This book is dedicated to all of our colleagues (faculty, residents, and medical students) who demonstrate a passion for learning, a curiosity that drives advancement in the care of children, and an amazing dedication to the patients and families we are honored to serve.
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Medicine and technology just don’t stop! The amazing advancements we hear about as our scientist colleagues further delineate the pathophysiology and mechanisms of diseases must eventually be translated to our daily care of patients. Our goal, as the editors and authors of this textbook, is not only to provide the classic, foundational knowledge we use every day but to include these advances in a readable and concise text for medical students and residents.

This new edition has been updated with the advances that have occurred since the last edition. We have also incorporated technology by linking this book to the second edition of *Pediatric Decision Making Strategies* by Pomeranz, Busey, Sabnis, and Kliegman. This will allow you to read about the medical issues and then follow a link to an algorithm to facilitate efficient and effective evaluations.

We believe this integration will help you investigate the common and classic pediatric disorders in a time-honored, logical format to both acquire knowledge and apply knowledge to your patients. We have also once again asked our colleagues who serve as clerkship directors to write many of the sections so that you can gain the knowledge and skills necessary to succeed both in caring for patients and in preparing for clerkship or in-service examinations.

We are honored to be part of the journey of thousands of learners who rotate through pediatrics as well as those who will become new providers of pediatric care in the years to come.

Karen J. Marcdante, MD  
Robert M. Kliegman, MD
The editors could never have published this edition without the assistance and attention to detail of James Merritt and Jennifer Shreiner. We also couldn’t have accomplished this without Carolyn Redman, whose prompting, organizing, and overseeing of the process helped us create this new edition.
Health care professionals need to appreciate the interactions between medical conditions and social, economic, and environmental influences associated with the provision of pediatric care. New technologies and treatments help improve morbidity, mortality, and the quality of life for children and their families, but the costs may exacerbate disparities in medical care. The challenge for pediatricians is to deliver care that is socially equitable; integrates psychosocial, cultural, and ethical issues into practice; and ensures that health care is available to all children.

**CURRENT CHALLENGES**

Many challenges affect children’s health outcomes. These include access to health care; health disparities; supporting their social, cognitive, and emotional lives in the context of families and communities; and addressing environmental factors, especially poverty. Early experiences and environmental stresses interact with the genetic predisposition of every child and, ultimately, may lead to the development of diseases seen in adulthood. Thus, pediatricians have the unique opportunity to address not only acute and chronic illnesses but also the aforementioned issues and toxic stressors to promote wellness and health maintenance in children.

Many scientific advances have an impact on the growing role of pediatricians. Incorporating the use of newer genetic technologies allows the diagnosis of diseases at the molecular level, aids in the selection of medications and therapies, and provides information on the prognosis of some diseases. Prenatal diagnosis and newborn screening improve the accuracy of early diagnosis of a variety of conditions, allowing for earlier treatment even when a cure is impossible. Functional magnetic resonance imaging allows a greater understanding of psychiatric and neurologic problems, such as dyslexia and attention-deficit/hyperactivity disorder.

Challenges persist with the incidence and prevalence of chronic illness having increased in recent decades. Chronic illness is now the most common reason for hospital admissions among children (excluding trauma and newborn admissions). From middle school and beyond, mental illness is the main non–childbirth-related reason for hospitalization among children. Pediatricians must also address the increasing concern about environmental toxins and the prevalence of physical, emotional, and sexual abuse, as well as violence. Since the September 11, 2001, destruction of the World Trade Center in New York City, fear of terrorism in the United States has increased the level of anxiety for many families and children.

To address these ongoing challenges, pediatricians must practice as part of a health care team. Many pediatricians already practice collaboratively with psychiatrists, psychologists, nurses, and social workers. Team composition can change, depending on location and patient needs. Although school health and school-based health clinics have improved access and outcomes for many common childhood and adolescent conditions, the shortage of available general pediatricians and family physicians has led to the development of retail medical facilities in pharmacies and retail stores.

Childhood antecedents of adult health conditions, such as alcoholism, depression, obesity, hypertension, and hyperlipidemias, are increasingly being recognized. Maternal health status can affect the fetus. Infants who are a smaller size and relatively underweight at birth because of maternal malnutrition have increased rates of coronary heart disease, stroke, type 2 diabetes mellitus, obesity, metabolic syndrome, and osteoporosis in later life. Because of improved neonatal care, a greater percentage of preterm, low birth weight, or very low birth weight newborns survive, increasing the number of children with chronic medical conditions and developmental delays with lifelong implications.

**LANDSCAPE OF HEALTH CARE FOR CHILDREN IN THE UNITED STATES**

Complex health, economic, and psychosocial challenges greatly influence the well-being and health outcomes of children. National reports from the Centers for Disease Control and Prevention (CDC) (e.g., [http://www.cdc.gov/nchs/data/hus/hus11.pdf#102](http://www.cdc.gov/nchs/data/hus/hus11.pdf#102)) provide information about many of these issues. Some of the key issues include the following:

- **Health insurance coverage.** In 2010 over eight million children in the United States had no health insurance coverage. In addition, 10 to 20 million were underinsured. Many children, despite public sector insurance, do not receive recommended immunizations. Although
Medicaid and the State Children’s Health Insurance Program covered more than 42 million children in 2010 who otherwise would not have health care access, over a million U.S. children are unable to get needed medical care because their families cannot afford it.

- **Prenatal and perinatal care.** Ten to 25% of women do not receive prenatal care during the first trimester. In addition, a significant percentage of women continue to smoke, use illicit drugs, and consume alcohol during pregnancy.

- **Preterm births.** The incidence of preterm births (<37 weeks) peaked in 2006 and has been slowly declining (11.99% in 2010). However, the 2010 rates of low birth weight infants (≤2500 g [8.15% of all births]) and very low birth weight infants (≤1500 g [1.45% of all births]) are essentially unchanged since 2006.

- **Birth rate in adolescents.** The national birth rate among adolescents has been steadily dropping since 1990, reaching its lowest rate (3.4.2 per 1000) for 15- to 19-year-old adolescents in 2010.

- **Adolescent abortions.** In 2009 nearly 800,000 abortions were reported to the CDC, a continued decline over the last decade. Adolescents from 15 to 19 years of age accounted for 15.5% of abortions. Approximately 60% of sexually active adolescents report using effective contraception.

- **Infant mortality.** Although infant mortality rates have declined since 1960, the disparity among the ethnic groups persists. In 2011 the overall infant mortality rate was 6.05 per 1000 live births with a rate per 1000 live births of 5.05 for non-Hispanic whites, 5.27 for Hispanic infants, and 11.42 for black infants. In 2008 the United States ranked thirty-first in infant mortality. Marked variations in infant mortality exist by state with highest mortality rates in the South and Midwest.

- **Initiation and maintenance of breastfeeding.** Seventy-seven percent of women initiate breastfeeding following the birth of their infants. Breastfeeding rates vary by ethnicity (higher rates in non-Hispanic whites and Hispanic mothers) and education (highest in women with a bachelor’s degree or higher). Only 47% of women continue breastfeeding for 6 months, with about 25% continuing at 12 months.

- **Cause of death in U.S. children.** The overall causes of death in all children (1 to 24 years of age) in the United States in 2010, in order of frequency, were accidents (unintentional injuries), assaults (homicide), suicide, malignant neoplasms, and congenital malformations (Table 1-1). There was a slight improvement in the rate of death from all causes.

- **Hospital admissions for children and adolescents.** In 2010 2.4% of children were admitted to a hospital at least once. Respiratory illnesses (asthma, pneumonia, and bronchitis/bronchiolitis) and injury are the causes of over 28% of hospitalization in children under 18 years of age. Mental illness is the most common cause of admissions for children 13 to 17 years of age.

- **Significant adolescent health challenges: substance use and abuse.** There is considerable substance use and abuse in U.S. high school students. Forty-six percent of high school students reported having tried cigarettes in 2009. In 2011 nearly 71% of high school students reported having had at least one drink; 21.9% admitted to more than five drinks on one day in the previous month, and 8.2% admitted to driving after drinking. Nearly 40% of high school students have tried marijuana; 11.4%, inhalants; 6.8%, cocaine; 3.8%, methamphetamine; 2.9%, heroin; and 2%, injectables.

- **Children in foster care.** Currently there are about 400,000 children in the foster care system. Approximately 25,000 of these children must leave the child welfare system each year. Of those who leave, 25% to 50% experience homelessness and/or joblessness and will not graduate from high school. These children have a high incidence of mental health problems, substance abuse, and early pregnancy for females with an increased likelihood of having a low birth weight baby.

### Table 1-1 Causes of Death by Age in the United States, 2005

<table>
<thead>
<tr>
<th>AGE GROUP (YR)</th>
<th>CAUSES OF DEATH IN ORDER OF FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4</td>
<td>Unintentional injuries (accidents)</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
</tr>
<tr>
<td></td>
<td>Homicide</td>
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<td></td>
<td>Malignant neoplasms</td>
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<tr>
<td></td>
<td>Diseases of the heart</td>
</tr>
<tr>
<td>5–14</td>
<td>Unintentional injuries (accidents)</td>
</tr>
<tr>
<td></td>
<td>Malignant neoplasms</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
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<tr>
<td></td>
<td>Homicide</td>
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<td></td>
<td>Diseases of the heart</td>
</tr>
<tr>
<td>15–24</td>
<td>Unintentional injuries (accidents)</td>
</tr>
<tr>
<td></td>
<td>Homicide</td>
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<tr>
<td></td>
<td>Suicide</td>
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<td></td>
<td>Malignant neoplasms</td>
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<tr>
<td></td>
<td>Diseases of the heart</td>
</tr>
</tbody>
</table>


### OTHER HEALTH ISSUES THAT AFFECT CHILDREN IN THE UNITED STATES

- **Obesity.** The prevalence of obesity continues to increase. The prevalence of overweight children 6 to 19 years of age has increased more than fourfold from 4% in 1965 to over 18% in 2010. Currently it is estimated that 32% of children 2 to 19 years of age are overweight or obese. An estimated 300,000 deaths a year and at least $147 billion in health care costs are associated with the 68% of Americans who are overweight or obese.

- **Sedentary lifestyle.** Among 6 to 11 year olds, 62% do not engage in recommended amounts of moderate or vigorous physical activity. Nearly 40% spend more than 2 hours of screen time (television/videos) per school day.

- **Motor vehicle accidents and injuries.** In 2009, 1314 children 14 years of age or younger died in motor vehicle crashes, and 179,000 were injured. Other causes of childhood injury included drowning, child abuse, and poisonings. The estimated cost of all unintentional childhood injuries is nearly $300 billion per year in the United States.
• **Child maltreatment.** Although there has been a slow decline in the prevalence of child maltreatment, there were over 760,000 reported cases of abuse in 2009. The majority (71%) of children were neglected; 16% suffered physical abuse, and nearly 9% were victims of sexual abuse.

• **Current social and economic stress on the U.S. population.** There are considerable societal stresses affecting the physical and mental health of children, including rising unemployment associated with the economic slowdown, financial turmoil, and political unrest. Millions of families have lost their homes or are at risk for losing their homes after defaulting on mortgage payments.

• **Toxic stress in childhood leading to adult health challenges.** The growing understanding of the interrelationship between biologic and developmental stresses, environmental exposure, and the genetic potential of patients is helping us recognize the adverse impact of toxic stressors on health and well-being. Pediatricians must screen for and act upon factors that promote or hinder early development to provide the best opportunity for long-term health.

• **Military deployment and children.** Current armed conflicts and political unrest have affected millions of adults and their children. There are an estimated 1.5 million active duty and National Guard/Reserve servicemen and women, parents to over a million children. An estimated 31% of troops returning from armed conflicts have a mental health condition (alcoholism, depression, and posttraumatic stress disorder) or report having experienced a traumatic brain injury. Their children are affected by these morbidities as well as by the psychological impact of deployment on children of all ages. Child maltreatment is more prevalent in families of U.S.-enlisted soldiers during combat deployment than in nondeployed soldiers.

**HEALTH DISPARITIES IN HEALTH CARE FOR CHILDREN**

Health disparities are the differences that remain after taking into account patients' needs, preferences, and the availability of health care. Social conditions, social inequity, discrimination, social stress, language barriers, and poverty are antecedents to and associated causes of health disparities. The disparities in infant mortality relate to poor access to prenatal care during pregnancy and the lack of access and appropriate health services for women, such as preventive services, family planning, and appropriate nutrition and health care, throughout their life span.

- Infant mortality increases as the mother’s level of education decreases.
- Children from poor families are less likely to be immunized at 4 years of age and less likely to receive dental care.
- Rates of hospital admission are higher for people who live in low-income areas.
- Children of ethnic minorities and children from poor families are less likely to have physician office or hospital outpatient visits and more likely to have hospital emergency department visits.

- Children with Medicaid/public coverage are less likely to be in excellent health than children with private health insurance.
- Access to care for children is easier for whites and for children of higher income families than for minority and low-income families.

**CHANGING MORBIDITY: THE SOCIAL/EMOTIONAL ASPECTS OF PEDIATRIC PRACTICE**

• **Changing morbidity** reflects the relationship among environmental, social, emotional, and developmental issues; child health status; and outcome. These observations are based on significant interactions of biopsychosocial influences on health and illness, such as school problems, learning disabilities, and attention problems; child and adolescent mood and anxiety disorders; adolescent suicide and homicide; firearms in the home; school violence; effects of media violence, obesity, and sexual activity; and substance use and abuse by adolescents.

- Currently 20% to 25% of children are estimated to have some mental health problems; 5% to 6% of these problems are severe. Unfortunately it is estimated that pediatricians identify only 50% of mental health problems. The overall prevalence of psychosocial dysfunction of preschool and school-age children is 10% and 13%, respectively. Children from poor families are twice as likely to have psychosocial problems than children from higher income families. Nationwide, there is a lack of adequate mental health services for children.

Important influences on children’s health, in addition to poverty, include homelessness, single-parent families, parental divorce, domestic violence, both parents working, and inadequate child care. Related pediatric challenges include improving the quality of health care, social justice, equality in health care access, and improving the public health system. For adolescents, there are special concerns about sexuality, sexual orientation, pregnancy, substance use and abuse, violence, depression, and suicide.

**CULTURE**

Culture is an active, dynamic, and complex process of the way people interact and behave in the world. Culture encompasses the concepts, beliefs, values (including nurturing of children), and standards of behavior, language, and dress attributable to people that give order to their experiences in the world, offer sense and purpose to their interactions with others, and provide meaning for their lives. The growing diversity of the United States requires that health care workers make an attempt to understand the impact of health, illness, and treatment on the patient and family from their perspective. This requires open-ended questions, such as: “What worries (concerns) you the most about your child’s illness?” and “What do you think has caused your child’s illness?” These can facilitate a discussion of parents’ thoughts and feelings about the illness and its causes. Addressing concepts and beliefs about how one interacts with health professionals as well as the family’s spiritual and religious approach to health and health care from a cultural perspective allows the pediatrician, patient, and family to
incorporate differences in perspectives, values, or beliefs into the care plan. Significant conflicts may arise because religious or cultural practices may lead to the possibility of child abuse and neglect. In this circumstance, the pediatrician is required by law to report the suspected child abuse and neglect to the appropriate social service authorities (see Chapter 22).

Complementary and alternative medicine (CAM) practices constitute a part of the broad cultural perspective. Therapeutic modalities for CAM include biochemical, lifestyle, biomechanical, and bioenergetic treatments, as well as homeopathy. It is estimated that 20% to 30% of all children and 50% to 75% of adolescents use CAM. Of children with chronic illness, 30% to 70% use CAM therapies, especially for asthma and cystic fibrosis. Only 30% to 60% of children and families tell their physicians about their use of CAM. Some modalities may be effective, whereas others may be ineffective or even dangerous.

Historically the most privileged professions have depended on their legitimacy for serving the public interest. The public trust of physicians is based on the physician’s commitment to altruism. Many medical schools include variations on the traditional Hippocratic Oath as part of the commencement ceremonies as a recognition of a physician’s responsibility to put the interest of others ahead of self-interest.

The core of professionalism is embedded in the daily healing work of the physician and encompassed in the patient-physician relationship. Professionalism includes an appreciation for the cultural and religious/spiritual health beliefs of the patient, incorporating the ethical and moral values of the profession and the moral values of the patient. Unfortunately, the inappropriate actions of a few practicing physicians, physician investigators, and physicians in positions of power in the corporate world have created a societal demand to punish those involved and have led to the erosion of respect for the medical profession.

The American Academy of Pediatrics (AAP), the American Board of Pediatrics (ABP), the American Board of Internal Medicine, the LCME, the Medical School Objectives Project of the Association of American Medical Colleges, and the ACGME Outcome Project have called for increasing attention to professionalism in the practice of medicine and in the education of physicians.
also must be insightful regarding the impact of his or her behavior on others and cognizant of appropriate professional boundaries.

- **Communication/collaboration** is crucial to providing the best care for patients. Pediatricians must work cooperatively and communicate effectively with patients and their families and with all health care providers involved in the care of their patients.

- **Altruism/advocacy** refers to unselfish regard for and devotion to the welfare of others. It is a key element of professionalism. Self-interest or the interests of other parties should not interfere with the care of one’s patients and their families.

**ETHICS AND LEGAL ISSUES**

**ETHICS IN HEALTH CARE**

The ethics of health care and medical decision making relies on values to determine what kinds of decisions are best or appropriate for all. Sometimes ethical decision making in medical care is a matter of choosing the least harmful option among many adverse alternatives. In the day-to-day practice of medicine, although all clinical encounters may have an ethical component, major ethical challenges are infrequent.

The legal system defines the minimal standards of behavior required of physicians and the rest of society through the legislative, regulatory, and judicial systems. Laws exist to provide for social order and adjudicate disputes, not to address ethical concerns. The laws support the principle of confidentiality for teenagers who are competent to decide about such issues. Using the concept of limited confidentiality, parents, teenagers, and the pediatrician may all agree to openly discuss serious health challenges, such as suicidal ideation and pregnancy. This reinforces the long-term goal of supporting the autonomy and identity of the teenager while encouraging appropriate conversations with parents.

Ethical problems derive from value differences among patients, families, and clinicians about choices and options in the provision of health care. Resolving these value differences involves several important ethical principles. Autonomy, which is based on the principle of respect for persons, means that competent adult patients can make choices about health care that they perceive to be in their best interests, after being appropriately informed about their particular health condition and the risks and benefits of alternatives of diagnostic tests and treatments. Paternalism challenges the principle of autonomy and involves the clinician deciding what is best for the patient, based on how much information is provided. Paternalism, under certain circumstances (e.g., when a patient has a life-threatening medical condition or a significant psychiatric disorder and is threatening self or others), may be more appropriate than autonomy. Weighing the values of autonomy and paternalism can challenge the clinician.

Other important ethical principles are those of beneficence (doing good), nonmaleficence (doing no harm or as little harm as possible), and justice (the values involved in the equality of the distribution of goods, services, benefits, and burdens to the individual, family, or society). End-of-life decision making must address quality of life and suffering in the provision of palliative and hospice care (see Chapter 4).

**ETHICAL PRINCIPLES RELATED TO INFANTS, CHILDREN, AND ADOLESCENTS**

Children vary from being totally dependent on parents or guardians to meet their health care needs to being more independent. Infants and young children do not have the capacity for making medical decisions. Paternalism by parents and pediatricians in these circumstances is appropriate. Adolescents (<18 years of age), if competent, have the legal right to make medical decisions for themselves. Children 8 to 9 years old can understand how the body works and the meaning of certain procedures; by age 14 to 15, young adolescents may be considered autonomous through the process of being designated a mature or emancipated minor or by having certain medical conditions. It is ethical for pediatricians to involve children in the decision-making process with information appropriate to their capacity to understand. The process of obtaining the assent of a child is consistent with this goal.

The principle of shared decision making is appropriate, but the process may be limited because of issues of confidentiality in the provision of medical care. A parent's concern about the side effects of immunization raises a conflict between the need to protect and support the health of the individual and the public with the rights of the individual and involves ethical issues of distributive justice in regard to the costs and distribution of the vaccinations and responsibility for side effects.

