrounding tissue.

Treatment planning involves:

1. Accurate tumour imaging often using CT scans or MRIs. This outlines a treatment field so that measurements can be collated in order to ascertain the most appropriate form of radiotherapy and the shape and angle of the beams that would be necessary. Margins for treatment are identified that include the tumour and an area of surrounding healthy tissue; this accounts for microscopic tumour extension (Hopkins 1999). Consideration must be given to: limitations of imaging investigations, characteristics of the type of radiation used, and slight changes in body positioning.
2. Determining the dose of radiation energy. This is dependent on protocol, tumour histology and clinical assessment.
3. Identifying the type of radiotherapy. The depth of penetration of the radiation must be considered.

9.3.5 Simulation

Simulation is the process of developing a treatment plan. When planning the shape and angle of the beam it is vital that these factors are simulated with diagnostic radiographic imaging that uses a fluoroscopic unit (Hopkins 1999). This technique uses computer generated fields and simulates the specific number/angle of beams directed at the tumor. Physics calculations enable a computer to simulate the radiation beams that will be delivered.

9.3.6 Protection of health care professionals

Due to the risk of radiation damage to all cells, staff must be protected from any unnecessary exposure. Radiotherapy departments are legally obliged to appoint a radiation protection officer and follow stringent guidelines for radiation monitoring and protection (Byrne 2000). Radiography and radiotherapy staff, and staff caring for patients receiving brachytherapy or unsealed sources of radiation treatments, must wear badges that contain radiographic film that records the cumulative amount of radiation exposure per month.

9.4 Potential side effects

The side effects of radiation therapy are directly related to the amount of radiation received and the location of the field, age of child (younger children more vulnerable to side effects) and adjunctive chemotherapy.

Side effects can be:

- Acute: Acute side effects usually occur within the first few weeks of radiation therapy and are manifested in fast-growing cells located in the radiation field, such as the skin or oral mucosa.

- Delayed (sub)-acute: Delayed acute effects can occur weeks to months after completion of treatment. These are both self-limiting and resolve with time.
- Late: Late effects are the result of irreversible damage. The risk of secondary tumors in the radiation field is also a significant late effect of radiotherapy.

Part 4 of the book will detail the side effects of treatment.

9.5 Special considerations

9.5.1 Ensuring accuracy of treatment: Patient issues

Following planning, the delivery of the angles of the beams must be maintained throughout every treatment. Radiation energy decreases over distance and the energy decreases uniformly along the path. It is therefore possible to calculate the distance the child must be from the radiation source in order that the correct dose is received. Identical body positioning is essential.

9.5.1.1 Marking

External markings using ink or tattoo are applied to the patient's skin to mark the positioning field. These are not easily removed. DO NOT REMOVE markings! If the markings fade the radiographers may need to re-draw the lines. *If the marks fade, while on weekend leave, the family should be asked to redraw over the marks using a different colour of felt tip pen. This will enable the radiographers to distinguish between the two (Hopkins 1999).*

9.5.1.2 Patient immobilisation

Various methods of immobilisation are applied often dependent on the area of the body to be treated. When treating brain tumours or head and neck tumours, a shell is made for individual use to ensure that the head is immobilised. The shell is an exact fit and even small movements will be restricted. These immobilization shells/moulds are also used to reproduce positioning of the child over consecutive treatments. These moulds may sometimes be frightening to the child, depending on his or her developmental level. Developmentally appropriate explanations should be given to the child during radiation planning (McGuire Cullen et al., 2002). To ensure the accuracy and safety of the delivery of radiation treatment, it is also essential during the planning stages to assess the child's ability to cooperate.

Other immobilisation techniques include:

- Head rests, knee rolls
- Vacuum bean bags filled with Styrofoam beads
- Development of immobilizers/blocks
- Plaster of Paris casts.

9.5.1.3 Sedation and general anaesthesia

Because of consecutive days of being unable to eat prior to radiation, the nutritional status of children receiving sedation for radiation should be monitored closely. When possible, it is often best to treat sedation cases early in the morning.

Children may require sedation due to young age, developmental immaturity or extreme distress. Sedation methods range from a mild antianxiolytic to conscious sedation or a short-acting general anesthetic. Short acting drugs such as ketamine may be used. These children will require to be treated early in the day to avoid repeated extended periods of fasting. Hydration and nutrition will need particular attention.

If the child is anaesthetised, an anaesthetist must be present to monitor the child. This will be with the aid of audiovisual monitoring and the electrocardiographic and respiratory monitors for the short period that the child requires to be alone when the radiation treatment is being delivered. Another point to consider is that radiotherapy is usually delivered to children in an adult centre. Adequate, safe recovery must be assured.

If the child requires another procedure such as lumbar puncture, the team will often organise to have these procedures carried out with the same anaesthetic.

9.5.1.4 Preparation of children and young people

Receiving radiation therapy can be a very frightening ordeal. Good preparation will help elicit children's cooperation. Young people may also not be willing to cooperative if they are not adequately informed and prepared for the process involved. Parent's anxiety can also impact the child's anxiety. It may be stressful for everyone that the child is left in the room alone.

9.5.2 Brachytherapy

Although rarely used it may have significant advantages in children and young people due to significant local control and fewer late effects. Initially the mould may need to be inserted or stitched in place using a general anaesthetic.

9.5.3 Unsealed sources of radiation treatment

^{131}I-MIBG is given intravenously under extremely protected conditions. Patent venous access is imperative. The ^{131}I-MIBG contains a specific radioactive isotope of iodine.

Protection of the thyroid gland is imperative. Oral iodine is administered before, during and after the radioactive material is given. This ensures saturation of the thyroid gland with non-radioactive iodine.

All body tissues become radioactive. Therefore all bodily fluids must be handled as radioactive waste (Hopkins 1999). This leads to the need for extreme caution in the care of a child. Unfortunately, the child's contact with family must be kept to a minimum.

9.6 Future Perspectives

There have been several recent advances in the field of radiation oncology. The goal of the research is to deliver the highest tolerated amount of radiation while decreasing exposure to surrounding normal tissue. Several techniques have been developed to reach this goal. Proton radiation therapy is the newest technique that delivers a large dose to the tumor and a smaller dose to normal tissue (Tarbell and Kooy, 2002). The advances in radiation therapy are decreasing side effects, but the cost to update and create new equipment limits the availability of new radiation treatments.