**LEGAL ISSUES**

All competent patients of an age defined legally by each state (usually ≥18 years of age) are considered autonomous with regard to their health decisions. To have the capacity to decide, patients must meet the following requirements:

- Understand the nature of the medical interventions and procedures, understand the risks and benefits of these interventions, and be able to communicate their decision.
- Reason, deliberate, and weigh the risks and benefits using their understanding about the implications of the decision on their own welfare.
- Apply a set of personal values to the decision-making process and show an awareness of the possible conflicts or differences in values as applied to the decisions to be made.

These requirements need to be placed within the context of medical care and applied to each case with its unique characteristics. Most young children are not able to meet the requirements for competency and need others, usually the parent, to make decisions for them. Legally parents are given great discretion in making decisions for their children. This discretion is legally limited when there is child abuse and neglect, which triggers a further legal process in determining the best interests of the child.

It is important to become familiar with state law because state law, not federal law, determines when an adolescent can
consent to medical care and when parents may access confidential adolescent medical information. The Health Insurance Portability and Accountability Act (HIPAA) of 1996, which became effective in 2003, requires a minimal standard of confidentiality protection. The law confers less confidentiality protection to minors than to adults. It is the pediatrician’s responsibility to inform minors of their confidentiality rights and help them exercise these rights under the HIPAA regulations.

Under special circumstances, nonautonomous adolescents are granted the legal right to consent under state law when they are considered mature or emancipated minors or because of certain public health considerations, as follows:

- **Mature minors.** Some states have legally recognized that many adolescents age 14 and older can meet the cognitive criteria and emotional maturity for competence and may decide independently. The Supreme Court has decided that pregnant, mature minors have the constitutional right to make decisions about abortion without parental consent. Although many state legislatures require parental notification, pregnant adolescents wishing to have an abortion do not have to seek parental consent. The state must provide a judicial procedure to facilitate this decision making for adolescents.

- **Emancipated minors.** Children who are legally emancipated from parental control may seek medical treatment without parental consent. The definition varies from state to state but generally includes children who have graduated from high school, are members of the armed forces, married, pregnant, runaways, are parents, live apart from their parents, and are financially independent or declared emancipated by a court.

- **Interests of the state (public health).** State legislatures have concluded that minors with certain medical conditions, such as sexually transmitted infections and other contagious diseases, pregnancy (including prevention with the use of birth control), certain mental illnesses, and drug and alcohol abuse, may seek treatment for these conditions autonomously. States have an interest in limiting the spread of disease that may endanger the public health and in eliminating barriers to access for the treatment of certain conditions.

### ETHICAL ISSUES IN PRACTICE

From an ethical perspective, clinicians should engage children and adolescents, based on their developmental capacity, in discussions about medical plans so that they have a good understanding of the nature of the treatments and alternatives, the side effects, and expected outcomes. There should be an assessment of the patient’s understanding of the clinical situation, how the patient is responding, and the factors that may influence the patient’s decisions. Pediatricians should always listen to and appreciate patients’ requests for confidentiality and their hopes and wishes. The ultimate goal is to help nourish children’s capacity to become as autonomous as is appropriate to their developmental stage.

**Confidentiality**

Confidentiality is crucial to the provision of medical care and is an important part of the basis for a trusting patient-family-physician relationship. Confidentiality means that information about a patient should not be shared without consent. If confidentiality is broken, patients may experience great harm and may not seek needed medical care. See Chapter 67 for a discussion of confidentiality in the care of adolescents.

### Ethical Issues in Genetic Testing and Screening in Children

The goal of **screening** is to identify diseases when there is no clinically identifiable risk factor for disease. Screening should take place only when there is a treatment available or when a diagnosis would benefit the child. **Testing** usually is performed when there is some clinically identifiable risk factor. Genetic testing and screening present special problems because test results have important implications. Some genetic screening (sickle cell anemia or cystic fibrosis) may reveal a carrier state, which may lead to choices about reproduction or create financial, psychosocial, and interpersonal problems (e.g., guilt, shame, social stigma, and discrimination in insurance and jobs). Collaboration with, or referral to, a clinical geneticist is appropriate in helping the family with the complex issues of genetic counseling when a genetic disorder is detected or likely to be detected.

Newborn screening should not be used as a surrogate for parental testing. Examples of diseases that can be diagnosed by genetic screening, even though the manifestations of the disease process do not appear until later in life, are polycystic kidney disease; Huntington disease; certain cancers, such as breast cancer in some ethnic populations; and hemochromatosis. Parents may pressure the pediatrician to order genetic tests when the child is still young, for the parents’ purposes. Testing for these disorders should be delayed until the child has the capacity for informed consent or assent and is competent to make decisions, unless there is a direct benefit to the child at the time of testing.

### Religious Issues and Ethics

The pediatrician is required to act in the best interests of the child, even when religious tenets may interfere with the health and well-being of the child. When an infant or child whose parents have a religious prohibition against a blood transfusion needs a transfusion to save his or her life, the courts always have intervened to allow a transfusion. In contrast, parents with strong religious beliefs under some state laws may refuse immunizations for their children. However, state governments can mandate immunizations for all children during disease outbreaks or epidemics. By requiring immunization of all, including individuals who object on religious grounds, the state government is using the principle of **distributive justice**, which states that all members of society must share in the burdens and the benefits to have a just society.

### Children as Human Subjects in Research

The goal of research is to develop new and generalized knowledge. Parents may give informed permission for children to participate in research under certain conditions. Children cannot give consent but may assent or dissent to research protocols. Special federal regulations have been developed to protect child and adolescent participants in human investigation.
These regulations provide additional safeguards beyond the safeguards provided for adult participants in research, while still providing the opportunity for children to benefit from the scientific advances of research.

Many parents with seriously ill children hope that the research protocol will have a direct benefit for their particular child. The greatest challenge for researchers is to be clear with parents that research is not treatment. This fact should be addressed as sensitively and compassionately as possible.

PALLIATIVE CARE AND END-OF-LIFE ISSUES

The death of a child is one of life’s most difficult experiences. The palliative care approach to a child’s medical care should be instituted when medical diagnosis, intervention, and treatment cannot reasonably be expected to affect the imminence of death. In these circumstances, the goals of care focus on improving the quality of life, maintaining dignity, and ameliorating the suffering of the seriously ill child. Central to this approach is the willingness of clinicians to look beyond the traditional medical goals of curing disease and preserving life. They need to look toward enhancing the life of the child and working with family members and close friends when the child’s needs are no longer met by curative goals. High-quality palliative care is an expected standard at the end of life.

Palliative care in pediatrics is not simply end-of-life care. There are conditions where death is not predictably imminent, and a child’s needs are best met by the palliative care approach. Children needing palliative care have been described as having conditions that fall into four basic groups, based on the goal of treatment. These include conditions of the following scenarios:

- A cure is possible, but failure is not uncommon (e.g., cancer with a poor prognosis).
- Long-term treatment is provided with a goal of maintaining quality of life (e.g., cystic fibrosis).
- Treatment that is exclusively palliative after the diagnosis of a progressive condition is made (e.g., trisomy 13 syndrome).
- Treatments are available for severe, nonprogressive disability in patients who are vulnerable to health complications (e.g., severe spastic quadriplegia with difficulty in controlling symptoms).

These conditions present different timelines and different models of medical intervention. Yet they all share the need to attend to concrete elements, which affect the quality of a child’s death, mediated by medical, psychosocial, cultural, and spiritual concerns.

The sudden death of a child also requires elements of the palliative care approach, although conditions do not allow for the full spectrum of involvement. Many of these deaths involve emergency medicine caregivers and first responders in the field, and they may involve dramatic situations where no relationship may exist between caregivers and the bereaved family. Families who have not had time to prepare for the tragedy of an unexpected death require considerable support. Palliative care can make important contributions to the end-of-life and bereavement issues that families face in these circumstances. This may become complicated in circumstances where the cause of the death must be fully explored. The need to investigate the possibility of child abuse or neglect subjects the family to intense scrutiny and may create guilt and anger directed at the medical team.

PALLIATIVE AND END-OF-LIFE CARE

Palliative treatment is directed toward the relief of symptoms as well as assistance with anticipated adaptations that may cause distress and diminish the quality of life of the dying child. Elements of palliative care include pain management; expertise with feeding and nutritional issues at the end of life; and management of symptoms, such as minimizing nausea and vomiting, bowel obstruction, labored breathing, and fatigue. Psychological elements of palliative care have a profound importance and include sensitivity to bereavement, a developmental perspective of a child’s understanding of death, clarification of the goals of care, and ethical issues. Curative care and palliative care can coexist; aggressive pain medication may be provided while curative treatment is continued in the hopes of a remission or improved health status. Palliative care is delivered with a multidisciplinary approach, giving a broad range of expertise to patients and families as well as providing a supportive network for the caregivers. Caregivers involved may be pediatricians, nurses, mental health professionals, social workers, and pastors.

A model of integrated palliative care rests on the following principles:

- Article I. Respect for the dignity of patients and families. The clinician should respect and listen to patient and family goals, preferences, and choices. School-age children can articulate preferences about how they wish to be treated. Adolescents, by the age of 14, can engage in decision making (see Section 12). The pediatrician should assist the patient and the family in understanding the diagnosis, treatment options, and prognosis; help clarify the goals of care; promote informed choices; allow for the free flow of information; and listen to and discuss the social-emotional concerns. Advanced care (advance directives) should be instituted with the child and parents, allowing discussions about what they would like as treatment options as the end of life nears. Differences of opinion between the family and the pediatrician should be addressed by identifying the multiple perspectives, reflecting on possible conflicts, and altruistically coming to agreements that validate the patient and family perspectives, yet reflect sound practice. Hospital ethics committees and consultation services are important resources for the pediatrician and family members.
- Article II. Access to comprehensive and compassionate palliative care. The clinician should address the physical symptoms, comfort, and functional capacity, with special attention to pain and other symptoms associated with the dying process, and respond empathically to the psychological distress and human suffering, providing treatment options. Respite should be available at any time during the illness to allow the family caregivers to rest and renew.
• Article III. **Use of interdisciplinary resources.** Because of the complexity of care, no one clinician can provide all of the needed services. The team members may include primary and subspecialty physicians, nurses in the hospital/facility or for home visits, the pain management team, psychologists, social workers, pastoral ministers, schoolteachers, friends of the family, and peers of the child. The child and family should be in a position to decide who should know what during all phases of the illness process.

• Article IV. **Acknowledgment and support provisions for caregivers.** The death of a child is difficult to accept and understand. The primary caregivers of the child, family, and friends need opportunities to address their own emotional concerns. Siblings of the child who is dying react emotionally and cognitively, based on their developmental level. Team meetings to address thoughts and feelings of team members are crucial. Soon after the death of the child, the care team should review the experience with the parents and family and share their reactions and feelings. Institutional support may include time to attend funerals, counseling for the staff, opportunities for families to return to the hospital, and scheduled ceremonies to commemorate the death of the child.

• Article V. **Commitment to quality improvement of palliative care through research and education.** Hospitals should develop support systems and staff to monitor the quality of care continually, assess the need for appropriate resources, and evaluate the responses of the patient and family members to the treatment program. Issues often arise over less than completely successful attempts to control the dying child's symptoms or differences between physicians and family members in the timing of the realization that death is imminent. Consensus results in better palliative care from the medical and psychosocial perspective.

Hospice care is a treatment program for the end of life, providing the range of palliative care services by an interdisciplinary team, including specialists in the bereavement and end-of-life process. Typically, the hospice program uses the adult Medicare model, requiring a prognosis of death within 6 months and the cessation of curative efforts for children to receive hospice services. Recently some states have developed alternative pediatric models where curative efforts may continue while the higher level of coordinated end-of-life services may be applied.

**BEREAVEMENT**

Bereavement refers to the process of psychological and spiritual accommodation to death on the part of the child and the child’s family. Grief has been defined as the emotional response caused by a loss, including pain, distress, and physical and emotional suffering. It is a normal adaptive human response to death. Palliative care attends to the grief reaction. Assessing the coping resources and vulnerabilities of the affected family before death takes place is central to the palliative care approach.

Parental grief is recognized as being more intense and sustained than other types of grief. Most parents work through their grief. Complicated grief, a pathologic manifestation of continued and disabling grief, is rare. Parents who share their problems with others during the child’s illness, who have had access to psychological support during the last month of their child’s life, and who have had closure sessions with the attending staff, are more likely to resolve their grief.

A particularly difficult issue for parents is whether to talk with their child about the child’s imminent death. Although evidence suggests that sharing accurate and truthful information with a dying child is beneficial, each individual case presents its own complexities, based on the child’s age, cognitive development, disease, timeline of disease, and parental psychological state. Parents are more likely to regret not talking with their child about death than having done so. Among those who did not talk with their child about death, parents who sensed their child was aware of imminent death, parents of older children, and mothers more than fathers were more likely to feel regretful.

**COGNITIVE ISSUES IN CHILDREN AND ADOLESCENTS: UNDERSTANDING DEATH AND DYING**

The pediatrician should communicate with children about what is happening to them, while respecting the cultural and personal preferences of the family. A developmental understanding of children’s concepts of health and illness helps frame the discussion with children and can help parents understand how their child is grappling with the situation. Piaget’s theories of cognitive development, which help illustrate children’s concepts of death and disease, are categorized as sensorimotor, preoperational, concrete operations, and formal operations.

For very young children, up to 2 years of age (sensorimotor), death is seen as a separation, and there is probably no concept of death. The associated behaviors in grieving children of this age usually include protesting and difficulty of attachment to other adults. The degree of difficulty depends on the availability of other nurturing people with whom the child has had a good previous attachment.

Children from 3 to 5 years of age (preoperational) (sometimes called the magic years) have trouble grasping the meaning of the illness and the permanence of the death. Their language skills at this age make understanding their moods and behavior difficult. Because of a developing sense of guilt, death may be viewed as punishment. If a child previously wished a younger sibling to have died, the death may be seen psychologically as being caused by the child’s wishful thinking. They can feel overwhelmed when confronted with the strong emotional reactions of their parents.

In children ages 6 to 11 years of age (late preoperational to concrete operational), the finality of death gradually comes to be understood. Magical thinking gives way to a need for detailed information to gain a sense of control. Older children in this range have a strong need to control their emotions by compartmentalizing and intellectualizing.

In adolescents (≥12 years of age) (formal operations), death is a reality and is seen as universal and irreversible. Adolescents handle death issues at the abstract or philosophical level and can be realistic. They may also avoid emotional expression and information, instead relying on anger or disdain. Adolescents can discuss withholding treatments. Their wishes, hopes, and fears should be attended to and respected.
CULTURAL, RELIGIOUS, AND SPIRITUAL CONCERNS ABOUT PALLIATIVE CARE AND END-OF-LIFE DECISIONS

Understanding the family's religious/spiritual or cultural beliefs and values about death and dying can help the pediatrician work with the family to integrate these beliefs, values, and practices into the palliative care plan. Cultures vary regarding the roles family members have, the site of treatment for dying people, and the preparation of the body. Some ethnic groups expect the clinical team to speak with the oldest family member or to only the head of the family outside of the patient's presence. Some families involve the entire extended family in decision making. For some families, dying at home can bring the family bad luck, whereas others believe that the patient's spirit will become lost if the death occurs in the hospital. In some traditions, the health care team cleans and prepares the body, whereas, in others, family members prefer to complete this ritual. Religious/spiritual or cultural practices may include prayer, anointing, laying on of the hands, an exorcism ceremony to undo a curse, amulets, and other religious objects placed on the child or at the bedside. Families differ in the idea of organ donation and the acceptance of autopsy. Decisions, rituals, and withholding of palliative or lifesaving procedures that could harm the child or are not in the best interests of the child should be addressed. Quality palliative care attends to this complexity and helps parents and families through the death of a child while honoring the familial, cultural, and spiritual values.

ETHICAL ISSUES IN END-OF-LIFE DECISION MAKING

Before speaking with a child about death, the caregiver should assess the child's age, experience, and level of development; the child's understanding and involvement in end-of-life decision making; the parents' emotional acceptance of death; their coping strategies; and their philosophical, spiritual, and cultural views of death. These may change over time, and the use of open-ended questions to repeatedly assess these areas contributes to the end-of-life process. The care of a dying child can create ethical dilemmas involving autonomy, beneficence (doing good), nonmaleficence (doing no harm), truth telling, confidentiality, or the physician's duty. It is extremely difficult for parents to know when the burdens of continued medical care are no longer appropriate for their child. The beliefs and values of what constitutes quality of life, when life ceases to be worth living, and religious/spiritual, cultural, and philosophical beliefs may differ between families and health care workers. The most important ethical principle is what is in the best interest of the child as determined through the process of shared decision making, informed permission/consent from the parents, and assent from the child. Sensitive and meaningful communication with the family, in their own terms, is essential. The physician, patient, and family must negotiate the goals of continued medical treatment while recognizing the burdens and benefits of the medical intervention plan. There is no ethical or legal difference between withholding treatment and withdrawing treatment, although many parents and physicians see the latter as more challenging. Family members and the patient should agree about what are appropriate do not resuscitate (also called DNR) orders. Foregoing some measures does not preclude other measures being implemented, based on the needs and wishes of the patient and family. When there are serious differences among parents, children, and physicians on these matters, the physician may consult with the hospital ethics committee or, as a last resort, turn to the legal system by filing a report about potential abuse or neglect.

Suggested Reading

Deviations in growth patterns may be nonspecific or may be important indicators of serious and chronic medical disorders. An accurate measurement of length/height, weight, and head circumference should be obtained at every health supervision visit and compared with statistical norms on growth charts. Table 5-1 summarizes several convenient benchmarks to evaluate normal growth. Serial measurements are much more useful than single measurements to detect deviations from a particular growth pattern, even if the value remains within statistically defined normal limits (percentiles). Following the trend helps define whether growth is within acceptable limits or warrants further evaluation.

Growth is assessed by plotting accurate measurements on growth charts and comparing each set of measurements with previous measurements obtained at health visits. Please see examples in Figures 5-1 to 5-4. Complete charts can be found at www.cdc.gov/growthcharts/who_charts.htm for birth to 2 years and www.cdc.gov/growthcharts for 2 to 20 years. The body mass index is defined as body weight in kilograms divided by height in meters squared; it is used to classify adiposity and is recommended as a screening tool for children and adolescents to identify those overweight or at risk for being overweight (see Chapter 29).

Normal growth patterns have spurts and plateaus, so some shifting on percentile graphs can be expected. Large shifts in percentiles warrant attention, as do large discrepancies in height, weight, and head circumference percentiles. When caloric intake is inadequate, the weight percentile falls first, then the height, and the head circumference is last. Caloric intake may be poor as a result of inadequate feeding or because the child is not receiving adequate attention and stimulation (nonorganic failure to thrive [see Chapter 21]).

Caloric intake also may be inadequate because of increased caloric needs. Children with chronic illnesses, such as heart failure or cystic fibrosis, may require a significantly higher caloric intake to sustain growth. An increasing weight percentile in the face of a falling height percentile suggests hypothyroidism. Head circumference may be disproportionately

### Table 5-1 Rules of Thumb for Growth

<table>
<thead>
<tr>
<th>Weight</th>
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<tbody>
<tr>
<td>Weight loss in first few days: 5%–10% of birth weight</td>
<td></td>
</tr>
<tr>
<td>Return to birth weight: 7–10 days of age</td>
<td></td>
</tr>
<tr>
<td>Double birth weight: 4–5 months</td>
<td></td>
</tr>
<tr>
<td>Triple birth weight: 1 year</td>
<td></td>
</tr>
<tr>
<td>Daily weight gain:</td>
<td></td>
</tr>
<tr>
<td>20–30 g for first 3–4 months</td>
<td></td>
</tr>
<tr>
<td>15–20 g for rest of the first year</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average length: 20 in. at birth, 30 in. at 1 year</td>
<td></td>
</tr>
<tr>
<td>At age 4 years, the average child is double birth length or 40 in.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Head Circumference (HC)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Average HC: 35 cm at birth (13.5 in.)</td>
<td></td>
</tr>
<tr>
<td>HC increases: 1 cm per month for first year (2 cm per month for first 3 months, then slower)</td>
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</tr>
</tbody>
</table>
Chapter 5  ♦  Normal Growth  11

Birth to 24 months: Boys
Length-for-age and Weight-for-age percentiles

Figure 5-1 Length-by-age and weight-by-age percentiles for boys, birth to 2 years of age. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. (From Centers for Disease Control and Prevention: WHO Child Growth Standards, Atlanta, Ga, 2009. Available at http://www.cdc.gov/growthcharts/who_charts.htm.)

Birth to 24 months: Boys
Head circumference-for-age and Weight-for-length percentiles

Figure 5-2 Head circumference and weight-by-length percentiles for boys, birth to 2 years of age. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. (From Centers for Disease Control and Prevention: WHO Child Growth Standards, Atlanta, Ga, 2009. Available at http://www.cdc.gov/growthcharts/who_charts.htm.)

2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

Figure 5-3 Stature-for-age and weight-for-age percentiles for girls, 2 to 20 years of age. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. (From Centers for Disease Control and Prevention, Atlanta, Ga, 2001. Available at http://www.cdc.gov/growthcharts.)

2 to 20 years: Girls
Body mass index-for-age percentiles

Figure 5-4 Body mass index-for-age percentiles for girls, 2 to 20 years of age. Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion. (From Centers for Disease Control and Prevention Atlanta, Ga, 2001. Available at http://www.cdc.gov/growthcharts.)
large when there is familial megalocephaly, hydrocephalus, or merely catch-up growth in a neurologically normal premature infant. A child is considered microcephalic if the head circumference is less than the third percentile, even if length and weight measurements also are proportionately low. Serial measurements of head circumference are crucial during infancy, a period of rapid brain development, and should be plotted regularly until the child is 2 years of age. Any suspicion of abnormal growth warrants at least a close follow-up, further evaluation, or both.

**Chapter 6**

**DISORDERS OF GROWTH**

The most common reasons for deviant measurements are technical (i.e., faulty equipment and human errors). Repeating a deviant measurement is the first step. Separate growth charts are available and should be used for very low birth weight infants (weight <1500 g) and for those with Turner syndrome, Down syndrome, achondroplasia, and various other dysmorphology syndromes.

Variability in body proportions occurs from fetal to adult life. Newborns’ heads are significantly larger in proportion to the rest of their body. This difference gradually disappears. Certain growth disturbances result in characteristic changes in the proportional sizes of the trunk, extremities, and head. Patterns requiring further assessment are summarized in Table 6-1.

Evaluating a child over time, coupled with a careful history and physical examination, helps determine whether the growth pattern is normal or abnormal. Parental heights may be useful when deciding whether to proceed with a further evaluation. Children, in general, follow their parents’ growth pattern, although there are many exceptions.

For a girl, midparental height is calculated as follows:

\[
\text{Paternal height (inches)} + \frac{\text{Maternal height (inches)}}{2} - 2.5
\]

For a boy, midparental height is calculated as follows:

\[
\frac{\text{Paternal height (inches)} + \text{Maternal height (inches)}}{2} + 2.5
\]

Actual growth depends on too many variables to make an accurate prediction from midparental height determination for every child. The growth pattern of a child with low weight, length, and head circumference is commonly associated with familial short stature (see Chapter 173). These children are genetically normal but are smaller than most children. A child who, by age, is preadolescent or adolescent and who starts puberty later than others may have the normal variant called constitutional short stature (see Chapter 173); careful examination for abnormalities of pubertal development should be done, although most are normal. An evaluation for primary amenorrhea should be considered for any female adolescent who has not reached menarche by 15 years or has not done so within 3 years of thelarche. Lack of breast development by age 13 years also should be evaluated (see Chapter 174).

Starting out in high growth percentiles, many children assume a lower percentile between 6 and 18 months until they match their genetic programming, then grow along new, lower percentiles. They usually do not decrease more than two major percentiles and have normal developmental, behavioral, and physical examinations. These children with catch-down growth should be followed closely, but no further evaluation is warranted.

Infants born small for gestational age, or prematurely, ingest more breast milk or formula and, unless there are complications that require extra calories, usually exhibit catch-up growth in the first 6 months. These infants should be fed on demand and provided as much as they want unless they are vomiting (not just spitting up [see Chapter 128]). Some may benefit from a higher caloric content formula. Many psychosocial risk factors that may have led to being born small or early may contribute to nonorganic failure to thrive (see Chapter 21). Conversely infants who recover from being low birth weight or premature have an increased risk of developing childhood obesity.

Growth of the nervous system is most rapid in the first 2 years, correlating with increasing physical, emotional, behavioral, and cognitive development. There is again rapid change during adolescence. Osseous maturation (bone age) is determined from radiographs on the basis of the number and size of calcified epiphyseal centers; the size, shape, density, and sharpness of outline of the ends of bones; and the distance separating the epiphyseal center from the zone of provisional calcification.

**Table 6-1** Specific Growth Patterns Requiring Further Evaluation

<table>
<thead>
<tr>
<th>PATTERN</th>
<th>REPRESENTATIVE DIAGNOSES TO CONSIDER</th>
<th>FURTHER EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, length, head circumference all &lt;5th percentile</td>
<td>Familial short stature</td>
<td>Midparental heights</td>
</tr>
<tr>
<td>Constitutional short stature</td>
<td>Evaluation of pubertal development</td>
<td></td>
</tr>
<tr>
<td>Intrauterine insult</td>
<td>Examination of prenatal records</td>
<td></td>
</tr>
<tr>
<td>Genetic abnormality</td>
<td>Chromosome analysis</td>
<td></td>
</tr>
<tr>
<td>Discrepant percentiles (e.g., weight 5th, length 5th, head circumference 50th, or other discrepancies)</td>
<td>Normal variant (familial or constitutional)</td>
<td>Midparental heights</td>
</tr>
<tr>
<td>Endocrine growth failure</td>
<td>Thyroid hormone</td>
<td></td>
</tr>
<tr>
<td>Caloric insufficiency</td>
<td>Growth factors, growth hormone testing</td>
<td></td>
</tr>
<tr>
<td>Declining percentiles</td>
<td>Catch-down growth</td>
<td>Evaluation of pubertal development</td>
</tr>
<tr>
<td>Caloric insufficiency</td>
<td>Endocrine growth failure</td>
<td></td>
</tr>
</tbody>
</table>

Decision-Making Algorithm

Available @ StudentConsult.com
NORMAL DEVELOPMENT

PHYSICAL DEVELOPMENT
Parallel to the changes in the developing brain (i.e., cognition, language, behavior) are changes in the physical development of the body.

NEWBORN PERIOD
Observation of any asymmetric movement or altered muscle tone and function may indicate a significant central nervous system abnormality or a nerve palsy resulting from the delivery and requires further evaluation. Primitive neonatal reflexes are unique in the newborn period and can further elucidate or eliminate concerns over asymmetric function. The most important reflexes to assess during the newborn period are as follows:
The Moro reflex is elicited by allowing the infant’s head to gently move back suddenly (from a few inches off of the mattress onto the examiner’s hand), resulting in a startle, then abduction and upward movement of the arms followed by adduction and flexion. The legs respond with flexion.
The rooting reflex is elicited by touching the corner of the infant’s mouth, resulting in lowering of the lower lip on the same side with tongue movement toward the stimulus. The face also turns toward the stimulus.
The sucking reflex occurs with almost any object placed in the newborn’s mouth. The infant responds with vigorous sucking. The sucking reflex is replaced later by voluntary sucking.
The grasp reflex occurs when placing an object, such as a finger, onto the infant’s palm (palmar grasp) or sole (plantar grasp). The infant responds by flexing fingers or curling the toes.
The asymmetric tonic neck reflex is elicited by placing the infant supine and turning the head to the side. This placement results in ipsilateral extension of the arm and the leg into a “fencing” position. The contralateral side flexes as well.
A delay in the expected disappearance of the reflexes may also warrant an evaluation of the central nervous system.
See Sections 11 and 26 for additional information on the newborn period.

LATER INFANCY
With the development of gross motor skills, the infant is first able to control his or her posture, then proximal musculature, and, last, distal musculature. As the infant progresses through these stages, the parents may notice orthopedic deformities (see Chapters 202 and 203). The infant also may have deformities that are related to intrauterine positioning. Physical examination should indicate whether the deformity is fixed or can be moved passively into the proper position. When a joint held in an abnormal fashion can be moved passively into the proper position, there is a high likelihood of resolving with the progression of gross motor development. Fixed deformities warrant immediate pediatric orthopedic consultation (see Section 26).

Evaluation of vision and ocular movements is important to prevent the serious outcome of strabismus. The cover test and light reflex should be performed at early health maintenance visits; interventions after age 2 decrease the chance of preserving binocular vision or normal visual acuity (see Chapter 179).

SCHOOL AGE/PREADOLESCENT
Older school-age children who begin to participate in competitive sports should have a comprehensive sports history and physical examination, including a careful evaluation of the cardiovascular system. The American Academy of Pediatrics 4th edition sports preparticipation form is excellent for documenting cardiovascular and other risks. The patient and parent should complete the history form and be interviewed to assess cardiovascular risk. Any history of heart disease or a murmur must be referred for evaluation by a pediatric cardiologist. A child with a history of dyspnea or chest pain on exertion, irregular heart rate (i.e., skipped beats, palpitations), or syncope should also be referred to a pediatric cardiologist. A family history of a primary (immediate family) or secondary (immediate family’s immediate family) atherosclerotic disease (myocardial infarction or cerebrovascular disease) before 50 years of age or sudden unexplained death at any age requires additional assessment.

Children interested in contact sports should be assessed for special vulnerabilities. Similarly vision should be assessed as a crucial part of the evaluation before participation in sports.

ADOLESCENCE
Adolescents need annual comprehensive health assessments to ensure progression through puberty without major problems (see Chapters 67 and 68). Sexual maturity is an important issue in adolescents. All adolescents should be assessed to monitor progression through sexual maturity rating stages (see Chapter 67). Other issues in physical development include scoliosis, obesity, and trauma (see Chapters 29 and 203). Most scoliosis is mild and requires only observation for progression. Obesity may first manifest during childhood and is an issue for many adolescents.

DEVELOPMENTAL MILESTONES
The use of milestones to assess development focuses on discrete behaviors that the clinician can observe or accept as present by parental report. This approach is based on comparing the patient’s behavior with that of many normal children whose behaviors evolve in a uniform sequence within specific age ranges (see Chapter 8). The development of the neuromuscular system, similar to that of other organ systems, is determined first by genetic endowment and then molded by environmental influences.

Although a sequence of specific, easily measured behaviors can adequately represent some areas of development (gross motor, fine motor, and language), other areas, particularly
social and emotional development, are not as easy to assess. Easily measured developmental milestones are well established through age 6 years only. Other types of assessment (e.g., intelligence tests, school performance, and personality profiles) that expand the developmental milestone approach are available for older children but generally require time and expertise in administration and interpretation.

**PSYCHOSOCIAL ASSESSMENT**

**Bonding and Attachment in Infancy**
The terms *bonding* and *attachment* describe the affective relationships between parents and infants. *Bonding* occurs shortly after birth and reflects the feelings of the parents toward the newborn (unidirectional). *Attachment* involves reciprocal feelings between parent and infant and develops gradually over the first year.

Attachment of infants outside of the newborn period is crucial for optimal development. Infants who receive extra attention, such as parents responding immediately to any crying or fussiness, show less crying and fussiness at the end of the first year. *Stranger anxiety* develops between 9 and 18 months of age, when infants normally become insecure about separation from the primary caregiver. The infant's new motor skills and attraction to novelty may lead to headlong plunges into new adventures that result in fright or pain followed by frantic efforts to find and cling to the primary caregiver. The result is dramatic swings from stubborn independence to clinging dependence that can be frustrating and confusing to parents. With secure attachment, this period of ambivalence may be shorter and less tumultuous.

**Developing Autonomy in Early Childhood**
Toddlers build on attachment and begin developing autonomy that allows separation from parents. In times of stress, toddlers often cling to their parents, but in their usual activities they may be actively separated. Ages 2 to 3 years are a time of major accomplishments in fine motor skills, social skills, cognitive skills, and language skills. The dependency of infancy yields to developing independence and the "I can do it myself" age. Limit setting is essential to a balance of the child's emerging independence.

**Early Childhood Education**
There is a growing body of evidence that notes that children who are in high quality early learning environments are more prepared to succeed in school. Every dollar invested in early childhood education may save taxpayers up to 13 dollars in future costs. These children commit fewer crimes and are better prepared to enter the workforce after school. Early Head Start (less than 3 years), Head Start (3 to 4 years), and prekindergarten programs (4 to 5 years) all demonstrate better educational attainment, although the earlier the start, the better the results.

**School Readiness**
Readiness for preschool depends on the development of autonomy and the ability of the parent and the child to separate for hours at a time. Preschool experiences help children
develop socialization skills; improve language; increase skill building in areas such as colors, numbers, and letters; and increase problem solving (puzzles).

Readiness for school (kindergarten) requires emotional maturity, peer group and individual social skills, cognitive abilities, and fine and gross motor skills (Table 7-1). Other issues include chronologic age and gender. Children tend to do better in kindergarten if their fifth birthday is at least 4 to 6 months before the beginning of school. Girls usually are ready earlier than boys. If the child is in less than the average developmental range, he or she should not be forced into early kindergarten. Holding a child back for reasons of developmental delay, in the false hope that the child will catch up, can also lead to difficulties. The child should enroll on schedule, and educational planning should be initiated to address any deficiencies.

Physicians should be able to identify children at risk for school difficulties, such as those who have developmental delays or physical disabilities. These children may require specialized school services.

**Adolescence**
Some define adolescence as 10 to 25 years of age but adolescence is perhaps better characterized by the developmental stages (early, middle, and late adolescence) that all teens must negotiate to develop into healthy, functional adults. Different behavioral and developmental issues characterize each stage. The age at which each issue manifests and the importance of these issues vary widely among individuals, as do the rates of cognitive, psychosexual, psychosocial, and physical development.

During *early adolescence*, attention is focused on the present and on the peer group. Concerns are primarily related

### Table 7-1: Evaluating School Readiness

<table>
<thead>
<tr>
<th>PHYSICIAN OBSERVATIONS (BEHAVIORS OBSERVED IN THE OFFICE)</th>
<th>PARENT OBSERVATIONS (QUESTIONS ANSWERED BY HISTORY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ease of separation of the child from the parent</td>
<td>Does the child play well with other children?</td>
</tr>
<tr>
<td>Speech development and articulation</td>
<td>Does the child separate well, such as a child playing in the backyard alone with occasional monitoring by the parent?</td>
</tr>
<tr>
<td>Understanding of and ability to follow complex directions</td>
<td>Does the child show interest in books, letters, and numbers?</td>
</tr>
<tr>
<td>Specific pre-academic skills</td>
<td>Can the child sustain attention to quiet activities?</td>
</tr>
<tr>
<td>Knowledge of colors</td>
<td>How frequent are toilet-training accidents?</td>
</tr>
<tr>
<td>Counts to 10</td>
<td></td>
</tr>
<tr>
<td>Knows age, first and last names, address, and phone number</td>
<td></td>
</tr>
<tr>
<td>Ability to copy shapes</td>
<td></td>
</tr>
<tr>
<td>Motor skills</td>
<td></td>
</tr>
<tr>
<td>Stand on one foot, skip, and catch a bounced ball</td>
<td></td>
</tr>
<tr>
<td>Dresses and undresses without assistance</td>
<td></td>
</tr>
</tbody>
</table>

...
to the body’s physical changes and normality. Strivings for independence are ambivalent. These young adolescents are difficult to interview because they often respond with short, clipped conversation and may have little insight. They are just becoming accustomed to abstract thinking.

**Middle adolescence** can be a difficult time for adolescents and the adults who have contact with them. Cognitive processes are more sophisticated. Through abstract thinking, middle adolescents can experiment with ideas, consider things as they might be, develop insight, and reflect on their own feelings and the feelings of others. As they mature, these adolescents focus on issues of identity not limited solely to the physical aspects of their body. They explore their parents’ and culture’s values, sometimes by expressing the contrary side of the dominant value. Many middle adolescents explore these values in their minds only; others do so by challenging their parents’ authority. Many engage in high-risk behaviors, including unprotected sexual intercourse, substance abuse, or dangerous driving. The strivings of middle adolescents for independence, limit testing, and need for autonomy often distress their families, teachers, or other authority figures. These adolescents are at higher risk for morbidity and mortality from accidents, homicide, or suicide.

**Late adolescence** usually is marked by formal operational thinking, including thoughts about the future (e.g., educational, vocational, and sexual). Late adolescents are usually more committed to their sexual partners than are middle adolescents. Unresolved separation anxiety from previous developmental stages may emerge, at this time, as the young person begins to move physically away from the family of origin to college or vocational school, a job, or military service.

**MODIFYING PSYCHOSOCIAL BEHAVIORS**

Child behavior is determined by heredity and by the environment. Behavioral theory postulates that behavior is primarily a product of external environmental determinants and that manipulation of the environmental antecedents and consequences of behavior can be used to modify maladaptive behavior and to increase desirable behavior (operant conditioning). The four major methods of operant conditioning are positive reinforcement, negative reinforcement, extinction, and punishment. Many common behavioral problems of children can be ameliorated by these methods.

**Positive reinforcement** increases the frequency of a behavior by following the behavior with a favorable event (e.g., praising a child for excellent school performance). **Negative reinforcement** usually decreases the frequency of a behavior by removal, cessation, or avoidance of an unpleasant event. Conversely sometimes this reinforcement may occur unintentionally, increasing the frequency of an undesirable behavior. For example, a toddler may purposely try to stick a pencil in a light socket to obtain attention, whether it be positive or negative. **Extinction** occurs when there is a decrease in the frequency of a previously reinforced behavior because the reinforcement is withheld. Extinction is the principle behind the common advice to ignore behavior such as crying at bedtime or temper tantrums, which parents may unwittingly reinforce through attention and comforting. **Punishment** decreases the frequency of a behavior through unpleasant consequences.

Positive reinforcement is more effective than punishment. Punishment is more effective when combined with positive reinforcement. A toddler who draws on the wall with a crayon may be punished, but he or she learns much quicker when positive reinforcement is given for the proper use of the crayon—on paper, not the wall. Interrupting and modifying behaviors are discussed in detail in Section 3.

**TEMPERAMENT**

Significant individual differences exist within the normal development of temperament (behavioral style). Temperament must be appreciated because, if an expected pattern of behavior is too narrowly defined, normal behavior may be inappropriately labeled as abnormal or pathologic. Three common constellations of temperamental characteristics are as follows:

1. The **easy child** (about 40% of children) is characterized by regularity of biologic functions (consistent, predictable times for eating, sleeping, and elimination), a positive approach to new stimuli, high adaptability to change, mild or moderate intensity in responses, and a positive mood.
2. The **difficult child** (about 10%) is characterized by irregularity of biologic functions, negative withdrawal from new stimuli, poor adaptability, intense responses, and a negative mood.
3. The **slow to warm up child** (about 15%) is characterized by a low activity level, withdrawal from new stimuli, slow adaptability, mild intensity in responses, and a somewhat negative mood.

The remaining children have more mixed temperaments. The individual temperament of a child has important implications for parenting and for the advice a pediatrician may give in anticipatory guidance or behavioral problem counseling.

Although, to some degree, temperament may be hard-wired (nature) in each child, the environment (nurture) in which the child grows has a strong effect on the child’s adjustment. Social and cultural factors can have marked effects on the child through differences in parenting style, educational approaches, and behavioral expectations.

**DISORDERS OF DEVELOPMENT**

**DEVELOPMENTAL SURVEILLANCE AND SCREENING**

Developmental and behavioral problems are more common than any category of problems in pediatrics, except acute infections and trauma. In 2008 15% of children ages 3 to 7 had a developmental disability, and others had behavioral disabilities. As many as 25% of children have serious psychosocial problems. Parents often neglect to mention these problems because they think the physician is uninterested or cannot help. It is necessary to monitor development and screen for
the presence of these problems at health supervision visits, particularly in the years before preschool or early childhood learning center enrollment.

Development surveillance, done at every office visit, is an informal process comparing skill levels to lists of milestones. If suspicion of developmental or behavioral issues recurs, further evaluation is warranted (Table 8-1). Surveillance does not have a standard, and screening tests are necessary.