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Hematopoietic Stem Cell Transplantation

Robbie Norville

Contents

10.1 Principles of Treatment

The purpose of hematopoietic stem cell transplantation (HSCT) is to replace diseased, damaged, or absent hematopoietic stem cells with healthy hematopoietic stem cells. In general, allogeneic transplants are used when the hematopoietic stem cells are diseased (e.g., leukemia), damaged (e.g., sickle cell disease), or absent (e.g., severe immunodeficiency disease). Autologous transplants are used to provide stem cell rescue after higher doses of chemotherapy or radiation therapy (e.g., solid tumors).

Higher doses of chemotherapy and radiation therapy can cause dose-limiting myelosuppression. Infusing healthy stem cells allows the bone marrow to recover after intensive therapy. In the allogeneic setting, the new immune system from the donor may be effective in preventing disease recurrence by providing a graft-versus-tumor effect.

HSCT is an important treatment modality for children with aggressive malignancies in first remission or those who have recurrent disease.

Types of HSCT include the following (see Table 1):

- Allogeneic: Stem cells are collected from someone other than the recipient. These donor cells can be obtained from a variety of donor sources. A matched related donor is a family member, usually a sibling, with a 6/6 antigen match. A mismatched related donor is a family member, usually a sibling or parent, with a 3/6, 4/6, or 5/6 antigen match. A matched unrelated donor is one who is not genetically related to the recipient, with a 5/6 or 6/6 antigen match.

Table 10.1. Comparison of advantages and disadvantages of types of HSCT and different donor sources

Type of HSCT	Advantages	Disadvantages
Allogeneic		
Matched related	Healthy source of cells Easy access to donor	Some risk of GvHD 30% likelihood of sibling match
Mismatched related	Healthy source of cells Easy access to donor Availability of donor for most patients	Greater risk of GvHD Risk of graft failure
Matched unrelated	Healthy source of cells	Risk of GvHD 3–6 month waiting period for donor procurement Limited ethnic minority donors Expensive donor charges
Autologous	Easy access to donor No GvHD	No graft versus tumor effect Possible tumor contamination
Syngeneic	Healthy source of cells	Some risk of GvHD
Donor Source	Advantages	Disadvantages
Bone marrow	Well-tested collection method	General anesthesia risks Pain at harvest site
Peripheral blood	Faster engraftment	Venous access
Cord blood	Easy procurement of cells Decreased chance of viral transmission	Limited number of cells per unit Potential transmission of genetic diseases Costs for cryopreservation and storage

- Autologous: Stem cells are collected (or harvested) from the recipient
- Syngeneic: Stem cells are collected from a donor who is an identical twin of the recipient

If bone marrow is the donor source, the stem cells are collected directly from the bone marrow space, with the posterior iliac crest being the most common harvest site. The collection is done in the operating room, and the donor will usually receive general anesthesia for the procedure. If peripheral blood is used, the stem cells are collected by pheresis, usually in an outpatient setting. Temporary pheresis catheters may be placed prior to the procedure when venous access is difficult. Stem cells may also be collected directly from the umbilical cord at the time of birth. These cells are then cryopreserved (frozen) and stored for use at a later time.

Human leukocyte antigens (HLA) are a complex series of proteins on the surface of human leukocytes used for identifying a donor match (Fig. 10.1). These proteins, called antigens, make up the major histocompatibility complex, which helps the body recognize foreign proteins and cells. One set of antigens is inherited from each parent; therefore, a biological parent will be at least a 3/6 match for a child. The antigens of primary concern for HLA typing are A, B, and DR. The more disparity that exists between the donor and the recipient, the greater the risk of graft versus host disease (GvHD) and graft failure. HSCT is used for a variety of malignant and nonmalignant diseases (Table 10.2).

Figure 10.1
Example of HLA typing

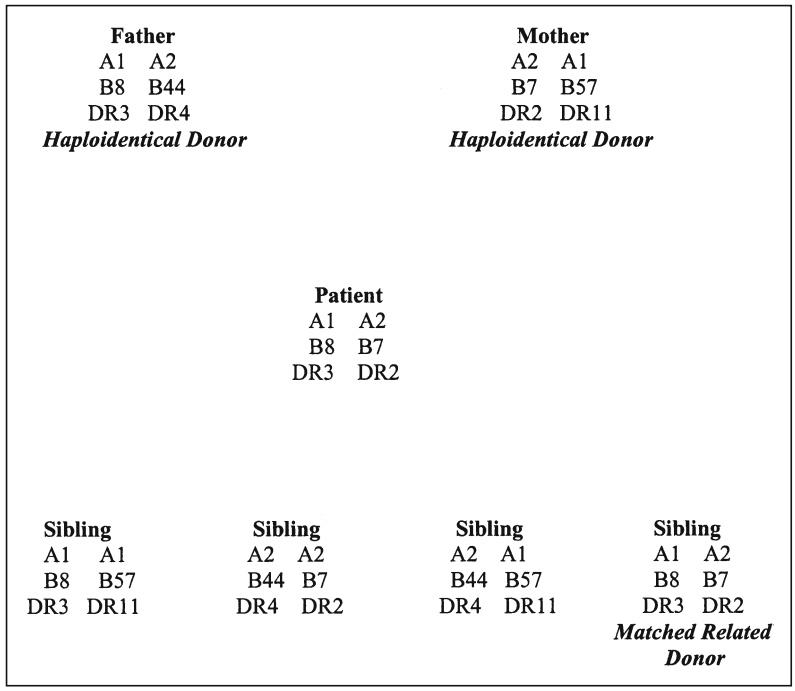

Table 10.2. Diseases for which HSCT is a treatment option (from Forte and Norville, 1998)

Disease	Rationale for hematopoietic stem cell transplantation
Leukemias, lymphomas	Chemotherapy, with or without total body irradiation, is used to eradicate tumor cells and to make room for engraftment of healthy cells. Irradiation is often used in mismatched and unrelated transplants.
Solid tumors: neuroblastoma, sarcoma, brain tumor	High doses of chemotherapy or radiation therapy are given to kill tumor cells. An autologous "rescue" is given to prevent prolonged myelosuppression.
Hematologic diseases: thalassemia, sickle-cell disease, severe aplastic anemia, Fanconi's anemia	Chemotherapy is given to eradicate cells in the bone marrow and to make space for engraftment of healthy allogeneic cells. The new donor cells will produce normal white cells, red cells, and platelets.
Immunodeficiency diseases: Wiskott-Aldrich syndrome, severe combined immunodeficiency syndrome (SCIDS), cartilage-hair hypoplasia	Chemotherapy is given to eradicate cells in the bone marrow and to make space for engraftment of healthy allogeneic cells. In the case of SCIDS, chemotherapy may not always be used.
Genetic diseases: adrenoleukodystrophy, metachromatic leukodystrophy, Hurler's syndrome	Chemotherapy is given to eradicate cells in the bone marrow. Donor cells, which will eventually produce the deficient enzyme, are infused.