Developmental screening involves the use of standardized screening tests to identify children who require further diagnostic assessment. The American Academy of Pediatrics recommends the use of validated standardized screening tools at three of the health maintenance visits: 9 months, 18 months, and 30 months. Clinics and offices that serve a higher risk patient population (children living in poverty) often perform a screening test at every health maintenance visit. A child who fails to pass a developmental screening test requires more comprehensive evaluation but does not necessarily have a delay; definitive testing must confirm. Developmental evaluations for children with suspected delays and intervention services for children with diagnosed disabilities are available free to families. A combination of U.S. state and federal funds provides these services.

Screening tests can be categorized as general screening tests that cover all behavioral domains or as targeted screens that focus on one area of development. Some may be administered in the office by professionals, and others may be completed at home (or in a waiting room) by parents. Good developmental/behavioral screening instruments have a sensitivity of 70% to 80% in detecting suspected problems and a specificity of 70% to 80% in detecting normal development. Although 30% of children screened may be over-referred for definitive developmental testing, this group also includes children whose skills are below average and who may benefit from testing that may help address relative developmental deficits. The 20% to 30% of children who have disabilities that are not detected by the single administration of a screening instrument are likely to be identified on repeat screening at subsequent health maintenance visits.

<table>
<thead>
<tr>
<th>AGE</th>
<th>GROSS MOTOR</th>
<th>FINE MOTOR–ADAPTIVE</th>
<th>PERSONAL-SOCIAL</th>
<th>LANGUAGE</th>
<th>OTHER COGNITIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 wk</td>
<td>Moves head side to side</td>
<td>Regards face</td>
<td>Alerts to bell</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mo</td>
<td>Lifts shoulder while prone</td>
<td>Tracks midline</td>
<td>Smiles responsively</td>
<td>Cooing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lifts up on hands</td>
<td>Reaches for object</td>
<td>Looks at hand</td>
<td>Searches for sound with eyes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rolls front to back</td>
<td>Raking grasps</td>
<td>Begins to work toward toy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If pulled to sit from supine, no head lag</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>Sits alone</td>
<td>Transfers object hand to hand</td>
<td>Feeds self</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Holds bottle</td>
<td>Babbles</td>
<td></td>
</tr>
<tr>
<td>9 mo</td>
<td>Pulls to stand</td>
<td>Starting to pincer grasp</td>
<td>Waves bye-bye</td>
<td>Says Dada and Mama, but nonspecific</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gets into sitting position</td>
<td>Bangs two blocks together</td>
<td>Plays pat-a-cake</td>
<td>Two-syllable sounds</td>
<td></td>
</tr>
<tr>
<td>12 mo</td>
<td>Walks</td>
<td>Puts block in cup</td>
<td>Drinks from a cup</td>
<td>Says Mama and Dada, specific</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stoops and stands</td>
<td></td>
<td>Imitates others</td>
<td>Says one to two other words</td>
<td></td>
</tr>
<tr>
<td>15 mo</td>
<td>Walks backward</td>
<td>Scribbles</td>
<td>Uses spoon and fork</td>
<td>Says three to six words</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stacks two blocks</td>
<td>Helps in housework</td>
<td>Follows commands</td>
<td></td>
</tr>
<tr>
<td>18 mo</td>
<td>Runs</td>
<td>Stacks four blocks</td>
<td>Removes garment</td>
<td>Says at least six words</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kids a ball</td>
<td>“Feeds” doll</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 yr</td>
<td>Walks up and down stairs</td>
<td>Stacks six blocks</td>
<td>Washes and dries hands</td>
<td>Puts two words together</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Throws overhand</td>
<td>Copies line</td>
<td>Brushes teeth</td>
<td>Points to pictures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Puts on clothes</td>
<td>Knows body parts</td>
<td>Understands concept of today</td>
</tr>
<tr>
<td>3 yr</td>
<td>Walks steps alternating feet</td>
<td>Stacks eight blocks</td>
<td>Uses spoon well, spilling little</td>
<td>Names pictures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Broad jump</td>
<td>Wiggles thumb</td>
<td>Puts on T-shirt</td>
<td>Speech understandable to stranger 75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Says three-word sentences</td>
<td>Understands concepts of tomorrow and yesterday</td>
</tr>
<tr>
<td>4 yr</td>
<td>Balances well on each foot</td>
<td>Copies O, maybe +</td>
<td>Brushes teeth without help</td>
<td>Names colors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hops on one foot</td>
<td>Draws person with three parts</td>
<td></td>
<td>Understands adjectives</td>
<td></td>
</tr>
<tr>
<td>5 yr</td>
<td>Skips</td>
<td>Copies □</td>
<td></td>
<td></td>
<td>Counts</td>
</tr>
<tr>
<td></td>
<td>Heel-to-toe walks</td>
<td></td>
<td></td>
<td></td>
<td>Understands opposites</td>
</tr>
<tr>
<td>6 yr</td>
<td>Balances on each foot</td>
<td>Copies △</td>
<td></td>
<td></td>
<td>Defines words</td>
</tr>
<tr>
<td>6 sec</td>
<td></td>
<td>Draws person with six parts</td>
<td></td>
<td></td>
<td>Begins to understand right and left</td>
</tr>
</tbody>
</table>

Mo, Month; sec, second; wk, week; yr, year.
The Denver Developmental Screening Test II was the classic test used by general pediatricians (Figs. 8-1 and 8-2). The Denver II assesses the development of children from birth to 6 years of age in the following four domains:
1. Personal-social
2. Fine motor–adaptive
3. Language
4. Gross motor

The advantage of this test is that it teaches developmental milestones when administered. Items on the Denver II are carefully selected for their reliability and consistency of norms across subgroups and cultures. The Denver II is a useful screening instrument, but it cannot assess adequately the complexities of socioemotional development. Children with suspect or untestable scores must be followed carefully.

The pediatrician asks questions (items labeled with an “R” may be asked of parents to document the task “by report”) or directly observes behaviors. On the scoring sheet, a line is drawn at the child’s chronologic age. Tasks that are entirely to the left of the line that the child has not accomplished are considered delayed. If the test instructions are not followed accurately or if items are omitted, the validity of the test becomes compromised.

Section 2  Growth and Development

**DIRECTIONS FOR ADMINISTRATION**

1. Try to get child to smile by smiling, talking or waving. Do not touch him/her.
2. Child must stare at hand several seconds.
3. Parent may guide toothbrush and put toothpaste on brush.
4. Child does not have to be able to tie shoes or button/zip in the back.
5. Move yarn slowly in an arc from one side to the other, about 6” above child’s face.
6. Pass if child grasps rattle when it is touched to the backs or tips of fingers.
7. Pass if child tries to see where yarn went. Yarn should be dropped quickly from sight from tester’s hand without arm movement.
8. Child must transfer cube from hand to hand without help of body, mouth, or table.
9. Pass if child picks up raisin with any part of thumb and finger.
10. Line can vary only 30 degrees or less from tester’s line.
11. Make a fist with thumb pointing upward and wiggle only the thumb. Pass if child imitates and does not move any fingers other than the thumb.

13. Which line is longer? (Not bigger.) Turn paper upside down and repeat.
15. Have child copy first. If failed, demonstrate.

When giving items 12, 14, and 15, do not name the forms. Do not demonstrate 12 and 14.

16. When scoring, each pair (2 arms, 2 legs, etc.) counts as one part.
17. Place one cube in cup and shake gently near child’s ear, but out of sight. Repeat for other ear.
18. Point to picture and have child name it. (No credit is given for sounds only.)

If less than 4 pictures are named correctly, have child point to picture as each is named by tester.

19. Using doll, tell child: Show me the nose, eyes, ear, mouth, hands, feet, tummy, hair. Pass 6 of 8.
22. Ask child: What do you do with a cup? What is a chair used for? What is a pencil used for?

Action words must be included in answers.

23. Pass if child correctly places and says how many blocks are on paper. (1,5)

(Do not help child by pointing, moving head or eyes.)

25. Ask child: What is a ball?...lake?...desk?...house?...banana?...curtain?...fence?...ceiling? Pass if defined in terms of use, shape, what it is made of, or general category (such as banana is fruit, not just yellow). Pass 5 of 8, 7 of 8.

26. Ask child: If a horse is big, a mouse is ___? If fire is hot, ice is ___? If the sun shines during the ____? Pass 2 of 3.

27. Child may use wall or rail only. Not person. May not crawl.
28. Child must throw ball horizontally 3 feet to within arm’s reach of tester.
29. Child must perform standing broad jump over width of test sheet (8 1/2 inches).
30. Tell child to walk forward, feel within 1 inch of toe. Tester may demonstrate.

Child must walk 4 consecutive steps.
31. In the second year, half of normal children are non-compliant.

**OBSERVATIONS:**

Denver Developmental Materials, Inc.
P.O. Box 371075
Denver, Colorado 80237-5075
Tel.: (303) 355-4729
(800) 419-4729

Figure 8-2 Instructions for the Denver II. Numbers are coded to a scoring form (see Fig. 8-1). “Abnormal” is defined as two or more delays (failure of an item passed by 90% at that age) in two or more categories or two or more delays in one category with one other category having one delay and an age line that does not intersect one item that is passed. (From Frankenburg WK: Denver I Training Manual. ©1967, 1970 William K. Frankenburg and Josiah B. Dodds; 1975, 1976, 1978 William K. Frankenburg; 1990, 1992 William K. Frankenburg and Josiah B. Dodds; © 2009 Wilhelmine R. Frankenburg - Contact DDM, Inc. 1-800-419-4729 or info@denverii.com.)

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worse. To assist physicians in using the Denver II, the scoring sheet also features a table to document confounding behaviors, such as interest, fearfulness, or an apparent short attention span. Repeat screening at subsequent health maintenance visits often detects abnormalities that a single screen was unable to detect.

Other developmental screening tools include parent-completed Ages and Stages Questionnaires (also milestone driven), and Parents’ Evaluation of Developmental Status. The latter is a simple, 10-item questionnaire that parents complete at office visits based on concerns with function and progression of development. Parent-reported screens have good validity compared to office-based screening measures.

**Autism screening** is recommended for all children at 18 to 24 months of age. Although there are several tools, many pediatricians use the Modified Checklist for Autism in Toddlers (M-CHAT). M-CHAT is an office-based questionnaire that asks parents about 23 typical behaviors, some of which are more predictive than others for autism or other pervasive developmental disorders. If the child demonstrates more than two predictive or three total behaviors, further assessment
with an interview algorithm is indicated to distinguish normal variant behaviors from those children needing a referral for definitive testing. The test is freely distributed on the Internet (see Chapter 20).

**Language screening** correlates best with cognitive development in the early years. Table 8-2 provides some rules of thumb for language development that focus on speech production (expressive language). Although expressive language is the most obvious language element, the most dramatic changes in language development in the first years involve recognition and understanding (receptive language).

Whenever there is a speech and/or language delay, a hearing deficit must be considered. The implementation of universal newborn hearing screening detects many, if not most, of these children in the newborn period, and appropriate early intervention services may be provided. Conditions that present a high risk of an associated hearing deficit are listed in Table 8-3. Dysfluency (*stuttering*) is common in a 3- and 4-year-old child. Unless the dysfluency is severe, is accompanied by tics or unusual posturing, or occurs after 4 years of age, parents should be counseled that it is normal and transient and to accept it calmly and patiently.

After the child’s sixth birthday and until adolescence, developmental assessment is initially done by inquiring about school performance (academic achievement and behavior). Inquiring about concerns raised by teachers or other adults who care for the child (after-school program counselor, coach, religious leader) is prudent. Formal developmental testing of these older children is beyond the scope of the primary care pediatrician. Nonetheless the health care provider should be the coordinator of the testing and evaluation performed by other specialists (e.g., psychologists, psychiatrists, developmental pediatricians, and educational professionals).

**OTHER ISSUES IN ASSESSING DEVELOPMENT AND BEHAVIOR**

Ignorance of the environmental influences on child behavior may result in ineffective or inappropriate management (or both). Table 8-4 lists some contextual factors that should be considered in the etiology of a child’s behavioral or developmental problem.

Building rapport with the parents and the child is a prerequisite for obtaining the often sensitive information that is essential for understanding a behavioral or developmental issue. Rapport usually can be established quickly if the parents sense that the clinician respects them and is genuinely interested in listening to their concerns. The clinician develops rapport with the child by engaging the child in developmentally appropriate conversation or play, perhaps providing toys while interviewing the parents, and being sensitive to the fears the child may have. Too often the child is ignored until it is time for the physical examination. Similar to their parents, children feel more comfortable if they are greeted by name

<table>
<thead>
<tr>
<th>Table 8-2</th>
<th>Rules of Thumb for Speech Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE (YR)</strong></td>
<td><strong>SPEECH PRODUCTION</strong></td>
</tr>
<tr>
<td>1</td>
<td>One to three words</td>
</tr>
<tr>
<td>2</td>
<td>Two- to three-word phrases</td>
</tr>
<tr>
<td>3</td>
<td>Routine use of sentences</td>
</tr>
<tr>
<td>4</td>
<td>Routine use of sentence sequences; conversational give-and-take</td>
</tr>
<tr>
<td>5</td>
<td>Complex sentences; extensive use of modifiers, pronouns, and prepositions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8-3</th>
<th>Conditions Considered High Risk for Associated Hearing Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hearing loss in first cousin or closer relative</td>
<td></td>
</tr>
<tr>
<td>Bilirubin level of ≥20 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Congenital rubella or other nonbacterial intrauterine infection</td>
<td></td>
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<tr>
<td>Defects in the ear, nose, or throat</td>
<td></td>
</tr>
<tr>
<td>Birth weight of ≤1500 g</td>
<td></td>
</tr>
<tr>
<td>Multiple apneic episodes</td>
<td></td>
</tr>
<tr>
<td>Exchange transfusion</td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td></td>
</tr>
<tr>
<td>Five-minute Apgar score of ≤5</td>
<td></td>
</tr>
<tr>
<td>Persistent fetal circulation (primary pulmonary hypertension)</td>
<td></td>
</tr>
<tr>
<td>Treatment with ototoxic drugs (e.g., aminoglycosides and loop diuretics)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8-4</th>
<th>Context of Behavioral Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHILD FACTORS</strong></td>
<td></td>
</tr>
<tr>
<td>Health (past and current)</td>
<td></td>
</tr>
<tr>
<td>Developmental status</td>
<td></td>
</tr>
<tr>
<td>Temperament (e.g., difficult, slow to warm up)</td>
<td></td>
</tr>
<tr>
<td>Coping mechanisms</td>
<td></td>
</tr>
<tr>
<td><strong>PARENTAL FACTORS</strong></td>
<td></td>
</tr>
<tr>
<td>Misinterpretations of stage-related behaviors</td>
<td></td>
</tr>
<tr>
<td>Mismatch of parental expectations and characteristics of child</td>
<td></td>
</tr>
<tr>
<td>Mismatch of personality style between parent and child</td>
<td></td>
</tr>
<tr>
<td>Parental characteristics (e.g., depression, lack of interest, rejection, overprotective)</td>
<td></td>
</tr>
<tr>
<td>Coping mechanisms</td>
<td></td>
</tr>
<tr>
<td><strong>ENVIRONMENTAL FACTORS</strong></td>
<td></td>
</tr>
<tr>
<td>Stress (e.g., marital discord, unemployment, personal loss)</td>
<td></td>
</tr>
<tr>
<td>Support (e.g., emotional, material, informational, child care)</td>
<td></td>
</tr>
<tr>
<td>Poverty</td>
<td></td>
</tr>
<tr>
<td>Racism</td>
<td></td>
</tr>
</tbody>
</table>
and involved in pleasant interactions before they are asked sensitive questions or threatened with examinations. Young children can be engaged in conversation on the parent's lap, which provides security and places the child at the eye level of the examiner.

With adolescents emphasis should be placed on building a physician-patient relationship that is distinct from the relationship with the parents. The parents should not be excluded; however the adolescent should have the opportunity to express concerns to and ask questions of the physician in confidence. Two intertwined issues must be taken into consideration—consent and confidentiality. Although laws vary from state to state, in general, adolescents who are able to give informed consent (i.e., mature minors) may consent to visits and care related to high-risk behaviors (i.e., substance abuse; sexual health, including prevention, detection, and treatment of sexually transmitted infections; and pregnancy). Most states support the physician who wishes the visit to be confidential. Physicians should become familiar with the governing law in the state where they practice (see www.guttmacher.org/statecenter/updates/index.html).

Providing confidentiality is crucial, allowing for optimal care (especially for obtaining a history of risk behaviors). When assessing development and behavior, confidentiality can be achieved by meeting with the adolescent alone for at least part of each visit. However parents must be informed when the clinician has significant and immediate concerns about the health and safety of the child. Often the clinician can convince the adolescent to inform the parents directly about a problem or can reach an agreement with the adolescent about how the parents will be informed by the physician (see Chapter 67).

**EVALUATING DEVELOPMENTAL AND BEHAVIORAL ISSUES**

Responses to open-ended questions often provide clues to underlying, unstated problems and identify the appropriate direction for further, more directed questions. Histories about developmental and behavioral problems are often vague and confusing; to reconcile apparent contradictions, the interviewer frequently must request clarification, more detail, or mere repetition. By summarizing an understanding of the information at frequent intervals and by recapitulating at the close of the visit, the interviewer and patient and family can ensure that they understand each other.

If the clinician's impression of the child differs markedly from the parent's description, there may be a crucial parental concern or issue that has not yet been expressed, either because it may be difficult to talk about (e.g., marital problems), because it is unconscious, or because the parent overlooks its relevance to the child's behavior. Alternatively the physician's observations may be atypical, even with multiple visits. The observations of teachers, relatives, and other regular caregivers may be crucial in sorting out this possibility. The parent also may have a distorted image of the child, rooted in parental psychopathology. A sensitive, supportive, and noncritical approach to the parent is crucial to appropriate intervention. More information about referral and intervention for behavioral and developmental issues is covered in Chapter 10.

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**Table 9-1**

<table>
<thead>
<tr>
<th><strong>FOCUS ON THE CHILD</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerns (parent's or child's)</td>
<td></td>
</tr>
<tr>
<td>Past problem follow-up</td>
<td></td>
</tr>
<tr>
<td>Immunization and screening test update</td>
<td></td>
</tr>
<tr>
<td>Routine care (e.g., eating, sleeping, elimination, and health habits)</td>
<td></td>
</tr>
<tr>
<td>Developmental progress</td>
<td></td>
</tr>
<tr>
<td>Behavioral style and problems</td>
<td></td>
</tr>
</tbody>
</table>

**FOCUS ON THE CHILD'S ENVIRONMENT**

<table>
<thead>
<tr>
<th><strong>Family</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregiving schedule for caregiver who lives at home</td>
<td></td>
</tr>
<tr>
<td>Parent-child and sibling-child interactions</td>
<td></td>
</tr>
<tr>
<td>Extended family role</td>
<td></td>
</tr>
<tr>
<td>Family stresses (e.g., work, move, finances, illness, death, marital and other interpersonal relationships)</td>
<td></td>
</tr>
<tr>
<td>Family supports (relatives, friends, groups)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Community</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caregivers outside of the family</td>
<td></td>
</tr>
<tr>
<td>Peer interaction</td>
<td></td>
</tr>
<tr>
<td>School and work</td>
<td></td>
</tr>
<tr>
<td>Recreational activities</td>
<td></td>
</tr>
</tbody>
</table>

**Physical environment**

<table>
<thead>
<tr>
<th>Appropriate stimulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td></td>
</tr>
</tbody>
</table>
and the Children's Health Insurance Program, along with many insurers. Health maintenance and immunizations now are covered without co-pays for insured patients as part of the Patient Protection and Affordable Care Act.

**SCREENING TESTS**

Children usually are quite healthy and only the following screening tests are recommended: newborn metabolic screening with hemoglobin electrophoresis, hearing and vision evaluation, anemia and lead screening, and tuberculosis testing. Children born to families with dyslipidemias or early heart disease should also be screened for lipid disorders. (Items marked by a * in Bright Futures' recommendations should be performed if a risk factor is found.) Sexually experienced adolescents should be screened for sexually transmissible infections. When an infant or child begins care after the newborn period, the pediatrician should perform any missing screening tests and immunizations.

**Newborn Screening**

**Metabolic Screening**

Every state in the United States mandates newborn metabolic screening. Each state determines its own priorities and procedures, but the following diseases are usually included in metabolic screening: phenylketonuria, galactosemia, congenital hypothyroidism, maple sugar urine disease, and organic aciduria (see Section 10). Many states now screen for cystic fibrosis, testing for immunoreactive trypsinogen. If that test is positive, then a deoxyribonucleic acid (commonly referred to as DNA) analysis for cystic fibrosis mutations is performed.

**Hemoglobin Electrophoresis**

Children with hemoglobinopathies are at higher risk for infection and complications from anemia, which early detection may prevent or ameliorate. Infants with sickle cell disease are begun on oral penicillin prophylaxis to prevent sepsis, the major cause of mortality in these infants (see Chapter 150).

**Hearing Evaluation**

Because speech and language are central to a child's cognitive development, the hearing screening is performed before discharge from the newborn nursery. An infant's hearing is tested by placing headphones over the infant's ears and electrodes on the head. Standard sounds are played, and the transmission of the impulse to the brain is documented. If abnormal, a further evaluation is indicated, using evoked response technology of sound transmission.

**Hearing and Vision Screening of Older Children**

**Infants and Toddlers**

Inferences about hearing are drawn from asking parents about responses to sound and speech and by examining speech and language development closely. Inferences about vision may be made by examining gross motor milestones (children with vision problems may have a delay) and by physical examination of the eye. Parental concerns about vision should be sought until the child is 3 years of age and about hearing until the child is 4 years of age. If there are concerns, definitive testing should be arranged. Hearing can be screened by auditory evoked responses, as mentioned for newborns. For toddlers and older children who cannot cooperate with formal audiologic testing with headphones, behavioral audiometry may be used. Sounds of a specific frequency or intensity are provided in a standard environment within a soundproof room, and responses are assessed by a trained audiologist. Vision may be assessed by referral to a pediatric ophthalmologist and by visual evoked responses.

**Children 3 Years of Age and Older**

At various ages, hearing and vision should be screened objectively using standard techniques as specified in the Bright Futures' recommendations. Asking the family and child about any concerns or consequences of poor hearing or vision accomplishes subjective evaluation. At 3 years of age, children are screened for vision for the first time if they are developmentally able to be tested. Many children at this age do not have the interactive language or interpersonal skills to perform a vision screen; these children should be re-examined at a 3- to 6-month interval to ensure that their vision is normal. Because most of these children do not yet identify letters, using a Snellen eye chart with standard shapes is recommended. When a child is able to identify letters, the more accurate letter-based chart should be used. Audiologic testing of sounds with headphones should be begun on the fourth birthday (although Head Start requires that pediatricians attempt the hearing screening at 3 years of age). Any suspected audiologic problem should be evaluated by a careful history and physical examination, with referral for comprehensive testing. Children who have a documented vision problem, failed screening, or parental concern should be referred, preferably to a pediatric ophthalmologist.

**Anemia Screening**

Children are screened for anemia at ages when there is a higher incidence of iron deficiency anemia. Infants are screened at birth and again at 4 months if there is a documented risk, such as low birth weight or prematurity. Healthy term infants usually are screened at 12 months of age because this is when a high incidence of iron deficiency is noted. Children are assessed at other visits for risks or concerns related to anemia (denoted by a ★ in the Bright Futures' recommendations at [http://brightfutures.aap.org/clinical_practice.html](http://brightfutures.aap.org/clinical_practice.html)). Any abnormalities detected should be evaluated for etiology. Anemic infants do not perform as well on standard developmental testing. When iron deficiency is strongly suspected, a therapeutic trial of iron may be used (see Chapter 150).

**Lead Screening**

Lead intoxication may cause developmental and behavioral abnormalities that are not reversible, even if the hematologic and other metabolic complications are treated. Although the Centers for Disease Control and Prevention (CDC) recommends environmental investigation at blood lead levels of 20 μg/dL on a single visit or persistent 15 μg/dL over a 3-month period, levels of 5 to 10 μg/dL may cause learning problems. Risk
factors for lead intoxication include living in older homes with cracked or peeling lead-based paint, industrial exposure, use of foreign remedies (e.g., a diarrhea remedy from Central or South America), and use of pottery with lead paint glaze. Because of the significant association of lead intoxication with poverty, the CDC recommends blood lead screening at 12 and 24 months. In addition, standardized screening questions for risk of lead intoxication should be asked for all children between 6 months and 6 years of age (Table 9-2). Any positive or suspect response is an indication for obtaining a blood lead level. Capillary blood sampling may produce false-positive results, thus, a venous blood sample should be obtained. County health departments, community organizations, and private companies provide lead inspection and detection services to determine the source of the lead. Standard decontamination techniques should be used to remove the lead while avoiding aerosolizing the toxic metal that a child might breathe or creating dust that a child might ingest (see Chapters 149 and 150).

**Tuberculosis Testing**

The prevalence of tuberculosis is increasing, largely as a result of the adult human immunodeficiency virus (HIV) epidemic. Children often present with serious and multisystem disease (miliary tuberculosis). All children should be assessed for risk of tuberculosis at health maintenance visits, especially after 1 year of age. The high-risk groups, as defined by the CDC, are listed in Table 9-3. In general the standardized purified protein derivative intradermal test is used with evaluation by a health care provider 48 to 72 hours after injection. The size of induration, not the color of any mark, denotes a positive test. For most patients, 10 mm of induration is a positive test. For HIV-positive patients, those with recent tuberculosis contacts, patients with evidence of old healed tuberculosis on chest film, or immunosuppressed patients, 5 mm is a positive test (see Chapter 124). The CDC has approved (in adults) the QuantiFERON-TB Gold Test, which has the advantage of needing one office visit only.

**Cholesterol**

Children and adolescents who have a family history of cardiovascular disease or have at least one parent with a high blood cholesterol level are at increased risk of having high blood cholesterol levels as adults and increased risk of coronary heart disease. The American Academy of Pediatrics (AAP) recommends dyslipidemia screening in the context of regular health care for at-risk populations (Table 9-4) by obtaining a fasting lipid profile. The recommended screening levels are the same for all children 2 to 18 years. Total cholesterol of less than 170 mg/dL is normal, 170 to 199 mg/dL is borderline, and greater than 200 mg/dL is elevated. In addition, in 2011, the AAP endorsed the National Heart, Lung, and Blood Institute of the National Institutes of Health recommendation to test all children between ages 9 and 11.

**Sexually Transmitted Infection Testing**

Annual office visits are recommended for adolescents. A full adolescent psychosocial history should be obtained in confidential fashion (see Section 12). Part of this evaluation is a comprehensive sexual history that often requires creative questioning. Not all adolescents identify oral sex as sex, and some adolescents misinterpret the term sexually active to mean that one has many sexual partners or is very vigorous during intercourse. The questions, “Are you having sex?” and “Have you ever had sex?” should be asked. In the Bright Futures guidelines, any child or adolescent who has had any form of sexual intercourse should have at least an annual evaluation (more often if there is a history of high-risk sex) for sexually transmitted diseases by physical examination (genital warts, genital herpes, and pediculosis) and laboratory testing (chlamydia, gonorrhea, syphilis, and HIV) (see Chapter 116). Young women should be assessed for human papillomavirus and precancerous lesions by Papanicolaou smear at 21 years of age.

**IMMUNIZATIONS**

Immunization records should be checked at each office visit, regardless of the reason. Appropriate vaccinations should be administered (see Chapter 94).

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**Table 9-2** Lead Poisoning Risk Assessment Questions to be Asked between 6 Months and 6 Years

<table>
<thead>
<tr>
<th>Question</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the child spend any time in a building built before 1960 (e.g., home, school, barn) that has cracked or peeling paint?</td>
<td>6 months</td>
</tr>
<tr>
<td>Is there a brother, sister, housemate, playmate, or community member being followed or treated (or even rumored to be) for lead poisoning?</td>
<td>6 years</td>
</tr>
<tr>
<td>Does the child live with an adult whose job or hobby involves exposure to lead (e.g., lead smelting and automotive radiator repair)?</td>
<td>6 years</td>
</tr>
<tr>
<td>Does the child live near an active lead smelter, battery recycling plant, or other industry likely to release lead?</td>
<td>6 years</td>
</tr>
<tr>
<td>Does the family use home remedies or pottery from another country?</td>
<td>6 years</td>
</tr>
</tbody>
</table>

**Table 9-3** Groups at High Risk for Tuberculosis

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Close contact with persons known to have tuberculosis (TB), positive TB test, or suspected to have TB</td>
</tr>
<tr>
<td>Foreign-born persons from areas with high TB rates (Asia, Africa, Latin America, Eastern Europe, Russia)</td>
</tr>
<tr>
<td>Health care workers</td>
</tr>
<tr>
<td>High-risk racial or ethnic minorities or other populations at higher risk (Asian, Pacific Islander, Hispanic, African American, Native American, groups living in poverty [e.g., Medicaid recipients], migrant farm workers, homeless persons, substance abusers)</td>
</tr>
<tr>
<td>Infants, children, and adolescents exposed to adults in high-risk categories</td>
</tr>
</tbody>
</table>

**Table 9-4** Cholesterol Risk Screening Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk screening at ages 2, 4, 6, 8, 10 and annually in adolescence:</td>
</tr>
<tr>
<td>1. Children and adolescents who have a family history of high cholesterol or heart disease</td>
</tr>
<tr>
<td>2. Children whose family history is unknown</td>
</tr>
<tr>
<td>3. Children who have other personal risk factors: obesity, high blood pressure, or diabetes</td>
</tr>
<tr>
<td>Universal screening at ages 9–11 and ages 18–20</td>
</tr>
</tbody>
</table>
DENTAL CARE
Many families in the United States, particularly poor families and ethnic minorities, underuse dental health care. Pediatricians may identify gross abnormalities, such as large caries, gingival inflammation, or significant malocclusion. All children should have a dental examination by a dentist at least annually and a dental cleaning by a dentist or hygienist every 6 months. Dental health care visits should include instruction about preventive care practiced at home (brushing and flossing). Other prophylactic methods shown to be effective at preventing caries are concentrated fluoride topical treatments (dental varnish) and acrylic sealants on the molars. Pediatric dentists recommend beginning visits at age 1 year to educate families and to screen for milk bottle caries. Some recommend that pediatricians apply dental varnish to the children’s teeth, especially in communities that do not have pediatric dentists. Fluoridation of water or fluoride supplements in communities that do not have fluoridation are important in the prevention of cavities (see Chapter 127).

NUTRITIONAL ASSESSMENT
Plotting a child’s growth on the standard charts is a vital component of the nutritional assessment. A dietary history should be obtained because the content of the diet may suggest a risk of nutritional deficiency (see Chapters 27 and 28).

ANTICIPATORY GUIDANCE
Anticipatory guidance is information conveyed to parents verbally, in written materials, or even directing parents to certain Internet websites to assist them in facilitating optimal growth and development for their children. Anticipatory guidance that is age relevant is another part of the Bright Futures guidelines. Bright Futures has a “toolkit” that includes the topics and one-page handouts for families (and for older children) about the highest yield issues for the specific age. Table 9-5 summarizes representative issues that might be discussed. It is important to review briefly the safety topics previously discussed at other visits for reinforcement. Age-appropriate discussions should occur at each visit.

Safety Issues
The most common cause of death for infants 1 month to 1 year of age is motor vehicle crashes. No newborn should be discharged from a nursery unless the parents have a functioning and properly installed car seat. Many automobile dealerships offer services to parents to ensure that safety seats are installed properly in their specific model. Most states have laws that mandate use of safety seats until the child reaches 4 years of age or at least 40 pounds in weight. The following are age-appropriate recommendations for car safety:

- Infants and toddlers should ride in a rear-facing safety seat until they are 2 years of age, or until they reach the highest weight or height allowed by the safety seat manufacturer.
- Toddlers and preschoolers over age 2 or who have outgrown the rear-facing car seat should use a forward-facing car seat with harness for as long as possible, up to the highest weight or height recommended by the manufacturer.
- School-age children, whose weight or height is above the forward-facing limit for their car seat, should use a belt-positioning booster seat until the vehicle seat belt fits properly, typically when they have reached 4 ft 9 in. in height and are between 8 and 12 years of age.
- Older children should always use lap and shoulder seat belts for optimal protection. All children younger than 13 years should be restrained in the rear seats of vehicles for optimal protection. This is specifically to protect them from airbags, which may cause more injury than the crash in young children.

The Back to Sleep initiative has reduced the incidence of sudden infant death syndrome (SIDS). Before the initiative, infants routinely were placed prone to sleep. Since 1992 when the AAP recommended this program, the annual SIDS rate has decreased by more than 50%. Another initiative is aimed at day care providers, because 20% of SIDS deaths occur in day care settings.

Fostering Optimal Development
See Table 9-5 as well as the Bright Futures’ recommendations (found at http://brightfutures.aap.org/clinical_practice.html) for presentation of age-appropriate activities that the pediatrician may advocate for families.

Discipline means to teach, not merely to punish. The ultimate goal is the child’s self-control. Overbearing punishment to control a child’s behavior interferes with the learning process and focuses on external control at the expense of the development of self-control. Parents who set too few reasonable limits may be frustrated by children who cannot control their own behavior. Discipline should teach a child exactly what is expected by supporting and reinforcing positive behaviors and responding appropriately to negative behaviors with proper limits. It is more important and effective to reinforce good behavior than to punish bad behavior.

Commonly used techniques to control undesirable behaviors in children include scolding, physical punishment, and threats. These techniques have potential adverse effects on children’s sense of security and self-esteem. The effectiveness of scolding diminishes the more it is used. Scolding should not be allowed to expand from an expression of displeasure about a specific event to derogatory statements about the child. Scolding also may escalate to the level of psychological abuse. It is important to educate parents that they have a good child who does bad things from time to time, so parents do not think and tell the child that he or she is “bad.”

Frequent mild physical punishment (corporal punishment) may become less effective over time and tempt the parent to escalate the physical punishment, increasing the risk of child abuse. Corporal punishment teaches a child that in certain situations it is proper to strike another person. Commonly in households that use spanking, older children who have been raised with this technique are seen responding to younger sibling behavioral problems by hitting their siblings.

Threats by parents to leave or to give up the child are perhaps the most psychologically damaging ways to control a child’s behavior. Children of any age may remain fearful and anxious about loss of the parent long after the threat is made; however many children are able to see through empty threats. Threatening a mild loss of privileges (no video games for 1 week or grounding a teenager) may be appropriate, but the consequence must be enforced if there is a violation.
<table>
<thead>
<tr>
<th>AGES</th>
<th>INJURY PREVENTION</th>
<th>VIOLENCE PREVENTION</th>
<th>SLEEP POSITION</th>
<th>NUTRITIONAL COUNSELING</th>
<th>FOSTERING OPTIMAL DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth and/or 3−5 days</td>
<td>Crib safety Hot water heaters &lt;120° F Car safety seats Smoke detectors</td>
<td>Assess bonding and attachment Identify family strife, lack of support, pathology Educate parents on nurturing</td>
<td>Back to sleep Crib safety</td>
<td>Exclusive breastfeeding encouraged Formula as a second-best option</td>
<td>Discuss parenting skills Refer for parenting education</td>
</tr>
<tr>
<td>2 weeks or 1 month</td>
<td>Falls</td>
<td>Reassess Discuss sibling rivalry Assess if guns in the home</td>
<td>Back to sleep</td>
<td>Assess breastfeeding and offer encouragement, problem solving</td>
<td>Recognize and manage postpartum blues Child care options</td>
</tr>
<tr>
<td>2 months</td>
<td>Burns/hot liquids</td>
<td>Reassess firearm safety</td>
<td>Back to sleep</td>
<td>Introduction of solid foods</td>
<td>Discuss central to peripheral motor development Praise good behavior</td>
</tr>
<tr>
<td>4 months</td>
<td>Infant walkers Choking/suffocation</td>
<td>Reassess</td>
<td>Back to sleep</td>
<td>INTRODUCTION OF SOLID FOODS</td>
<td>Praise good behavior</td>
</tr>
<tr>
<td>6 months</td>
<td>Burns/hot surfaces</td>
<td>Reassess</td>
<td></td>
<td>Assess status</td>
<td>Consistent limit-setting versus “spoiling” an infant Praise good behavior</td>
</tr>
<tr>
<td>9 months</td>
<td>Water safety Home safety review Ingestions/poisoning</td>
<td>Assess parents’ ideas on discipline and “spoiling”</td>
<td></td>
<td>Avoiding juice Begin to encourage practice with cup drinking</td>
<td>Assisting infants to sleep through the night if not accomplished Praise good behavior</td>
</tr>
<tr>
<td>12 months</td>
<td>Firearm hazards Auto-pedestrian safety</td>
<td>Discuss timeout versus corporal punishment Avoiding media violence Review firearm safety</td>
<td></td>
<td>Introduction of whole cow’s milk (and constipation with change discussed) Assess anemia, discuss iron-rich foods</td>
<td>Safe exploration Proper shoes Praise good behavior</td>
</tr>
<tr>
<td>15 months</td>
<td>Review and reassess topics</td>
<td>Encourage nonviolent punishments (timeout or natural consequences)</td>
<td></td>
<td>DISCUSS DECLINE IN EATING WITH SLOWER GROWTH Assess food choices and variety</td>
<td>Fostering independence Reinforce good behavior Ignore annoying but not unsafe behaviors</td>
</tr>
<tr>
<td>18 months</td>
<td>Review and reassess topics</td>
<td>Limit punishment to high yield (not spilled milk!) Parents consistent in discipline</td>
<td></td>
<td>DISCUSS FOOD CHOICES, PORTIONS, “FINICKY” FEEDERS</td>
<td>Preparation for toilet training Reinforce good behavior</td>
</tr>
<tr>
<td>2 years</td>
<td>Falls—play equipment</td>
<td>Assess and discuss any aggressive behaviors in the child</td>
<td></td>
<td>Assess body proportions and recommend low-fat milk Assess family cholesterol and atherosclerosis risk</td>
<td>Toilet training and resistance</td>
</tr>
<tr>
<td>3 years</td>
<td>Review and reassess topics</td>
<td>Review, especially avoiding media violence</td>
<td></td>
<td>DISCUSS OPTIMAL EATING AND THE FOOD PYRAMID Healthy snacks</td>
<td>Read to child Socializing with other children Head Start if possible</td>
</tr>
<tr>
<td>4 years</td>
<td>Booster seat versus seat belts</td>
<td></td>
<td></td>
<td>Healthy snacks</td>
<td>Read to child Head Start or pre-K options</td>
</tr>
<tr>
<td>5 years</td>
<td>Bicycle safety Water/pool safety</td>
<td>Developing consistent, clearly defined family rules and consequences Avoiding media violence</td>
<td></td>
<td>DISCUSS FOR ANEMIA DISCUSS IRON-RICH FOODS</td>
<td>Reinforcing school topics Read to child Library card</td>
</tr>
<tr>
<td>6 years</td>
<td>Fire safety</td>
<td>Reinforce consistent discipline Encourage nonviolent strategies Assess domestic violence Avoiding media violence</td>
<td></td>
<td>Assess content, offer specific suggestions</td>
<td>Reinforcing school topics Responsibility given for chores (and enforced)</td>
</tr>
<tr>
<td>7–10 years</td>
<td>Sports safety Firearm hazard</td>
<td>Reinforcement Assess domestic violence Assess discipline techniques Avoiding media violence Walking away from fights (either victim or spectator)</td>
<td></td>
<td>Assess content, offer specific suggestions</td>
<td>Reviewing homework and reinforcing school topics After-school programs Introduce smoking and substance abuse prevention (concrete)</td>
</tr>
</tbody>
</table>
Parenting involves a dynamic balance between setting limits on the one hand and allowing and encouraging freedom of expression and exploration on the other. A child whose behavior is out of control improves when clear limits on their behavior are set and enforced. However parents must agree on where the limit will be set and how it will be enforced. The limit and the consequence of breaking the limit must be clearly presented to the child. Enforcement of the limit should be consistent and firm. Too many limits are difficult to learn and may thwart the normal development of autonomy. The limit must be reasonable in terms of the child’s age, temperament, and developmental level. To be effective, both parents (and other adults in the home) must enforce limits. Otherwise, children may effectively split the parents and seek to test the limits with the more indulgent parent. In all situations, to be effective, punishment must be brief and linked directly to a behavior. More effective behavioral change occurs when punishment also is linked to praise of the intended behavior.