10.2 Description of Treatment

HSCT can be divided into three phases: pretransplant, transplant, and post-transplant. The pretransplant phase includes donor and recipient evaluation and administration of a conditioning regimen (chemotherapy agents selected for specific activity). Day 0, the day of stem cell infusion, constitutes the transplant phase. Donor stem cells collected on this day are administered as a fresh product infusion. Donor cells collected prior to the initiation of conditioning are cryopreserved for infusion on Day 0. During the post-transplant or engraftment phase, the recipient is monitored for side effects of the conditioning regimen, complications of the transplant, and engraftment, which is the term used to indicate that the donor cells have migrated to and are repopulating the bone marrow space.

Pretransplant evaluation of the donor assures healthy stem cells and a donor who is able to tolerate the collection procedure. The age range of donors varies from infancy (3–4 months) to 65 years. The donor evaluation should include physical examination, complete health history for genetic disorders, and serological testing that includes CBC with differential, confirmatory HLA typing, ABO cross-matching, chemistry profile, coagulation screen, infectious disease testing, and a pregnancy test (if appropriate). Donors may be offered an opportunity to donate, if needed, an autologous unit of blood prior to collection of stem cells for autotransfusion.

The donor should have an opportunity to discuss issues such as testing procedures, health risks, and psychosocial sequelae with appropriate healthcare providers. These issues are especially important in the case of child donors. Consultation with child life specialists, social workers, and clergy may be beneficial and make the procedure less stressful and easier to tolerate.

The purpose of the recipient evaluation is to determine disease status and identify any underlying medical issues such as organ dysfunction or infections that could pose additional risks to the recipient. The recipient will have a more extensive evaluation than the donor. In addition to the studies listed above, the evaluation should include an assessment of the recipient's disease status, which will depend on the type of disease and the areas of previous involvement or treatment. These studies may include diagnostic scans (e.g., CT, MRI) as well as bone marrow aspirate/biopsy and lumbar puncture. Studies useful in evaluating organ dysfunction include chest x-ray, echocardiogram, pulmonary function tests (if age-appropriate), creatinine clearance or glomerular filtration rate, and dental exam. An audiogram may be ordered for patients who have a history of hearing loss or have previously received ototoxic agents. An ophthalmology exam may be done if the recipient is to receive total body irradiation (TBI).

Baseline monitoring for late effects might include baseline neuropsychological testing, endocrine function studies, and bone scans. A central venous access device will be placed, and information regarding sperm banking and egg harvesting should be provided to age-appropriate patients.

Conditioning (preparative) regimens are used to prepare the bone marrow space for the incoming graft, immunosuppress the recipient to prevent GvHD, and eradicate tumor cells when treating a malignant disease. In general, the conditioning regimen is given for 4–10 days prior to the stem cell infusion. The conditioning regimen selection depends on the disease being treated and the type of HSCT.

Conditioning regimens can include chemotherapy, radiation therapy, and immunotherapy. Chemotherapy is the backbone of the conditioning regimen and is used for most HSCT. Commonly used agents include cyclophosphamide, busulfan, cytarabine, melphalan, thiotepa, cisplatin, carboplatin, and etoposide. Radiation therapy in the form of TBI provides immunosuppression as well as treatment for sanctuary sites (central nervous system and testes). TBI is usually delivered in fractionated doses twice a day for 4–5 days. Local control radiation therapy may be given before or after transplant to patients with a history of central nervous system disease. Immunotherapy includes agents such as antithymocyte globulin (ATG) and monoclonal antibodies, such as Campath and CD45 antibody. These agents are usually given once a day for 3–4 days and are used to bind with and destroy recipient circulating T-lymphocytes

in an attempt to decrease the risk of nonengraftment and GvHD.

10.2.1 Stem Cell Collection (Harvest)

Hematopoietic stem cells are immature progenitor cells that mature in the bone marrow space. After differentiation and maturation, they are released into the peripheral circulation as mature erythrocytes, lymphocytes, and thrombocytes. Stem cells can be obtained from the bone marrow, peripheral circulation, and cord blood. Stem cells from the bone marrow are most often collected under general anesthesia from the posterior iliac crest. The cells are placed in a sterile collection system, mixed with heparin, and filtered to remove bone spicules, fat globules, and blood clots.

Peripheral stem cells are collected by pheresis. Stem cells are mobilized into the peripheral circulation using granulocyte colony-stimulating factor (G-CSF) or chemotherapy (for autologous HSCT). Using a pheresis machine and large venous catheters, the desired stem cells are selected and removed from the peripheral blood based on weight. The remaining cells (red cells, platelets, and plasma) are then reinfused into the donor. The cells are placed in a sterile collection system, mixed with heparin, filtered, and mixed with a preservative prior to being cryopreserved. Cord blood stem cells are collected from a newborn's cord and placenta immediately after birth and cryopreserved for possible use at a later time.

Stem cell processing can include buffy-coating to deplete volume or erythrocyte contamination and purging to remove any remaining tumor cells. T-cell depletion and $CD34^+$ selection (collection of specific progenitor cells) are techniques used to reduce the number of T-lymphocytes in the final product.

Stem cell infusion is similar to a blood product transfusion, and the patient and family often perceive it as anticlimactic. Stem cells are infused through a central line and should not be filtered or irradiated. Side effects associated with the HCST are listed in Table 10.3. Fresh stem cell products are most often

Table 10.3. Common side effects of hematopoietic stem cell infusions

Type of product	Side effect	Nursing assessment	Nursing interventions
Fresh stem cells	Allergic reaction	Obtain baseline vital signs (VS) and breath sounds Assess skin for evidence of flushing, itching and urticaria	Premedicate with antihistamine, corticosteroid, and antipyretic Monitor VS and breath sounds frequently during and immediately after infusion per institutional policy
	Hemolytic transfusion reaction	Assess ABO compatibility of donor and recipient	Administer pre- and post-hydration fluids for ABO incompatibility Administer diuretic Maintain brisk urine output (1–2 ml/kg/hr) for 24 hours after infusion Monitor for fever, chills, chest or back pain, dark urine, dyspnea, tachycardia, hypotension, shock
	Fluid overload	Assess baseline weight and fluid status Assess baseline breath sounds and pulse oximetry	Monitor fluid status during and immediately after infusion Monitor for cough, dyspnea, decreased oxygen saturation, hypertension, tachycardia, edema Administer diuretic Maintain brisk urine output (1–2 ml/kg/hr) for 24 hours after infusion