**Extinction** is an effective and systematic way to eliminate a frequent, annoying, and relatively harmless behavior by ignoring it. First parents should note the frequency of the behavior to appreciate realistically the magnitude of the problem and to evaluate progress. Parents must determine what reinforces the child’s behavior and what needs to be consistently eliminated. An appropriate behavior is identified to give the child a positive alternative that the parents can reinforce. Parents should be warned that the annoying behavior usually increases in frequency and intensity (and may last for weeks) before it decreases when the parent ignores it (removes the reinforcement). A child who has an attention-seeking temper tantrum should be ignored or placed in a secure environment. This action may anger the child more, and the behavior may get louder and angrier. Eventually with no audience for the tantrum, the tantrums decrease in intensity and frequency. In each specific instance, when the child’s behavior has become appropriate, he or she should be praised, and extra attention should be given. This is an effective technique for early toddlers, before their capacity to understand and adhere to a timeout.

The **timeout** consists of a short period of isolation immediately after a problem behavior is observed. Timeout interrupts the behavior and immediately links it to an unpleasant consequence. This method requires considerable effort by the parents because the child does not wish to be isolated. A parent may need to hold the child physically in timeout. In this situation, the parent should become part of the furniture and should not respond to the child until the timeout period is over. When established, a simple isolation technique, such as making a child stand in the corner or sending a child to his or her room, may be effective. If such a technique is not helpful, a more systematic procedure may be needed. One effective protocol for the timeout procedure involves interrupting the child’s play when the behavior occurs and having the child sit in a dull, isolated place for a brief period, measured by a portable kitchen timer (the clicking noises document that time is passing and the bell alarm at the end signals the end of the punishment). Timeout is simply punishment and is not a time for a young child to think about the behavior (these children do not possess the capacity for abstract thinking) or a time to de-escalate the behavior. The amount of timeout should be appropriate to the child’s short attention span. One minute per year of a child’s age is recommended. This inescapable and unpleasant consequence of the undesired behavior motivates the child to learn to avoid the behavior.

### Table 9-5: Anticipatory Guidance Topics Suggested by Age—cont’d

<table>
<thead>
<tr>
<th>AGES</th>
<th>INJURY PREVENTION</th>
<th>VIOLENCE PREVENTION</th>
<th>SLEEP POSITION</th>
<th>NUTRITIONAL COUNSELING</th>
<th>FOSTERING OPTIMAL DEVELOPMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>11–13 years</td>
<td>Review and reassess</td>
<td>Discuss strategies to avoid interpersonal conflicts</td>
<td>Junk food versus healthy eating</td>
<td>Reviewing homework and reinforcing school topics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoiding media violence</td>
<td></td>
<td>Smoking and substance abuse prevention (begin abstraction)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoiding fights and walking away</td>
<td></td>
<td>Discuss and encourage abstinence; possibly discuss condoms and contraceptive options</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discuss conflict resolution techniques</td>
<td></td>
<td>Avoiding violence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Offer availability</td>
<td></td>
</tr>
<tr>
<td>14–16 years</td>
<td>Motor vehicle safety</td>
<td>Establish new family rules related to curfews, school, and household responsibilities</td>
<td>Junk food versus healthy eating</td>
<td>Review school work</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Begin career discussions and college preparation (PSAT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Review substance abuse, sexuality, and violence regularly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Discuss condoms, contraception options, including emergency contraception</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Discuss sexually transmitted diseases, HIV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Providing no questions—asked ride home from at-risk situations</td>
<td></td>
</tr>
<tr>
<td>17–21 years</td>
<td>Review and reassess</td>
<td>Establish new rules related to driving, dating, and substance abuse</td>
<td>Heart healthy diet for life</td>
<td>Continuation of above topics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Off to college or employment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>New roles within the family</td>
<td></td>
</tr>
</tbody>
</table>

*HIV, Human immunodeficiency virus; PSAT, Preliminary Scholastic Aptitude Test.

* Reassess means to review the issues discussed at the prior health maintenance visit.
EVALUATION OF THE CHILD WITH SPECIAL NEEDS

Children with disabilities, severe chronic illnesses, congenital defects, and health-related educational and behavioral problems are children with special health care needs (SHCN). Many of these children share a broad group of experiences and encounter similar problems, such as school difficulties and family stress. The term children with special health care needs defines these children noncategorically, without regard to specific diagnoses, in terms of increased service needs. Approximately 19% of children in the United States younger than 18 years of age have a physical, developmental, behavioral, or emotional condition requiring services of a type or amount beyond those required by children, generally.

The goal in managing a child with SHCN is to maximize the child's potential for productive adult functioning by treating the primary diagnosis and by helping the patient and family deal with the stresses and secondary impairments incurred because of the disease or disability. Whenever a chronic disease is diagnosed, family members typically grieve, show anger, denial, negotiation (in an attempt to forestall the inevitable), and depression. Because the child with SHCN is a constant reminder of the object of this grief, it may take family members a long time to accept the condition. A supportive physician can facilitate the process of acceptance by education and by allaying guilty feelings and fear. To minimize denial, it is helpful to confirm the family's observations about the child. The family may not be able to absorb any additional information initially, so written material and the option for further discussion at a later date should be offered.

The primary physician should provide a medical home to maintain close oversight of treatments and subspecialty services, provide preventive care, and facilitate interactions with school and community agencies. A major goal of family-centered care is for the family and child to feel in control. Although the medical management team usually directs treatment in the acute health care setting, the locus of control should shift to the family as the child moves into a more routine, home-based life. Treatment plans should allow the greatest degree of normalization of the child's life. As the child matures, self-management programs that provide health education, self-efficacy skills, and techniques such as symptom monitoring help promote good long-term health habits. These programs should be introduced at 6 or 7 years of age or when a child is at a developmental level to take on chores and benefit from being given responsibility. Self-management minimizes learned helplessness and the vulnerable child syndrome, both of which occur commonly in families with chronically ill or disabled children.

MULTIFACETED TEAM ASSESSMENT OF COMPLEX PROBLEMS

When developmental screening and surveillance suggest the presence of significant developmental lags, the physician should take responsibility for coordinating the further assessment of the child by the team of professionals and provide continuity of care. The physician should become aware of local facilities and programs for assessment and treatment. If the child is at high risk for delay (e.g., prematurity), a structured follow-up program to monitor the child's progress may already exist. Under federal law, all children are entitled to assessments if there is a suspected developmental delay or a risk factor for delay (e.g., prematurity, failure to thrive, and parental mental retardation [MR]). Special programs for children up to 3 years of age are developed by states to implement this policy. Developmental interventions are arranged in conjunction with third-party payers with local programs funding the cost only when there is no insurance coverage. After 3 years of age, development programs usually are administered by school districts. Federal laws mandate that special education programs be provided for all children with developmental disabilities from birth through 21 years of age.

Children with special needs may be enrolled in pre-K programs with a therapeutic core, including visits to the program by therapists, to work on challenges. Children who are of traditional school age (kindergarten through secondary school) should be evaluated by the school district and provided an individualized educational plan (IEP) to address any deficiencies. An IEP may feature individual tutoring time (resource time), placement in a special education program, placement in classes with children with severe behavioral problems, or other strategies to address deficiencies. As part of the comprehensive evaluation of developmental/behavioral issues, all children should receive a thorough medical assessment. A variety of other specialists may assist in the assessment and intervention, including subspecialist pediatricians (e.g., neurology, orthopedics, psychiatry, developmental/behavioral), therapists (e.g., occupational, physical, oral-motor), and others (e.g., psychologists, early childhood development specialists).

Medical Assessment

The physician's main goals in team assessment are to identify the cause of the developmental dysfunction, if possible (often a specific cause is not found), and identify and interpret other medical conditions that have a developmental impact. The comprehensive history (Table 10-1) and physical examination (Table 10-2) include a careful graphing of growth parameters and an accurate description of dysmorphic features. Many of the diagnoses are rare or unusual diseases or syndromes. Many of these diseases and syndromes are discussed further in Sections 9 and 24.

Motor Assessment

The comprehensive neurologic examination is an excellent basis for evaluating motor function, but it should be supplemented by an adaptive functional evaluation (see Chapter 179). Observing the child at play aids assessment of function. Specialists in early childhood development and therapists (especially occupational and physical therapists who have experience with children) can provide excellent input into the evaluation of age-appropriate adaptive function.
Psychological Assessment

Psychological assessment includes the testing of cognitive ability (Table 10-3) and the evaluation of personality and emotional well-being. The IQ and mental age scores, taken in isolation, are only partially descriptive of a person's functional abilities, which are a combination of cognitive, adaptive, and social skills. Tests of achievement are subject to variability based on culture, educational exposures, and experience and must be standardized for social factors. Projective and non-projective tests are useful in understanding the child's emotional status.

Educational Assessment

Educational assessment involves the evaluation of areas of specific strengths and weaknesses in reading, spelling, written expression, and mathematical skills. Schools routinely screen
Table 10-2  Information to Be Sought during the Physical Examination of a Child with Suspected Developmental Disabilities

<table>
<thead>
<tr>
<th>ITEM</th>
<th>POSSIBLE SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>General appearance</td>
<td>May indicate significant delay in development or obvious syndrome</td>
</tr>
<tr>
<td><strong>STATURE</strong></td>
<td></td>
</tr>
<tr>
<td>Short stature</td>
<td>Williams syndrome, malnutrition, Turner syndrome; many children with severe retardation have associated short stature.</td>
</tr>
<tr>
<td>Obesity</td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>Large stature</td>
<td>Sotos syndrome</td>
</tr>
<tr>
<td><strong>HEAD</strong></td>
<td></td>
</tr>
<tr>
<td>Macrocephaly</td>
<td>Alexander syndrome, Sotos syndrome, gangliosidosis, hydrocephalus, mucopolysaccharidosis, subdural effusion</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>Virtually any condition that can retard brain growth (e.g., malnutrition, Angelman syndrome, de Lange syndrome, fetal alcohol effects)</td>
</tr>
<tr>
<td><strong>FACE</strong></td>
<td></td>
</tr>
<tr>
<td>Coarse, triangular,</td>
<td>Specific measurements may provide clues to inherited, metabolic, or other diseases such as fetal alcohol syndrome, cri du chat syndrome (5p- syndrome), or Williams syndrome.</td>
</tr>
<tr>
<td>round, or flat face,</td>
<td></td>
</tr>
<tr>
<td>hypotelorism or</td>
<td></td>
</tr>
<tr>
<td>slanted or short</td>
<td></td>
</tr>
<tr>
<td>palpebral fissure;</td>
<td></td>
</tr>
<tr>
<td>unusual nose, maxilla</td>
<td></td>
</tr>
<tr>
<td>mandible</td>
<td></td>
</tr>
<tr>
<td><strong>EYES</strong></td>
<td></td>
</tr>
<tr>
<td>Prominent</td>
<td>Crouzon syndrome, Seckel syndrome, fragile X syndrome</td>
</tr>
<tr>
<td>Cataract</td>
<td>Galactosemia, Lowe syndrome, prenatal rubella, hypothyroidism</td>
</tr>
<tr>
<td>Cherry-red spot in</td>
<td>Gangliosidosis (GM1), metachromatic leukodystrophy, mucolipidosis, Tay-Sachs disease, Niemann-Pick disease, Faber lipogranulomatosis, sialidosis III</td>
</tr>
<tr>
<td>macula</td>
<td></td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>Congenital infection with cytomegalovirus, toxoplasmosis, or rubella</td>
</tr>
<tr>
<td>Corneal cloudiness</td>
<td>Mucopolysaccharidosis I and II, Lowe syndrome, congenital syphilis</td>
</tr>
<tr>
<td><strong>EARS</strong></td>
<td></td>
</tr>
<tr>
<td>Pinnae, low set or</td>
<td>Trisomies such as 18, Rubinstein-Taybi syndrome, Down syndrome, CHARGE association, cerebro-oculo-facio-skeletal syndrome, fetal phenytoin effects</td>
</tr>
<tr>
<td>malformed</td>
<td></td>
</tr>
<tr>
<td>Hearing</td>
<td>Loss of acuity in mucopolysaccharidosis; hyperacusis in many encephalopathies</td>
</tr>
<tr>
<td><strong>HEART</strong></td>
<td></td>
</tr>
<tr>
<td>Structural anomaly</td>
<td>CHARGE association, CATCH-22, velocardiofacial syndrome, glycosogen II, fetal alcohol effects, mucopolysaccharidosis I; chromosomal anomalies such as Down syndrome; maternal phenylketonuria; chronic cyanosis may impair cognitive development.</td>
</tr>
<tr>
<td>or hypertrophy</td>
<td></td>
</tr>
</tbody>
</table>

**ITEM**  **POSSIBLE SIGNIFICANCE**

<table>
<thead>
<tr>
<th>LIVER</th>
<th>Fructose intolerance, galactosemia, glycosogen types I to IV, mucopolysaccharidosis I and II, Niemann-Pick disease, Tay-Sachs disease, Zellweger syndrome, Gaucher disease, ceroid lipidofuscinosis, gangliosidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENITALIA</td>
<td>Macro-orchidism (usually not noted until puberty)</td>
</tr>
<tr>
<td></td>
<td>Hypogenitalism</td>
</tr>
<tr>
<td>EXTREMITIES</td>
<td>Hands, feet, dermatoglyphics, and creases</td>
</tr>
<tr>
<td></td>
<td>May indicate specific entity such as Rubinstein-Taybi syndrome or be associated with chromosomal anomaly</td>
</tr>
<tr>
<td></td>
<td>Joint contractures</td>
</tr>
<tr>
<td>SKIN</td>
<td>Café au lait spots</td>
</tr>
<tr>
<td></td>
<td>Eczema</td>
</tr>
<tr>
<td></td>
<td>Hemangiomas and telangiectasia</td>
</tr>
<tr>
<td></td>
<td>Hypopigmented macules, streaks, adenoma sebaceum</td>
</tr>
<tr>
<td>HAIR</td>
<td>Hirsutism</td>
</tr>
<tr>
<td></td>
<td><strong>NEUROLOGIC</strong></td>
</tr>
<tr>
<td></td>
<td>Asymmetry of strength and tone</td>
</tr>
<tr>
<td></td>
<td>Hypotonia</td>
</tr>
<tr>
<td></td>
<td>Hypertonia</td>
</tr>
</tbody>
</table>


CATCH-22, Cardiac defects, abnormal face, thymic hypoplasia, cleft palate, hypocalcemia, defects on chromosome 22, CHARGE, coloboma, heart defects, atresia choanae, retarded growth, genital anomalies, ear anomalies (deafness).
<table>
<thead>
<tr>
<th>Table 10-3</th>
<th>Tests of Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEST</strong></td>
<td><strong>AGE RANGE</strong></td>
</tr>
<tr>
<td><strong>INFANT SCALES</strong></td>
<td></td>
</tr>
<tr>
<td>Bayley Scales of Infant Development (3rd ed)</td>
<td>1–42 mo</td>
</tr>
<tr>
<td>Cattell Infant Intelligence Scale</td>
<td>2–30 mo</td>
</tr>
<tr>
<td>Gesell Developmental Observation-Revised (GDO-R)</td>
<td>Birth–3 yr</td>
</tr>
<tr>
<td>Ordinal Scales of Infant Psychological Development</td>
<td>Birth–24 mo</td>
</tr>
<tr>
<td><strong>PRESCHOOL SCALES</strong></td>
<td></td>
</tr>
<tr>
<td>Stanford-Binet Intelligence Scale (4th ed)</td>
<td>2 yr–adult</td>
</tr>
<tr>
<td>McCarthy Scales of Children’s Abilities</td>
<td>2½–8½ yr</td>
</tr>
<tr>
<td>Wechsler Primary and Preschool Test of Intelligence–Revised (WPPSI-R)</td>
<td>2 ½–7¼ yr</td>
</tr>
<tr>
<td>Merrill-Palmer Scale of Mental Tests</td>
<td>18 mo–4 yr</td>
</tr>
<tr>
<td>Differential Abilities Scale – II (2nd ed)</td>
<td>2½–18 yr</td>
</tr>
<tr>
<td><strong>SCHOOL-AGE SCALES</strong></td>
<td></td>
</tr>
<tr>
<td>Stanford-Binet Intelligence Scale (4th ed)</td>
<td>2 yr–adult</td>
</tr>
<tr>
<td>Wechsler Intelligence Scale for Children (4th ed) (WISC-IV)</td>
<td>6–16 yr</td>
</tr>
<tr>
<td>Leiter International Performance Scale, Revised</td>
<td>2–20 yr</td>
</tr>
<tr>
<td>Wechsler Adult Intelligence Scale–Revised (WAIS-III)</td>
<td>16 yr–adult</td>
</tr>
<tr>
<td>Differential Abilities Scale – II (2nd ed)</td>
<td>2½ yr–adult</td>
</tr>
<tr>
<td><strong>ADAPTIVE BEHAVIOR SCALES</strong></td>
<td></td>
</tr>
<tr>
<td>Vineland Adaptive Behavior Scale – II (2nd ed)</td>
<td>Birth–90 yr</td>
</tr>
<tr>
<td>American Association on Mental Retardation (AAMR) Adaptive Behavioral Scale</td>
<td>4–21 yr</td>
</tr>
</tbody>
</table>

For children with grouped tests to aid in problem identification and program evaluation. For the child with special needs, this screening ultimately should lead to individualized testing and the development of an IEP that would enable the child to progress comfortably in school. Diagnostic teaching, in which the child’s response to various teaching techniques is assessed, also may be helpful.

**Social Environment Assessment**
Assessments of the environment in which the child is living, working, playing, and growing are important in understanding the child’s development. A home visit by a social worker, community health nurse, and/or home-based intervention specialist can provide valuable information about the child’s social milieu. Often the home visitor can suggest additional adaptive equipment or renovations if there are challenges at home. If there is a suspicion of inadequate parenting, and, especially, if there is a suspicion of neglect or abuse (including emotional abuse), the child and family must be referred to the local child protection agency. Information about reporting hotlines and local child protection agencies usually is found inside the front cover of local telephone directories (see Chapter 22).

**MANAGEMENT OF DEVELOPMENTAL PROBLEMS**
**Intervention in the Primary Care Setting**
The clinician must decide whether a problem requires referral for further diagnostic workup and management or whether management in the primary care setting is appropriate. Counseling roles required in caring for these children are listed in Table 10-4. When a child is young, much of the counseling interaction takes place between the parents and the clinician, and, as the child matures, direct counseling shifts increasingly toward the child.

The assessment process may be therapeutic in itself. By assuming the role of a nonjudgmental, supportive listener, the clinician creates a climate of trust, allowing the family to express difficult or painful thoughts and feelings. Expressing emotions may allow the parent or caregiver to move on to the work of understanding and resolving the problem.
Table 10-4  Primary Care Counseling Roles

| Allow ventilation                      |
| Facilitate clarification              |
| Support patient problem solving       |
| Provide specific reassurance          |
| Provide education                     |
| Provide specific parenting advice     |
| Suggest environmental interventions   |
| Provide follow-up                     |
| Facilitate appropriate referrals      |
| Coordinate care and interpret reports after referrals |

Interview techniques may facilitate clarification of the problem for the family and for the clinician. The family’s ideas about the causes of the problem and attempts at coping can provide a basis for developing strategies for problem management that are much more likely to be implemented successfully because they emanate, in part, from the family. The clinician shows respect by endorsing the parent’s ideas when appropriate; this can increase self-esteem and sense of competency.

Educating parents about normal and aberrant development and behavior may prevent problems through early detection and anticipatory guidance and communicates the physician’s interest in hearing parental concerns. Early detection allows intervention before the problem becomes entrenched and associated problems develop.

The severity of developmental and behavioral problems ranges from variations of normal to problematic responses to stressful situations to frank disorders. The clinician must try to establish the severity and scope of the patient’s symptoms so that appropriate intervention can be planned.

Counseling Principles

For the child, behavioral change must be learned, not simply imposed. It is easiest to learn when the lesson is simple, clear, and consistent and presented in an atmosphere free of fear or intimidation. Parents often try to impose behavioral change in an emotionally charged atmosphere, most often at the time of a behavioral violation. Similarly clinicians may try to teach parents with hastily presented advice when the parents are distracted by other concerns or not engaged in the suggested behavioral change.

Apart from management strategies directed specifically at the problem behavior, regular times for positive parent-child interaction should be instituted. Frequent, brief, affectionate physical contact over the day provides opportunities for positive reinforcement of desirable child behaviors and for building a sense of competence in the child and the parent.

Most parents feel guilty when their children have a developmental/behavioral problem. Guilt may be caused by the fear that the problem was caused by inadequate parenting or by previous angry responses to the child’s behavior. If possible and appropriate, the clinician should find ways to alleviate guilt, which may be a serious impediment to problem solving.

Interdisciplinary Team Intervention

In many cases, a team of professionals is required to provide the breadth and quality of services needed to appropriately serve the child who has SHCN. The primary care physician should monitor the progress of the child and continually reassess that the requisite therapy is being accomplished.

Educational intervention for a young child begins as home-based infant stimulation, often with an early childhood specialist (e.g., nurse/therapist), providing direct stimulation for the child and training the family to provide the stimulation. As the child matures, a center-based nursery program may be indicated. For the school-age child, special services may range from extra attention in the classroom to a self-contained special education classroom.

Psychological intervention may be directed to the parent or family or, with an older child, primarily child-directed. Examples of therapeutic approaches are guidance therapies, such as directive advice giving, counseling to create their own solutions to problems, psychotherapy, behavioral management techniques, psychopharmacologic methods (from a psychiatrist), and cognitive therapy.

Motor intervention may be performed by a physical or occupational therapist. Neurodevelopmental therapy (NDT), the most commonly used method, is based on the concept that nervous system development is hierarchical and subject to some plasticity. The focus of NDT is on gait training and motor development, including daily living skills; perceptual abilities, such as eye-hand coordination; and spatial relationships. Sensory integration therapy is also used by occupational therapists to structure sensory experience from the tactile, proprioceptive, and vestibular systems to allow for adaptive motor responses.

Speech-language intervention by a speech and language therapist/pathologist (oral-motor therapist) is usually part of the overall educational program and is based on the tested language strengths and weaknesses of the child. Children needing this type of intervention may show difficulties in reading and other academic areas and develop social and behavioral problems because of their difficulties in being understood and in understanding others. Hearing intervention, performed by an audiologist (or an otolaryngologist), includes monitoring hearing acuity and providing amplification when necessary via hearing aids.

Social and environmental intervention generally includes nursing or social work involvement with the family. Frequently the task of coordinating services falls to these specialists. Case managers may be in the private sector, from the child’s insurance or Medicaid plan, or part of a child protection agency.

Medical intervention for a child with a developmental disability involves providing primary care as well as specific treatment of conditions associated with the disability. Although curative treatment often is not possible, functional impairment can be minimized through thoughtful medical management. Certain general medical problems are found more frequently in delayed and developmentally disabled people (Table 10-5), especially if the delay is part of a known syndrome. Some children may have a limited life expectancy. Supporting the family through palliative care, hospice, and bereavement is another important role of the primary care pediatrician.
SELECTED CLINICAL PROBLEMS: THE SPECIAL NEEDS CHILD

Mental Retardation

MR is defined as significantly subnormal intellectual functioning for a child’s developmental stage, existing concurrently with deficits in adaptive behaviors (self-care, home living, communication, and social interactions). MR is defined statistically as cognitive performance that is two standard deviations below the mean (roughly below the 3rd percentile) of the general population as measured on standardized intelligence testing. The last known estimate of the prevalence of MR is that about 2% of the U.S. population is affected. Levels of MR from IQ scores derived from two typical tests are shown in Table 10-6. Caution must be exercised in interpretation because these categories do not reflect actual functional level of the tested individual.

The etiology of the central nervous system insult resulting in MR may involve genetic disorders, teratogenic influences, perinatal insults, acquired childhood disease, and environmental and social factors (Table 10-7). Mild MR correlates with socioeconomic status, although profound MR does not. Although a single organic cause may be found, each individual’s performance should be considered a function of the interaction of environmental influences with the individual’s organic substrate. Behavioral difficulties resulting from the MR itself and from the family’s reaction to the child and the condition are common. More severe forms of MR can be traced to biologic factors. The earlier the cognitive slowing is recognized, the more severe the deviation from normal is likely to be.

The first step in the diagnosis and management of a child with MR is to identify functional strengths and weaknesses for purposes of medical and habilitative therapies. A history and physical examination may suggest a diagnostic approach that, then, may be confirmed by laboratory testing and/or imaging. Frequently used laboratory tests include chromosomal analysis and magnetic resonance imaging of the brain. Almost one third of individuals with MR do not have readily identifiable reasons for their disability.

Vision Impairment

Significant visual impairment is a problem in many children. Partial vision (defined as visual acuity between 20/70 and 20/200) occurs in 1 in 500 school-age children in the United States. Legal blindness is defined as distant visual acuity of 20/200 or worse and affects about 35,000 children in the United States. Such impairment can be a major barrier to optimal development.

The most common cause of severe visual impairment in children is retinopathy of prematurity (see Chapter 61). Congenital cataracts may lead to significant amblyopia. Cataracts also are associated with other ocular abnormalities and developmental disabilities. Amblyopia is a pathologic alteration of the visual system characterized by a reduction in visual acuity in one or both eyes with no clinically apparent organic abnormality that completely accounts for the visual loss. Amblyopia is due to a distortion of the normal clearly formed retinal image (from congenital cataracts or severe refractive errors); abnormal binocular interaction between the eyes as one eye competitively inhibits the other (strabismus); or a combination of both mechanisms. Albinism, hydrocephalus, congenital cytomegalovirus infection, and birth asphyxia are other significant contributors to blindness in children.
on parental concerns aroused by unusual behavior, such as lack of smiling in response to appropriate stimuli, the presence of nystagmus, other wandering eye movements, or motor delays in beginning to reach for objects. Fixation and visual tracking behavior can be seen in most infants by 6 weeks of age. This behavior can be assessed by moving a brightly colored object (or the examiner's face) across the visual field of a quiet but alert infant at a distance of 1 ft. The eyes also should be examined for red reflexes and pupillary reactions to light. Optical alignment (binocular vision with both eyes consistently focusing on the same spot) should not be expected until the infant is beyond the newborn period. Persistent nystagmus is abnormal at any age. If ocular abnormalities are identified, referral to a pediatric ophthalmologist is indicated.

During the newborn period, vision may be assessed by physical examination and by visual evoked response. This test evaluates the conduction of electrical impulses from the optic nerve to the occipital cortex of the brain. The eye is stimulated by a bright flash of light or with an alternating checkerboard of black-and-white squares, and the resulting electrical response is recorded from electrodes strategically placed on the scalp, similar to an electroencephalogram.

There are many developmental implications of visual impairment. Perception of body image is abnormal, and imitative behavior, such as smiling, is delayed. Delays in mobility may occur in children who are visually impaired from birth, although their postural milestones (ability to sit) usually are achieved appropriately. Social bonding with the parents also is often affected.

Visually impaired children can be helped in various ways. Classroom settings may be augmented with resource-room assistance to present material in a nonvisual format. Fine motor activity development, listening skills, and Braille reading and writing are intrinsic to successful educational intervention for a child with severe visual impairment.

### Hearing Impairment

The clinical significance of hearing loss varies with its type (conductive versus sensorineural), its frequency, and its severity as measured in the number of decibels of hearing lost. The most common cause of mild to moderate hearing loss in children is a conduction abnormality caused by acquired middle ear disease (acute and chronic otitis media). This abnormality may have a significant effect on the development of speech and language development, particularly if there is chronic fluctuating middle ear fluid. If hearing impairment is more severe, sensorineural hearing loss is more common. Causes of sensorineural deafness include congenital infections (e.g., rubella and cytomegalovirus), meningitis, birth asphyxia, kernicterus, ototoxic drugs (especially aminoglycoside antibiotics), and tumors and their treatments. Genetic deafness may be either dominant or recessive in inheritance; this is the main cause of hearing impairment in schools for the deaf. In Down syndrome, there is a predisposition to conductive loss caused by middle ear infection.
## Table 10-8: Neurodevelopmental-Behavioral Complications of Hearing Loss

<table>
<thead>
<tr>
<th>SEVERITY OF HEARING LOSS</th>
<th>POSSIBLE ETIOLOGIC ORIGINS</th>
<th>SPEECH-LANGUAGE</th>
<th>EDUCATIONAL</th>
<th>BEHAVIORAL</th>
<th>TYPES OF THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slight 15–25 dB (ASA)</td>
<td>Chronic otitis media/middle ear effusions</td>
<td>Difficulty with hearing distant or faint speech</td>
<td>Possible auditory learning dysfunction</td>
<td>Usually none</td>
<td>May require favorable class setting, speech therapy, or auditory training</td>
</tr>
<tr>
<td></td>
<td>Perforation of tympanic membrane</td>
<td></td>
<td></td>
<td>May reveal a slight verbal deficit</td>
<td>Possible value in hearing aid, surgery</td>
</tr>
<tr>
<td></td>
<td>Sensorineural loss</td>
<td></td>
<td></td>
<td></td>
<td>Favorable class setting</td>
</tr>
<tr>
<td></td>
<td>Tympanosclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild 25–40 dB (ASA)</td>
<td>Chronic otitis media/middle ear effusions</td>
<td>Difficulty with conversational speech over 3–5 ft</td>
<td>May miss 50% of class discussions</td>
<td>Psychological problems</td>
<td>Special education resource help, surgery</td>
</tr>
<tr>
<td></td>
<td>Perforation of tympanic membrane</td>
<td>May have limited vocabulary and speech disorders</td>
<td>Auditory learning dysfunction</td>
<td>May act inappropriately if directions are not heard well</td>
<td>Hearing aid, surgery</td>
</tr>
<tr>
<td></td>
<td>Sensorineural loss</td>
<td></td>
<td></td>
<td>Acting out behavior</td>
<td>Favorable class setting</td>
</tr>
<tr>
<td></td>
<td>Tympanosclerosis</td>
<td></td>
<td></td>
<td>Poor self-concept</td>
<td>Lip reading instruction</td>
</tr>
<tr>
<td>Moderate 40–65 dB (ASA)</td>
<td>Chronic otitis media/middle ear effusions</td>
<td>Conversation must be loud to be understood.</td>
<td>Learning disability</td>
<td>Emotional and social problems</td>
<td>Special education resource or special class, surgery</td>
</tr>
<tr>
<td></td>
<td>Middle ear anomaly</td>
<td>Defective speech</td>
<td>Difficulty with group learning or discussion</td>
<td>Behavioral reactions of childhood</td>
<td>Special help in speech-language development</td>
</tr>
<tr>
<td></td>
<td>Sensorineural loss</td>
<td>Deficient language use and comprehension</td>
<td>Auditory processing dysfunction Limited vocabulary</td>
<td>Acting out</td>
<td>Hearing aid and lip reading</td>
</tr>
<tr>
<td></td>
<td>Tympanosclerosis</td>
<td></td>
<td></td>
<td>Poor self-concept</td>
<td>Speech therapy</td>
</tr>
<tr>
<td>Severe 65–95 dB (ASA)</td>
<td>Sensorineural loss</td>
<td>Loud voices may be heard 2 ft from ear.</td>
<td>Marked educational retardation</td>
<td>Emotional and social problems that are associated with handicap</td>
<td>Full-time special education for deaf children, cochlear implant</td>
</tr>
<tr>
<td></td>
<td>Severe middle ear disease</td>
<td>Defective speech and language No spontaneous speech development if loss present before 1 yr</td>
<td>Marked learning disability limited vocabulary</td>
<td>Poor self-concept</td>
<td>Full-time special education for deaf children, hearing aid, lip reading, speech therapy, surgery, cochlear implant</td>
</tr>
<tr>
<td>Profound ≥95 dB (ASA)</td>
<td>Sensorineural or mixed loss</td>
<td>Relies on vision rather than hearing Defective speech and language Speech and language will not develop spontaneously if loss present before 1 yr</td>
<td>Marked learning disability because of lack of understanding of speech</td>
<td>Congenital and prelingually deaf may show severe emotional problems.</td>
<td>Full-time special education for deaf children, hearing aid, lip reading, speech therapy, surgery, cochlear implant</td>
</tr>
</tbody>
</table>


ASA, Acoustical Society of America.

and sensorineural loss caused by cochlear disease. Any hearing loss may have a significant effect on the child’s developing communication skills. These skills then affect all areas of the child’s cognitive and skills development (Table 10-8).

It is sometimes quite difficult to accurately determine the presence of hearing in infants and young children. Inquiring about a newborn’s or infant’s response to sounds or even observing the response to sounds in the office is unreliable for identifying hearing-impaired children. Universal screening of newborns is required prior to nursery discharge and includes the following:

- **Auditory brainstem response (ABR)** measures how the brain responds to sound. Clicks or tones are played through soft earphones into the infant’s ears. Three electrodes placed on the infant’s head measure the brain’s response.
Otoacoustic emissions measure sound waves produced in the inner ear. A tiny probe is placed just inside the infant's ear canal. It measures the response (echo) when clicks or tones are played into the infant's ears. Both of these tests are quick (5 to 10 minutes), painless, and may be performed while the infant is sleeping or lying still. The tests are sensitive but not as specific as more definitive tests. Infants who do not pass these tests are referred for more comprehensive testing. Many of these infants have normal hearing on definitive testing. Infants who do not have normal hearing should be immediately evaluated or referred for etiologic diagnosis and early intervention.

For children not screened at birth (such as children of immigrant parents) or children with suspected acquired hearing loss, later testing may allow early appropriate intervention. Hearing can be screened by means of an office audiogram, but other techniques are needed (ABR, behavior audiometry) for young, neurologically immature or impaired, and behaviorally difficult children. The typical audiology assessment includes pure-tone audiometry over a variety of sound frequencies (pitches), especially over the range of frequencies in which most speech occurs. Pneumatic otoscopy examination and tympanometry are used to assess middle ear function and the tympanic membrane compliance for pathology in the middle ear, such as fluid, ossicular dysfunction, and eustachian tube dysfunction (see Chapter 9).

The treatment of conductive hearing loss (largely due to otitis media and middle ear effusions) is discussed in Chapter 105. Treatment of sensorineural hearing impairment may be medical or surgical. If amplification is indicated, hearing aids can be tuned preferentially to amplify the frequency ranges in which the patient has decreased acuity. Educational intervention typically includes speech-language therapy and teaching American Sign Language. Even with amplification, many hearing-impaired children show deficits in processing auditory information, requiring special educational services for helping to read and for other academic skills. Cochlear implants are surgically implantable devices that provide hearing sensation to individuals with severe to profound hearing loss. The implants are designed to substitute for the function of the middle ear, cochlear mechanical motion, and sensory cells, transforming sound energy into electrical energy that initiates impulses in the auditory nerve. Cochlear implants are indicated for children older than 12 months with profound bilateral sensorineural hearing loss who have limited benefit from hearing aids, have failed to progress in auditory skill development, and have no radiologic or medical contraindications. Implantation in children as young as possible gives them the most advantageous auditory environment for speech-language learning.

Table 10-9: Clues to When a Child with a Communication Disorder Needs Help

<table>
<thead>
<tr>
<th>0–11 MONTHS</th>
<th>12–23 MONTHS</th>
<th>24–36 MONTHS</th>
<th>ALL AGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 6 months, the child does not startle, blink, or change immediate activity in response to sudden, loud sounds.</td>
<td>Before 6 months, the child does not respond to “no,” “bye-bye,” or “bottle.”</td>
<td>Before 24 months, the child does not point to body parts without gestural cues.</td>
<td>At any age, the child is consistently dysfluent with repetitions, hesitations; blocks or struggles to say words. Struggle may be accompanied by grimaces, eye blinks, or hand gestures.</td>
</tr>
</tbody>
</table>
| Before 6 months, the child does not attend to the human voice and is not soothed by his or her mother's voice. | By 15 months, the child does not respond to “no,” “bye-bye,” or “bottle.” | By 24 months, the child is not combining words into phrases (e.g., “go bye-bye,” “go car,” “want cookie”). | Parents often bring the concern of speech delay to the physician's attention when they compare their young child with others of the same age (Table 10-9). The most common causes of the speech delay are MR, hearing impairment, social deprivation, autism, and oral-motor abnormalities. If a problem is suspected based on screening with tests such as Ages and Stages Questionnaires or the Parents' Evaluation of Developmental Status test (see Chapter 8) or other standard screening test (Early Language Milestone Scale), a referral to a specialized hearing and speech center is indicated. While awaiting the results of testing or initiation of speech-language therapy, parents should be advised to speak slowly and clearly to the child (and avoid baby talk). Parents and older siblings should read frequently to the speech-delayed child. Speech disorders include articulation, fluency, and resonance disorders. Articulation disorders include difficulties producing sounds in syllables or saying words incorrectly to the point that other people cannot understand what is being said. Fluency disorders include problems such as stuttering, the condition in which the flow of speech is interrupted by abnormal stoppages, repetitions (st-st-stuttering), or prolonging...
Cerebral palsy (CP) refers to a group of nonprogressive, but often changing, motor impairment syndromes secondary to anomalies or lesions of the brain arising before or after birth. The prevalence of CP at age 6 in the United States is 3.6 per 1000; prevalence is much higher in premature and twin births. Prematurity and low birth weight infants (leading to perinatal asphyxia), congenital malformations, and kernicterus are causes of CP noted at birth. Ten percent of children with CP have acquired CP, developing at later ages. Meningitis and head injury (accidental and nonaccidental) are also vital in training parents and infants in other oral-motor skills, such as how to feed an infant born with a cleft lip and palate.

Speech-language therapy involves having a speech-language specialist work with a child on a one-on-one basis, in a small group, or directly in a classroom to overcome a specific disorder using a variety of therapeutic strategies. Language intervention activities involve having a speech-language specialist interact with a child by playing and talking to him or her, using pictures, books, objects, or ongoing events to stimulate language development. Articulation therapy involves having the therapist model correct sounds and syllables for a child, often during play activities.

Children enrolled in therapy early (<3 years of age) tend to have better outcomes than children who begin therapy later. Older children can make progress in therapy, but progress may occur more slowly because these children often have learned patterns that need to be modified or changed. Parental involvement is crucial to the success of a child’s progress in speech-language therapy.

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<tr>
<th>Table 10-10</th>
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ACQUIRED AFTER THE NEWBORN PERIOD

| Meningitis | |
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| Car crashes | |
| Child abuse | |
| Near-drowning | |
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Cerebral palsy (CP) includes problems with the pitch, volume, or quality of a child’s voice that distract listeners from what is being said. Language disorders can be either receptive or expressive. Receptive disorders refer to difficulties understanding or processing language. Expressive disorders include difficulty putting words together, limited vocabulary, or inability to use language in a socially appropriate way.

Speech-language pathologists (speech or oral-motor therapists) assess the speech, language, cognitive communication, and swallowing skills of children; determine what types of communication problems exist; and identify the best way to treat these challenges. Speech-language pathologists skilled at working with infants and young children are also vital in training parents and infants in other oral-motor skills, such as how to feed an infant born with a cleft lip and palate.

Speech-language therapy involves having a speech-language specialist work with a child on a one-on-one basis, in a small group, or directly in a classroom to overcome a specific disorder using a variety of therapeutic strategies. Language intervention activities involve having a speech-language specialist interact with a child by playing and talking to him or her, using pictures, books, objects, or ongoing events to stimulate language development. Articulation therapy involves having the therapist model correct sounds and syllables for a child, often during play activities.