Table 10.3. (Continued)

Type of product	Side effect	Nursing assessment	Nursing interventions
	Micropulmonary emboli	Assess preinfusion VS, breath sounds and pulse oximetry	Monitor respiratory rate and pulse oximetry during infusion Monitor for dyspnea, decreased oxygen saturation, sudden severe headache or chest pain
	Infection	Assess baseline VS, including temperature	Monitor temperature frequently during infusion Administer antipyretic for elevated temperature Obtain sample of product and blood sample from patient for cultures
Preserved stem cells	Bad taste in mouth (due to DMSO) Nausea and vomiting		Administer antiemetics prior to infusion Offer hard candy or chewing gum if patient not sedated
	Arrhythmia and hypertension	Assess baseline VS and EKG	Monitor VS and EKG during and immediately after infusion Administer antihypertensive and diuretic
	Hemoglobinuria		Administer pre- and post-hydration fluids Administer diuretic Maintain brisk urine output (1–2 ml/kg/hr) for 24 hours after infusion
	Allergic reaction	Obtain baseline VS and breath sounds Assess skin for evidence of flushing, itching and urticaria	Premedicate with antihistamine, corticosteroid and antipyretic Monitor VS and breath sounds frequently during and immediately after infusion per institutional policy
	Fluid overload	Assess baseline weight and fluid status Assess baseline breath sounds and pulse oximetry	Monitor fluid status during and immediately after infusion Monitor for cough, dyspnea, decreased oxygen saturation, hypertension, tachycardia, edema Administer diuretic Maintain brisk urine output (1–2 ml/kg/hr) for 24 hours after infusion
	Micropulmonary emboli	Assess preinfusion VS, breath sounds and pulse oximetry	Monitor respiratory rate and pulse oximetry during infusion Monitor for dyspnea, decreased oxygen saturation, sudden severe headache, or chest pain
	Infection	Assess baseline VS, including temperature	Monitor temperature frequently during infusion Obtain sample of product and blood sample from patient for cultures Administer antipyretic for elevated temperature

Table 10.4. Timing of potential complications associated with HSCT (adapted from Fort and Norville, 1998)

Early (conditioning to engraftment)	Intermediate (engraftment to first 100 days)	Late (after 100 days)
Bone marrow suppression	Infections	Immunosuppression
Nausea, vomiting, diarrhea, anorexia, mucositis	Acute GvHD	Chronic GvHD
Parotitis	Graft failure	Infections
Infections	Interstitial pneumonitis	Endocrine dysfunction
Skin erythema		Cataracts
Capillary leak syndrome		Disease recurrence
Acute renal insufficiency		Secondary malignancies
Hemorrhagic cystitis		
Veno-occlusive disease		
Seizures		

used for allogeneic transplants, which are generally infused within 48 hours of collection. The stem cell product is infused over 2–4 hours as a slow intravenous (IV) infusion. Red cell or volume depletion prior to infusion is dependent on the donor and recipient's ABO status and the volume of donor cells collected compared to the recipient's body weight.

Stem cells collected from any donor source can be frozen and infused at a later time. In general, frozen stem cells are most often used for autologous transplants. To minimize the destruction of red cells during the freezing and thawing processes, a preservative (dimethyl sulfoxide, DMSO) is added to the stem cell product. DMSO has a garlic-like odor that is excreted from the lungs of the recipient for 24–48 hours after the stem cell infusion. DMSO infusion can cause transient cardiac arrhythmias, most commonly bradycardia, and hypertension. For this reason, many institutions require cardiac monitoring during and immediately after the infusion. Once the product is thawed, a rapid IV infusion is recommended.

10.3 Potential Side Effects

Side effects and complications associated with HSCT can occur at any time during the transplant process (Table 10.4). The side effects commonly associated with the conditioning regimen and time period to engraftment tend to occur early, within the first few weeks of transplant. Side effects that occur from the time of engraftment and during the first 100 days thereafter usually result from the conditioning regimen, prolonged immunosuppression, or early engraftment. Complications occurring 100 days or more after transplant are categorized as late effects.

10.3.1 Early Side Effects

Early side effects of the conditioning regimen can include bone marrow suppression, nausea, vomiting, diarrhea, anorexia, mucositis, parotitis, skin erythema, infections, capillary leak syndrome, acute renal insufficiency, veno-occlusive disease, and seizures. Bone marrow suppression typically occurs 7–10 days after the conditioning regimen begins. Fully ablative conditioning regimens will eradicate all cell lines in the bone marrow, causing anemia, thrombocytopenia, and neutropenia, with an absolute neutrophil count (ANC) of 0. Bone marrow suppression is prolonged and will continue until engraftment occurs. The timing of engraftment is affected by the conditioning regimen administered, the stem cell source, manipulation of the cells, the recipient's past history of prior chemotherapy, and the recipient's clinical condition. An ANC of 500 and a platelet count of

20,000 mm^2 without transfusions indicate engraftment. The average time to engraftment is, in general, 14–28 days. Typically, platelets are the last cell line to become self-sustaining. As red cells engraft, the recipient's blood type will change to that of the donor when ABO differences are present.

Transfusions of leukocyte-depleted and irradiated red blood cells are often administered when hemoglobin levels fall below 8 g/dl. Leukocyte depletion minimizes the risk of viral contamination, particularly cytomegalovirus (CMV). Irradiation reduces the risk of GvHD from transfused blood products by eliminating the immunocompetent lymphocytes in the product without compromising its functional qualities (Ryan et al., 2002). There is a potential for cardiac and respiratory compromise associated with hemoglobin levels less than 7 g/dl.

Side effects of anemia include fatigue, irritability, pallor, tachycardia, shortness of breath, and dizziness. The administration of blood products or supplemental oxygen may be required. During transfusion, monitor for signs and symptoms of adverse effects.

The risk of bleeding is increased when the platelet count is <20,000 mm^2. The nurses must assess for signs and symptoms of bleeding or blood loss, including bruising, petechiae, epistaxis, or oozing from the gums or central venous line. If transfusion is required, platelet products should be leukocyte-depleted and irradiated.

When the ANC falls below 500 cells/mm^3, patients are at a significantly increased risk of infection. Physical examination should include detailed inspection of the mouth, rectum, IV sites, and all wounds for evidence of infection. Symptoms including dysuria, sore throat, cough, and rectal pain are particularly worrisome in the neutropenic patient.

Gastrointestinal toxicity in the form of nausea and vomiting can begin within the first 24 hours of starting the conditioning regimen and can continue for several days after the transplant. Antibiotics, infections, and mucositis can exacerbate vomiting. Diarrhea can occur anytime during the conditioning regimen and last as long as 2 weeks after the transplant. Although chemotherapy is the usual cause of diarrhea during this time period, an infectious cause must be excluded. Mucositis usually peaks 7–14 days after the start of the conditioning regimen and resolves as engraftment (return of WBCs) occurs. Anorexia often accompanies the nausea, vomiting, diarrhea, and mucositis and can continue for several months after the transplant, especially in adolescent and young adult patients.

Supportive care for gastrointestinal symptoms includes administering antiemetics on a scheduled basis, as well as nutritional supplements, fluids, and total parenteral nutrition. Meticulous oral hygiene, perirectal hygiene, and skin care to prevent skin breakdown and secondary infections are necessary. Blood and stool cultures may be needed to isolate infectious agents. Pain assessment must be performed each shift and more often if the child is in pain. Oral or IV analgesics, preferably patient-controlled analgesia, may be required for mucositis pain.

Parotitis, inflammation of the parotid gland, usually occurs after the first or second dose of TBI. Common complaints are bilateral swelling and pain in the jaws. This side effect is self-limited, often lasting only a day or two. Applying warm compresses externally to the jaw and administering mild analgesics will usually provide relief.

Skin erythema, darkening, and dryness is not uncommon after TBI. This condition is most often mild and typically responds to moisturizing lotions, creams, and gels. A head-to-toe skin assessment is required daily. To prevent additional skin damage, patients need to be instructed not to use oil-based skin products while receiving TBI.

Infections during the early phase of transplant are a result of neutropenia, immunosuppression, and alterations in mucosal integrity and indwelling central lines. Patients are susceptible to bacterial, viral, and fungal infections. Common bacterial pathogens are *E. coli*, *Klebsiella*, *Pseudomonas, Staphylococcus aureus,* and coagulase-negative *Staphylococcus*. Reactivation of herpes simplex virus (HSV) is the predominant viral pathogen complicating mucositis during this time period. *Candida* spp. can infect the gastrointestinal tract, complicate toxicities, and secondarily infect other wounds and IV sites.

Prevention of infections is multifactorial and includes handwashing, limits on the number of visitors, high-energy particulate air (HEPA) filter systems,

prophylactic antimicrobials, and administration of CMV-negative blood to CMV-seronegative recipients. A combination of broad-spectrum antibiotics is given from initiation of the conditioning regimen until engraftment as common prophylaxis against bacterial infections. Acyclovir or valacyclovir prophylaxis can reduce the risk of HSV reactivation. Fluconazole, voriconazole, or low-dose amphotericin is effective prophylaxis against fungal infections. Although controversial, intravenous immunoglobulin (IVIG) therapy is administered every 2–4 weeks to provide passive immunity.

Other interventions include monitoring the patient for fever and other signs of infection, obtaining blood and urine cultures at the onset of fever before starting antibiotics, drawing blood cultures daily for subsequent fevers, and obtaining other diagnostic studies (e.g., chest x-ray, CT) as appropriate. Patients who continue to be febrile after 3–5 days should receive treatment doses of amphotericin.

Hemorrhagic cystitis can occur within 24 hours of administration of chemotherapy and as late as several months after HSCT. The primary causes of hemorrhagic cystitis include cyclophosphamide, radiation therapy, and viruses. The active metabolite of cyclophosphamide, when allowed to remain in contact with the bladder mucosa, will cause irritation and bleeding. Viruses that can cause this complication include adenovirus, CMV, and BK virus.

Signs and symptoms of hemorrhagic cystitis include hematuria (microscopic or gross), urinary frequency, dysuria, suprapubic pain, and bladder spasms. A bladder ultrasound and urine cultures for bacteria and viruses are used for diagnosis.

Management includes pre- and post-hydration fluids and mesna for cyclophosphamide administration, placement of a Foley catheter or continuous bladder irrigation, and platelet transfusions.

If a urinary catheter has not been placed, the child must void at least every 1–2 hours during, and for 24 hours after, each dose of cyclophosphamide. Strict measuring of intake and output must be done in addition to platelet counts, coagulation studies, and close monitoring for microscopic hematuria. Administering blood products and providing pain control are other necessary supportive care measures.

Acute renal failure and nephritis are frequent complications after HSCT. Radiation therapy, immunosuppressive agents, and virus and bacterial toxins can cause nephritis. Acute renal failure can result from nephrotoxic drugs, infection, and inadequate renal perfusion.

Common symptoms of renal toxicity include increased weight, edema, decreased urine output, hypertension, elevated creatinine and BUN, and altered sensorium.

Medical management includes administration of diuretics, antihypertensives, vasopressors, and dialysis. Blood chemistries need to be monitored daily, and blood levels of nephrotoxic medications (e.g., cyclosporine, tacrolimus, vancomycin, gentamicin) must be checked until the appropriate dose level is reached and then routinely. Dose and frequency of nephrotoxic medications need to be adjusted as ordered, and renal doses of dopamine are given to promote renal perfusion.

Capillary leak syndrome, a shift of intravascular fluid into the extravascular space, often occurs 7–14 days after HSCT. Tissue damage from the conditioning regimen causes the release of cytokines that cause a capillary permeability. This permeability can lead to weight gain, fluid retention, ascites, cough, shortness of breath, and pulmonary edema. The child must be assessed for signs and symptoms of fluid overload, including weight gain, hypertension, abnormal breath sounds, and intake that is greater than output.

Veno-occlusive disease (VOD) results from the high-dose chemotherapy and radiation therapy administered during the conditioning regimen. The small vessels and central vein of the liver become occluded, causing congestion, venous outflow obstruction, and eventual hepatocyte damage. Onset is usually 7–21 days after transplant. The clinical features of VOD include weight gain, right upper quadrant pain, hepatomegaly, elevated serum bilirubin, ascites, and encephalopathy. Management includes maintaining fluid and electrolyte balance by strictly monitoring intake and output, obtaining accurate daily weights and measuring abdominal girth every shift, minimizing the adverse effects of ascites by restricting oral and IV fluids and administering diuretics and pain medications, adjusting medications to reflect hepatic

and renal function, avoiding compounding encephalopathy with medications that alter mental status, and preventing bleeding.

Neurotoxicity can occur anytime during the transplant process. Seizures can result from medication toxicity, infection, hemorrhage, hypertension, and electrolyte abnormalities. In the early phase of transplant, high levels of chemotherapeutic agents (busulfan) and immunosuppressive agents (cyclosporine, tacrolimus) can cause seizures. Cyclosporine and tacrolimus can also cause tremors and peripheral neuropathy. Monitoring blood levels and adjusting doses can prevent and minimize these side effects.

10.3.2 Intermediate Side Effects

Intermediate side effects and complications of HSCT can include infections, graft failure, acute GvHD, and interstitial pneumonitis. Infections during this phase are more common and more severe for allogeneic patients than autologous patients as a result of impaired cell-mediated and humoral immunity, immunosuppressive therapy to prevent GvHD, and the presence of indwelling lines. Common pathogens include gram-negative bacteria (*E. coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*), gram-positive bacteria (*Staphylococcus aureus,* coagulase-negative *Staphylococcus, Streptococcus pneumoniae*), fungus (*Candida*, *Aspergillus*), and viruses (adenovirus, CMV).

Predisposing factors associated with infections during this period include neutropenia, central venous lines, immunosuppressive therapy, and GvHD.

Strategies to prevent or minimize the risk of infections include handwashing, HEPA filtration, low-bacterial diets, avoidance of crowded places, and antibacterial, antifungal, and antiviral prophylaxis. Antibacterial and antifungal (fluconazole, low-dose amphotericin B) prophylaxis continues until engraftment (defined as an ANC >500 for 3 consecutive days).

CMV infection is a life-threatening infection that usually occurs within the first 2 months post-transplant. Most centers will provide some form of prophylaxis when the recipient or donor is CMV-seropositive pretransplant, either ganciclovir IV from engraftment through 100 days post-transplant or CMV antigenemia monitoring with ganciclovir treatment when virus is detected. Additional strategies to prevent CMV infection include administration of leukocyte-depleted blood products and CMV-seronegative blood products to seronegative recipients. IVIG may also be given to provide passive immunity during this phase of HSCT.

Treatment is aimed at specific pathogens causing infections. Initial treatment usually includes broad-spectrum antibiotics, followed by specific antimicrobials based on culture and sensitivity results. Treatment of CMV infection can include ganciclovir and IVIG, foscarnet, and cidofovir.

Acute GvHD (AGvHD) is an immune-mediated response in which the immunocompetent donor T-cells recognize the host (recipient) antigens as foreign and mount an attack. It is the consequence of alloreactivity between the donor and recipient. The immunocompetent donor T-cells recognize the alloantigens (major and minor histocompatibility antigens) of the recipient and become activated, which leads to further expansion of alloreactive T-cells. This leads to the release of cytokines, recruitment of other immune system effector cells, and eventual tissue damage.

Incidence and severity depend on the type of transplant and the degree of HLA disparity between the donor and recipient. The recipient's age, the number of T-cells transfused, and the GvHD prophylaxis used are additional risk factors. The onset of AGvHD usually coincides with engraftment and occurs within the first 100 days of transplant.

Clinical presentation typically involves one of three targeted organs: the skin, liver, or gut. Diagnosis can be made clinically based on symptoms and laboratory values. However, tissue biopsy is required for definitive diagnosis. Individual organ involvement is staged for severity, and an overall grade is assigned based on severity and combined organ involvement. Skin AGvHD is the most common initial presenting manifestation. The rash begins as a macular erythematous rash of the palms and soles. It can progress to a maculopapular erythematous rash on the trunk and extremities to bullae and generalized desquamation. Pruritus and pain are common associated symptoms (Table 10.5).

Table 10.5. Acute GvHD stage and grading systems

Staging of individual organ system(s)				
Organ	**Stage**	**Description**		
Skin	+1	Maculopapular (M-P) eruption over <25% of body area		
	+2	Maculopapular eruption over 25–50% of body area		
	+3	Generalized erythroderma		
	+4	Generalized erythroderma with bullous formation and often with desquamation		
Liver	+1	Bilirubin 2.0–3.0 mg/dl; SGOT 150–750 IU		
	+2	Bilirubin 3.1–6.0 mg/dl		
	+3	Bilirubin 6.1–15.0 mg/dl		
	+4	Bilirubin >15.0 mg/dl		
Gut	+1	Diarrhea >30 ml/kg or >500 ml/day		
	+2	Diarrhea >60 ml/kg or >1,000 ml/day		
	+3	Diarrhea >90 ml/kg or >1,500 ml/day		
	+4	Diarrhea >90 ml/kg or >2,000 ml/day; or severe abdominal pain and bleeding with or without ileus		
Overall grading of acute GvHD				
Grade	**Skin staging**	**Liver staging**		**Gut staging**
I	+1 to +2	0		0
II	+1 to +3	+1	and/or	+1
III	+2 to +3	+2 to +4	and/or	+2 to +3
IV	+2 to +4	+2 to +4	and/or	+2 to +4

Liver AGvHD causes degeneration of mucosa and small bile ducts and results in hepatitis-like symptoms (fatigue, abnormal liver function tests, right upper quadrant pain, hepatomegaly, jaundice, and pruritus). Increased bilirubin and alkaline phosphatase levels are the earliest and most common abnormalities noted.

Gut AGvHD is characterized by diarrhea and abdominal cramping, which can progress to severe ileus. Degeneration of the mucosal lining of the GI tract results in green, watery, guaiac-positive diarrhea; abdominal discomfort; nausea; vomiting; anorexia; malabsorption; and ascites. Both the upper and lower GI tract can be involved.

Prevention remains the key to effective management of AGvHD. Prevention strategies are aimed at preventing the activation of T-cells and depleting mature alloreactive T-cells from donor grafts. Cyclosporine, used in combination with other immunosuppressive agents, has been standard GvHD prophylaxis, but tacrolimus is being used instead of cyclosporine for unrelated and mismatched transplants because it has proven to be superior to cyclosporine in this group of patients (Ryan et al., 2002). New monoclonal antibodies, Campath and CD45 antibody, are being incorporated into conditioning regimens as GvHD prophylaxis. T-cell depletion, monoclonal antibodies, and $CD34^+$ selection are successful strategies to deplete alloreactive T-cells from donor grafts.

Treatment consists of adding corticosteroids and continuing cyclosporine or tacrolimus (Table 10.6). Antithymocyte globulin and newer monoclonal antibodies are added in cases of steroid-resistant or severe AGvHD.

Table 10.6. Agents used to prevent and treat GvHD (from Forte, 1997)

	Mechanism	Toxicities
Cyclosporine (Sandimmune)	Blocks synthesis of IL-2, suppresses development of cytotoxic T-lymphocytes	Renal toxicity, hypertension, magnesium wasting, hyperkalemia, tremors, seizures, gingival hypertrophy, hirsutism, cortical blindness
FK506 (Prograf)	Is similar to cyclosporine	Are similar to those associated with cyclosporine, hyperglycemia
Methotrexate (Mexate)	Inhibits DNA synthesis by competitively binding with dihydrofolate reductase	Renal toxicity, liver toxicity, mucositis
Glucocorticoids	Prevents production and release of IL-1 from macrophages	Myelosuppression, mood swings, hypertension, hyperglycemia, GI bleeding, osteoporosis, acne, cushingoid syndrome
Antithymocyte globulin (ATG) (an immune globulin)	Acts against human thymocytes	Fever, chills, rash, anaphylaxis, serum sickness
OKT3 (Orthoclone) (a monoclonal antibody)	Is specific for circulating CD3 T-cells	First-dose reaction: fever, chills, diarrhea, dizziness, chest pain, wheezing, tremor
Thalidomide	Decreases the number of helper T-cells and increases the number of suppressor T-cells	Peripheral neuropathies, constipation, sedation
Hydroxychloroquine (Plaquenil)	Reduces secretion of IL-1, IL-6, and tumor necrosis factor	Ocular toxicity, nausea, diarrhea, rash, photosensitivity

Graft failure or rejection occurs when the donor graft is not sustained in the recipient. This complication is relatively uncommon in allogeneic HSCT, with an incidence of approximately 1% with HLA-matched donors and 5–10% with mismatched donors (Guinan et al., 2002). Graft failure can occur when the stem cell dose is too low, the recipient marrow is not completely ablated, or the immunosuppression is inadequate. Infections and tumor recurrence can also cause graft failure. Treatment may include increased immunosuppression or infusion of donor T-lymphocytes.

Interstitial pneumonitis is the leading cause of respiratory failure in HSCT patients. It can result from infection or toxicity of the conditioning regimen. Idiopathic pneumonitis is a noninfectious interstitial pneumonia that often follows engraftment, strongly suggesting an immunologic response involved in the process. Clinical features include dyspnea, nonproductive cough, hypoxia, diffuse alveolar damage, and nonlobar infiltrates on x-ray. The mortality rate for this complication is extremely high despite aggressive treatment with antimicrobials, blood products, steroids, and ventilatory support (Ryan et al., 2002).

10.3.3 Late Side Effects

Late side effects and complications can include immunosuppression and infections, chronic GvHD, endocrine dysfunction, cataracts, disease recurrence, and secondary malignancies. Immunosuppression and infections remain a risk during this time despite neutrophil engraftment. Both cellular and humoral immunity remain depressed until full immune reconstitution occurs. This delayed immune recovery can lead to acute and chronic infections and nutritional deficits (Guinan et al., 2002; Ryan et al., 2002).

Table 10.7. Prophylaxis for PCP

Age	Primary recommendation	Second alternative
Infants (1–12 months)	* TMP-SMZ (150/750 mg/m^2) by mouth twice daily for 3 consecutive days	Dapsone (infants >1 month) 2 mg/kg by mouth daily
Children (>12 months)	TMP-SMZ (150/750 mg/m^2) by mouth twice daily for 3 consecutive days	Dapsone 2 mg/kg by mouth daily, maximum 100 mg by mouth daily
Adolescents	TPM-SMZ (160 mg/800 mg) by mouth three times a week	Dapsone 100 mg by mouth daily

* prophylaxis – sulfomethoxazole/trimethoprim/co-trimoxazole

Several factors contribute to this protracted impaired immunity: patient and donor age, conditioning regimen used, degree of HLA disparity between donor and recipient, presence of GvHD, presence of infection, and type of post-transplant immunosuppression used.

Common post-transplant infections include *Pneumocystis jiroveci* (formerly called *Pneumocystis carinii*), varicella-zoster, CMV, adenovirus, and Epstein-Barr virus lymphoproliferative disease. Management includes *Pneumocystis jiroveci* prophylaxis for 1 year post-transplant (Table 10.7) and frequent monitoring for evidence of infections and immune recovery.

Chronic GvHD (CGvHD) is a chronic autoimmune syndrome that resembles collagen vascular diseases such as scleroderma and systemic lupus erythematosus. The primary effect of CGvHD is the epithelial cell damage to tissue that can lead to fibrosis and atrophy. Chronic GvHD targets the same organs as AGvHD – the skin, liver, and gut – however, it may affect others as well, such as the eyes and lungs. The secondary effect of marked immunosuppression has a significant impact on morbidity and mortality post-transplant.

Risk factors for CGvHD include prior AGvHD, donor and recipient HLA disparity, and increasing patient age. The decreased incidence over the last decade can be attributed to improved HLA matching and effective AGvHD prevention. Chronic GvHD can occur as progression of acute GvHD, follow a period of quiescence after acute GvHD, or occur as de novo disease. Historically, GvHD that occurs 100 days after transplant is considered chronic. The increased use of donor T-lymphocytes in the post-transplant period requires careful assessment and diagnosis of GvHD symptoms.

Clinical presentation is remarkable for sicca syndrome, extreme dryness of mucous membranes and tissues, and infections (Table 10.8). Diagnosis can be made clinically based on symptoms and laboratory values. However, tissue biopsy is required for definitive diagnosis. Chronic GvHD is graded as limited or extensive: Limited is described as localized skin involvement and/or hepatic dysfunction, and extensive is described as generalized skin involvement with multiorgan involvement.

Treatment consists of immunosuppression with many of the same agents used to treat AGvHD (Table 10.6). Initial treatment usually includes cyclosporine or tacrolimus and steroids that are slowly tapered over several months. Several newer agents are now available. For severe CGvHD of the skin, both psoralen and ultraviolet radiation (PUVA) and extracorporeal photopheresis have been beneficial.

Endocrine dysfunction may present as growth failure, thyroid dysfunction, ovarian dysfunction, or testicular dysfunction. Risk factors include TBI and long-term steroid therapy, although fractionated TBI has decreased the incidence of hypothyroidism to 10% (Guinan et al., 2002). Treatment includes thyroid replacement therapy and growth hormone therapy, respectively, for thyroid dysfunction and growth delays. Females who have chemotherapy after puberty have more permanent infertility and menopausal symptoms than those treated before puberty. Testic-

Table 10.8. Chronic GvHD: clinical effects and nursing interventions

Organ/system involved	Clinical effects	Nursing interventions
Skin	Itching, burning, scleroderma, ulcerations, hyperpigmentation, erythema, dryness Erythema can be activated by sun exposure	Teach patient to use skin moisturizers and nondrying, nonabrasive soaps Teach patient to protect skin from sunlight and avoid prolonged sun exposure; emphasize need to use sunscreens
	Alopecia, nail ridging, joint contractures	Apply topical steroid creams to relieve itching and/or burning Provide range of motion exercises Practice specific exercise regimens recommended by PT/OT to prevent contractures
Liver	Obstructive jaundice	Monitor liver function tests
	Cirrhosis with esophageal varices and hepatic failure	Teach patient low-fat diet, if indicated
GI tract	Xerostomia, stomatitis, ulcerations, lichen planus-like striae and plaques, taste changes, dysphagia, retrosternal pain, diarrhea, malabsorption	Promote oral hygiene and regular dental follow-up Encourage use of artificial saliva or alkaline-saline mouthwash to relieve oral dryness Provide lanolin for lip moisturizing Provide nutritional counseling and dietary referral Monitor weights
Eyes	Decreased tear production Burning, photophobia, itching, sensation of grittiness in eyes	Promote regular ophthalmology exams Provide artificial tears to relieve ocular dryness Suggest use of sunglasses to decrease discomfort of photophobia
Lungs	Obstructive and restrictive lung changes	Provide chest PT and incentive spirometer, if indicated
	Cough, dyspnea, pneumothorax	Monitor pulmonary function tests on a regular basis
Immunosuppression	Increased risk of infection Slowed immune recovery	Maintain measures to prevent infections Promote good general hygiene Administer immunosuppressive therapy and monitor for side effects Monitor compliance with infection prophylaxis medications

ular dysfunction includes sterility, azoospermia, and premature ejaculation in males treated with TBI. Regardless of age, TBI may result in primary gonadal failure in both genders. Treatment may include hormone replacement therapy.

Cataracts, usually posterior and bilateral, can occur several years post-transplant in patients who receive TBI. Fractionated TBI has significantly reduced the incidence. Treatment is surgical removal of the cataracts.

Disease recurrence remains the primary cause of treatment failure after autologous and allogeneic HSCT. Patients at increased risk for relapse include those with high-risk diseases, poor response to initial therapy, unfavorable cytogenetic abnormalities, and significant disease/tumor burden at time of trans-

plant. Treatment can include donor lymphocyte infusions, second transplants, and discontinuing immunosuppressive therapy.

Secondary malignancies are potential problems for both autologous and allogeneic transplant recipients. High-dose chemotherapy, TBI, and immunosuppression are the primary etiologies. Myelodysplastic syndrome and leukemia occur at an incidence of 4–20% at 5–6 years after autologous transplant. Patients receiving an allogeneic transplant are at risk of developing post-transplant lymphoproliferative disease, which can occur within 6 months after transplant, and a variety of solid tumors at an incidence rate eight times higher than the normal (Guinan et al., 2002).

10.4 Special Considerations

Discharge planning and teaching become focused once engraftment begins. Discharge can be anticipated once engraftment has occurred. Engraftment is generally defined as an ANC >500 for 3 consecutive days. In general, patients are required to remain in close proximity to the transplant center for the first 100 days after allogeneic transplant. Autologous transplant patients may be referred to their primary physician once engraftment has occurred and HSCT complications have resolved.

General discharge criteria include the following:

- ANC >500
- Afebrile for 24 hours
- Able to take oral medications
- Oral intake of calories and fluids is 50% of nutritional needs
- Patient is on total parenteral nutrition or nasogastric feedings
- Any transplant complications are resolved or controlled
- Primary caregiver is able to care for central venous line and provide any nutritional support that is needed.

Instructions to patient and caregiver should include the following topics:

- Infection control practices: handwashing, social isolation, face masks, temperature monitoring, and avoidance of new pets and plants
- Activities of daily living: diet, personal hygiene, mouth care, sun exposure, exercise, and school reentry
- Central line care and parenteral medication administration
- Importance of oral medication compliance
- Reportable signs and symptoms: fever, cough, rash, vomiting, diarrhea, bleeding, pain, and inability to take oral medications.

Outpatient follow-up will be tailored to the patient's needs. The frequency of clinic appointments is based on type of transplant, engraftment status, and unresolved complications. Regular monitoring will include physical assessment, routine blood counts, serum chemistries and medication levels (cyclosporine and tacrolimus), symptom and toxicity management, medication compliance, and nutritional assessment.

Annual evaluations of recipients of allogeneic transplants are required for monitoring engraftment status and assessing for late effects. Typical tests performed on an annual basis include

- Complete blood count with differential
- Serum chemistries
- Immunoglobulin levels
- Immune function tests
- Endocrine function tests
- Pulmonary function tests
- Cardiac function tests
- Ophthalmologic examination
- Renal function tests
- Neuropsychological evaluation.

Psychosocial issues faced by patients and their families are numerous, with different issues presenting during each stage of transplant. Some of these include prolonged hospitalization, emotional isolation from family and friends, role changes within the family dynamics, invasive medical procedures, treatment-related side effects and complications, fear of relapse, and financial concerns. All of these can have a significant impact on the quality of life experienced

by the patient and the entire family. Consequently, a diverse multidisciplinary team of healthcare providers is required to assist the patient and family in successfully dealing with these issues.

10.5 Future Perspectives

Future direction in HSCT will consist of optimizing graft versus leukemia (GvL) effects, minimizing toxicity, engineering more precise grafts, moving to outpatient procedures, and combining stem cell transplantation with gene therapy.

GvL is an immune response to donor cells against recipient leukemia. There is evidence for GvL effect with the infusion of unmanipulated donor lymphocytes to relapsed patients after allogeneic HSCT. The future holds identification of minor antigens and their roles in GvL and GvHD.

Minimizing regimen-related toxicity would broaden the use of HSCT to nontraditional disorders such as autoimmune and degenerative diseases and improve long-term survival of transplant recipients. Monoclonal antibodies, such as Campath, CD45, and Rituxan, are being incorporated into conditioning regimens to substitute in part or in whole for the traditional cytotoxic and immunosuppressive drugs currently used. Many centers are developing submyeloablative conditioning regimens with less toxic chemotherapy. The use of adoptive immunotherapy in the form of cytotoxic T-lymphocytes has been demonstrated to prevent and treat transplant infections and post-transplant lymphoproliferative disorders.

T-cell depletion and $CD34^+$ selection are examples of more precise graft engineering to reduce complications such as graft failure and GvHD. Further identification of minor antigens could lead to more selective T-cell depletion techniques that might allow GvHD prevention without significant loss of GVL effect.

Several centers are exploring the possibility of providing stem cell transplants in the outpatient arena. This could have a significant impact on length of hospitalization and financial costs of HSCT in the future. As technology and basic science advance, HSCT will be combined with gene therapy as a vehicle for gene insertion, which will enhance applicability of stem cell transplantation, provide less toxic therapy, and improve survival.

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