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</table>
Table 10-12  Classification of Cerebral Palsy by Type of Motor Disorder

<table>
<thead>
<tr>
<th>Type of Motor Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic cerebral palsy</td>
<td>the most common form of cerebral palsy, it accounts for 70%–80% of cases. It results from injury to the upper motor neurons of the pyramidal tract. It may occasionally be bilateral. It is characterized by at least two of the following: abnormal movement pattern, increased tone, or pathologic reflexes (e.g., Babinski response, hyperreflexia).</td>
</tr>
<tr>
<td>Dyskinetic cerebral palsy</td>
<td>occurs in 10%–15% of cases. It is dominated by abnormal patterns of movement and involuntary, uncontrolled, recurring movements.</td>
</tr>
<tr>
<td>Ataxic cerebral palsy</td>
<td>accounts for &lt;5% of cases. This form results from cerebellar injury and features abnormal posture or movement and loss of orderly muscle coordination or both.</td>
</tr>
<tr>
<td>Dystonic cerebral palsy</td>
<td>also uncommon. It is characterized by reduced activity and stiff movement (hypokinesia) and hypotonia.</td>
</tr>
<tr>
<td>Choreoathetotic cerebral palsy</td>
<td>rare now that excessive hyperbilirubinemia is aggressively prevented and treated. This form is dominated by increased and stormy movements (hyperkinesia) and hypotonia.</td>
</tr>
<tr>
<td>Mixed cerebral palsy</td>
<td>accounts for 10%–15% of cases. This term is used when more than one type of motor pattern is present and when one pattern does not clearly dominate another. It typically is associated with more complications, including sensory deficits, seizures, and cognitive-perceptual impairments.</td>
</tr>
</tbody>
</table>

Educational attainment. CP cannot be cured, but a host of interventions can improve functional abilities, participation in society, and quality of life. Like all children, an assessment and reinforcement of strengths are important, especially for intellectually intact or gifted children who have simple motor deficits.

Suggested Reading
Crying and Colic

Infant crying, a sign of pain, distress, hunger, or fatigue, is interpreted by caregivers according to the context of the crying. The cry just after birth heralds the infant's health and vigor. The screams of the same infant, 6 weeks later, may be interpreted as a sign of illness, difficult temperament, or poor parenting. Crying is a manifestation of infant arousal influenced by the environment and interpreted through the lens of the family, social, and cultural context.

Normal Development

Crying is best understood by the characteristics of timing, duration, frequency, intensity, and modifiability of the cry (Fig. 11-1). Most infants cry little during the first 2 weeks of life, gradually increasing to 3 hours per day by 6 weeks and decreasing to 1 hour per day by 12 weeks.

Cry duration differs by culture and infant care practices. For example, !Kung San hunter-gatherer infants, who are continuously carried and fed four times per hour, cry 50% less than infants in the United States. Crying may also relate to health status. Premature infants cry little before 40 weeks gestational age but tend to cry more than term infants at 6 weeks' corrected age. Crying behavior in former premature infants also may be influenced by ongoing medical conditions, such as bronchopulmonary dysplasia, visual impairments, and feeding disorders. The duration of crying is often modifiable by caregiving strategies.

Frequency of crying is less variable than duration of crying. At 6 weeks of age, the mean frequency of combined crying and fussing is 10 episodes in 24 hours. Diurnal variation in crying is the norm, with crying concentrated in the late afternoon and evening.

The intensity of infant crying varies, with descriptions ranging from fussing to screaming. An intense infant cry (pitch and loudness) is more likely to elicit concern or even alarm from parents and caregivers than an infant who frets more quietly. Pain cries of newborns are remarkably loud: 80 dB at a distance of 30.5 cm from the infant's mouth. Although pain cries have a higher frequency than hunger cries, when not attended to for a protracted period, hunger cries become acoustically similar to pain cries. Fortunately, most infant crying is of a lesser intensity, consistent with fussing.

Colic

Colic often is diagnosed using Wessel's rule of threes—crying for more than 3 hours per day, at least 3 days per week, for more than 3 weeks. The limitations of this definition include the lack of specificity of the word crying (e.g., does this include fussing?) and the necessity to wait 3 weeks to make a diagnosis in an infant who has excessive crying. Colicky crying is often described as paroxysmal and may be characterized by facial grimacing, leg flexion, and passing flatus.

Etiology

Fewer than 5% of infants evaluated for excessive crying have an organic etiology. Because the etiology of colic is unknown, this syndrome may represent the extreme of the normal phenomenon of infant crying. Nonetheless evaluation of infants with excessive crying is warranted.

Epidemiology

Cumulative incidence rates of colic vary from 5% to 19% in different studies. Girls and boys are affected equally. Studies vary by how colic is defined and by data collection methodology, such as maintaining a cry diary or actual recording of infant vocalizations. Concern about infant crying also varies by culture, and this may influence what is recorded as crying or fussing.

Figure 11-1 Distribution of total crying time among 80 infants studied from 2 to 12 weeks of age. Data derived from daily crying diaries recorded by mothers. (From Brazelton TB: Crying in infancy. Pediatrics 29:582, 1962.)
Clinical Manifestations

The clinician who evaluates a crying infant must differentiate serious disease from colic, which has no identifiable etiology. The history includes a description of the crying, including duration, frequency, intensity, and modifiability. Associated symptoms, such as leg flexion, facial grimacing, vomiting, or back arching, should be identified. Other important historical clues include the onset, diurnal pattern, any changes in quality, and triggers or activities that relieve crying. A review of systems can identify or eliminate other serious illnesses. Medical history also is important because infants with perinatal problems are at increased risk for neurologic causes of crying. Attention to the feeding history can reveal feeding-related problems, including hunger, air swallowing (worsened by crying), gastroesophageal reflux, and food intolerance. Questions concerning the family's ability to handle the stress of the infant's crying and their knowledge of infant soothing strategies assist the clinician in assessing risk for parental mental health comorbidities and developing an intervention plan suitable for the family.

The diagnosis of colic is made only when the physical examination reveals no organic cause for the infant's excessive crying. The examination begins with vital signs, weight, length, and head circumference, looking for effects of systemic illness on growth. A thorough inspection of the infant is important to identify possible sources of pain, including skin lesions, corneal abrasions, hair tourniquets, skeletal infections, or signs of child abuse such as fractures (see Chapters 22 and 199). Infants with common conditions such as otitis media, urinary tract infections, mouth ulcerations, and insect bites may present with crying. A neurologic examination may reveal previously undiagnosed neurologic conditions, such as perinatal brain injuries, as the cause of irritability and crying. Observation of the infant during a crying episode is invaluable to assess the infant's potential for calming and the parents' skills in soothing the infant.

Laboratory and imaging studies are reserved for infants in whom there are history or physical examination findings suggesting an organic cause for excessive crying. An algorithm for the medical evaluation of an infant with excessive crying inconsistent with colic is presented in Figure 11-2.

Differential Diagnosis

The differential diagnosis for colic is broad and includes any condition that can cause pain or discomfort in the infant and conditions associated with nonpainful distress, such as fatigue or sensory overload. Cow's milk protein intolerance, maternal drug effects (including fluoxetine hydrochloride via breastfeeding), and anomalous left coronary artery all have been reported as causes of persistent crying. In addition, situations associated with poor infant regulation, including fatigue, hunger, parental anxiety, and chaotic environmental conditions, may increase the risk of excessive crying. In most cases, the
cause of crying in infants is unexplained. If the condition began before 3 weeks’ corrected age, the crying has a diurnal pattern consistent with colic (afternoon and evening clustering), the infant is otherwise developing and thriving, and no organic cause is found, a diagnosis of colic is indicated.

**Treatment**

The management of colic begins with education and demystification. When the family and the physician are reassured that the infant is healthy, without infection, trauma, or underlying disease, education about the normal pattern of infant crying is appropriate. Learning about the temporal pattern of colic can be reassuring; the mean crying duration begins to decrease at 6 weeks of age and decreases by half by 12 weeks of age. Colic does not always resolve by 3 months of age. Approximately 15% of infants with colic continue to have excessive crying after 3 months of age.

Helping families develop caregiving schedules for the infant’s fussy period is useful. Techniques for calming infants include soothing vocalizations or singing, swaddling, slow rhythmic rocking, walking, white noise, and gentle vibration (e.g., a ride in a car). Giving caregivers permission to allow the infant to rest when soothing strategies are not working may alleviate overstimulation in some infants; this also relieves families of guilt and allows them a wider range of responses to infant crying.

**Avoidance** of dangerous soothing techniques, such as shaking the infant or placing the infant on a vibrating clothes dryer (which has resulted in injury from falls), should be stressed.

**Medications**, including phenobarbital, diphenhydramine, alcohol, simethicone, dicyclomine, and lactase, are of no benefit in reducing colic and should be avoided. Parents, especially from Mexico and Eastern Europe, often use chamomile, fennel, vervain, licorice, and balm-mint teas. These teas have not been studied scientifically as remedies for colic. Families should be counseled to limit the volume of tea given because it displaces milk from the infant’s diet and may limit caloric intake.

In most circumstances, **dietary changes** are not effective in reducing colic but should be considered in certain specific circumstances. There is rationale for change to a non-cow’s milk formula if the infant has signs of cow’s milk protein colitis. If the infant is breastfeeding, the mother can eliminate dairy products from her diet.

**Prognosis**

There is no evidence that infants with colic have adverse long-term outcomes in health or temperament after the neonatal period. Similarly infantile colic does not have untoward long-term effects on maternal mental health. When colic subsides, the maternal distress resolves. Rarely cases of child abuse have been associated with inconsolable infant crying.

**Prevention**

Much can be done to prevent colic, beginning with education of prospective parents about the normal pattern of infant crying. Prospective parents often imagine that their infant will cry only briefly for hunger. Increased contact and carrying of the infant in the weeks before the onset of colic may decrease the duration of crying episodes. Similarly other soothing strategies may be more effective if the infant has experienced them before the onset of excessive crying. Infants who have been tightly swaddled for sleep and rest during the first weeks of life often calm to swaddling during a crying episode; this is not true for infants who have not experienced swaddling before a crying episode. Parents also can be coached to learn to read their infant’s cues of hunger, discomfort, boredom, or overstimulation. It is important to understand that there are times when the infant’s cry is not interpretable, and caregivers can do only their best.

**TEMPER TANTRUMS**

A temper tantrum, defined as out-of-control behavior, including screaming, stomping, hitting, head banging, falling down, and other violent displays of frustration, can include breathing, vomiting, and serious aggression, including biting. Tantrums are seen most often when the young child experiences frustration, anger, or simple inability to cope with a situation. Temper tantrums can be considered normal behavior in 1- to 3-year-old children, when the temper tantrum period is of short duration and the tantrums are not manipulative in nature.

**ETIOLOGY**

Temper tantrums are believed to be a normal human developmental stage. Child temperament may be a determinant of tantrum behavior.

**EPIDEMIOLOGY**

This behavior is common in children 18 months to 4 years of age. In U.S. studies, 50% to 80% of 2- to 3-year-old children have had regular tantrums, and 20% are reported to have daily tantrums. The behavior appears to peak late in the third year of life. Approximately 20% of 4-year-olds are still having regular temper tantrums, and explosive temper occurs in approximately 5% of school-age children. Tantrums occur equally in boys and girls during the preschool period.

**CLINICAL MANIFESTATIONS**

Temper tantrums are the most commonly reported behavioral problem in 2- and 3-year-old children. The typical frequency of tantrums is approximately one per week, with a great deal of variability (Fig. 12-1). The duration of each tantrum is 2 to 5 minutes, and duration increases with age (Fig. 12-2). Helping the family identify the typical antecedents of the child’s tantrums is essential to evaluation and intervention. A child who has tantrums only when he or she misses a routine nap can be treated differently than a child who has frequent tantrums related to minor difficulties or disappointments.

The **evaluation** of a child who is having temper tantrums requires a complete history, including perinatal and developmental information. Careful attention to the child’s daily routines may reveal problems associated with hunger, fatigue, inadequate physical activity, or overstimulation. A social
Most children who have temper tantrums have no underlying medical problem. Hearing loss and language delay may be associated with temper tantrums. Children with brain injury and other brain disorders are at increased risk for prolonged temper tantrum behavior. Children include former premature infants and children with autism, traumatic brain injury, cognitive impairment, and Prader-Willi and Smith-Magenis syndromes. Children with rare conditions, such as congenital adrenal hyperplasia and precocious puberty, also may present with severe and persistent tantrums. Children with intellectual disability may exhibit tantrums when their developmental age is comparable to 3 to 4 years.

**DIFFERENTIAL DIAGNOSIS**

Most children who have temper tantrums have no underlying medical problem. Hearing loss and language delay may be associated with temper tantrums. Children with brain injury and other brain disorders are at increased risk for prolonged temper tantrum behavior (in terms of actual tantrum duration and continued manifestation after the normal tantrum age). These children include former premature infants and children with autism, traumatic brain injury, cognitive impairment, and Prader-Willi and Smith-Magenis syndromes. Children with rare conditions, such as congenital adrenal hyperplasia and precocious puberty, also may present with severe and persistent tantrums. Children with intellectual disability may exhibit tantrums when their developmental age is comparable to 3 to 4 years.

**Figure 12-1** Mean tantrum frequency per week. Children 1 to 4 years of age who have tantrums typically have four to nine tantrums per week.

**Figure 12-2** Mean duration of tantrums. The typical duration of a tantrum increases with the age of the child.

**TREATMENT**

Intervention begins with parental education about temper tantrums, stressing that tantrums are a normal developmental phase. Parents may have unwarranted concerns about their child's mental health. The clinician can help parents understand their role in helping the child move toward self-regulation of frustration and anger. The environment can be structured to limit toddler frustration; age-inappropriate demands on the child; and hunger, fatigue, loneliness, or hyperstimulation. It is important to review the child's daily routine to understand whether the child's tantrums are communicating essential unmet needs. Children who behave well all day at day care and exhibit temper tantrums at home in the evening may be signaling fatigue or need for parental attention. Identification of underlying stress is the cornerstone of treatment because many stressors can be eliminated. Parents may consider some changes in the home environment so that they do not have to say "No" to the child as frequently.

In some cases, parents inadvertently reinforce tantrum behavior by complying with the child's demands. The child's behavior can be seen as manipulative or simply as learned behavior from a prior successful experience. Parental ambivalence about acceptable toddler behavior also may lead to inconsistent expectations and restrictions. Helping parents clarify what behavior is allowed and what is off limits can avert the temptation to give in when the child screams loudly or publicly.

Distraction is an effective means of short-circuiting impending tantrums. Physically removing the child from an environment that is associated with the child's difficulty is sometimes helpful. Further behavioral interventions are recommended only after engaging in strategies to help the child gain control by meeting basic needs, altering the environment, and anticipating meltdowns. Recommended behavioral strategies include behavior modification with positive and negative reinforcement or extinction. During the first week of any behavioral intervention, tantrum behavior may increase. Parents must be warned that it will probably get worse before it gets better. At the same time that parents are working to extinguish or decrease the tantrums, it is important that they provide positive reinforcement for good behavior.

**PREVENTION**

Providing parents with knowledge about the temper tantrum stage and strategies for assisting the child with emotional regulation is recommended at a health care maintenance visit between 12 and 18 months of age. Regular routines for sleeping, eating, and physical activity in a childproofed home (or day care center) provided by well-rested and psychologically healthy parents (or caregivers) usually result in a quick transition through this challenging period.
ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention deficit/hyperactivity disorder (ADHD) is a neurobehavioral disorder defined by symptoms of inattention, hyperactivity, and impulsivity. Clinical guidelines emphasize the use of the Diagnostic and Statistical Manual of Mental Health Disorders, Fifth Edition, criteria (available at http://www.cdc.gov/ncbddd/adhd/diagnosis.html) to diagnose ADHD. Diagnosis of children up to the age of 16 years requires the presence of at least 6 symptoms of inattention or 6 symptoms of hyperactivity-impulsivity for at least 6 months in two or more environments. Children 17 years of age and older must exhibit at least 5 symptoms of inattention or at least 5 symptoms of hyperactivity-impulsivity.

Symptoms of inattention include: failing to pay close attention to details, appearing to not listen when spoken to directly, failing to follow through on instructions or finish assigned work, having difficulty sustaining attention during tasks or play, having difficulty organizing tasks or activities, avoiding or disliking activities that require sustained mental effort (e.g., schoolwork), frequently losing things required for tasks and activities, becoming easily distracted, and experiencing frequent forgetfulness in daily activities. Symptoms of hyperactivity include: being fidgety or restless, leaving a seat when expected to remain seated, running or climbing excessively in inappropriate situations, having difficulty in playing quietly, acting as if “driven by a motor,” and talking excessively. Symptoms of impulsivity include: blurt out answers before a question has been completed, having difficulty awaiting his or her turn, and causing frequent interruptions or intrusions. In addition, several symptoms must have been present prior to 12 years of age; evidence of significant impairment in social, academic, or work settings must occur; and other mental disorders must be excluded.

ETIOLOGY

ADHD is multifactorial in origin, with genetic, neural, and environmental contributions. Twin studies and family studies demonstrate high heritability (0.8) and greater risk of developing ADHD in first-degree relatives. Candidate genes include those involving the dopaminergic and noradrenergic neurotransmitter systems. Neuroimaging studies (functional magnetic resonance imaging and positron emission tomography, commonly recognized as fMRI and PET, respectively) have shown structural and functional differences, particularly of the frontal lobes, inferior parietal cortex, basal ganglia, corpus callosum, and cerebellar vermis. Prenatal exposure to substances (e.g., nicotine, alcohol) and damage to the central nervous system from trauma or infection increase the risk of ADHD.

EPIDEMIOLOGY

U.S. prevalence rates for ADHD vary, depending on criteria used and population studied, with rates typically in the 5% to 10% range. The male to female ratio is 2 to 6:1, with greater male predominance for the hyperactive/impulsive and combined types. Girls often present with inattentive symptoms and are more likely to be underdiagnosed or to receive later diagnoses. Symptoms of ADHD, particularly impulsivity and inattention, persist into adolescence and adulthood in 60% to 80% of patients.

CLINICAL MANIFESTATIONS

ADHD is diagnosed clinically by history. Open-ended questions should focus on specific behaviors and their impact on academic performance, family and peer relationships, safety, self-esteem, and daily activities. Information should be gathered from the family and the school via ADHD-specific rating scales such as the Conners’ Rating Scales or the Vanderbilt Rating Scales.

A physical examination is essential to identify medical (e.g., neurologic, genetic) or developmental problems (e.g., cognitive impairment, language disorder, learning disability, autism spectrum disorder) that may underlie, coexist, or provide an alternative explanation for the child’s behaviors. Observation of the child, the parents, and their interactions is part of the evaluation. Keep in mind that children with ADHD can typically focus without hyperactivity in environments with low stimulation and little distraction (e.g., clinician’s office).

Laboratory and imaging studies are not routinely recommended but may help exclude other conditions. Consider thyroid function studies, blood lead levels, genetic studies, and brain imaging studies if indicated by medical history, environmental history, or physical examination.

DIFFERENTIAL DIAGNOSIS

The clinician should first consider the child’s developmental level to determine whether the behaviors are within the range of normal. Medical conditions, such as sleep disorder breathing, seizure disorders, substance use, hyperthyroidism, lead intoxication, and sensory deficits, should be considered as possible causes for a child’s hyperactivity and distractibility. Inattention and hyperactivity may be present as features of genetic disorders such as fragile X, 22q11.2 deletion syndrome, and neurofibromatosis 1. Chaotic living situations or psychological stress (e.g., bullying, abuse) can also lead to symptoms of hyperactivity, impulsivity, and inattention. Children who have symptoms of ADHD in only one setting may be having problems due to cognitive level, level of emotional maturity, or feelings of well-being in that setting.

More important, coexisting conditions are present in up to 60% of children with ADHD. These include psychiatric conditions, particularly oppositional defiant disorder, conduct disorder, anxiety disorder, and depression; learning disabilities; language disorders; and tic disorders. These conditions are also part of the differential diagnosis of ADHD.

TREATMENT

Management begins with recognizing ADHD as a chronic condition and educating affected children and their parents about the diagnosis, treatment options, and prognosis.
Anticipatory guidance includes providing proactive strategies to mediate adverse effects on learning, school functioning, social relationships, family life, and self-esteem. Children with ADHD respond to behavioral management, including structure, routine, consistency in adult responses to their behaviors, and appropriate behavioral goals. Children also benefit when parents and clinicians work with teachers to address the child’s needs. Daily behavior report cards and accommodations may be helpful. Social skills training or additional mental health treatments may assist some children with behavior change or preservation of self-esteem, particularly when they have coexisting developmental or mental health conditions also requiring treatment.

Stimulant medications (methylphenidate or amphetamine compounds) are the first-line agents for treatment of ADHD due to extensive evidence of effectiveness and safety. Stimulant medications are available in short-acting, intermediate-acting, and long-acting forms. Preparations include liquid, tablets, capsules, and a transdermal patch. These options allow the clinician to tailor the choice of medication to the child’s needs. Nonstimulant medications, including atomoxetine (norepinephrine-reuptake inhibitor), guanfacine, or clonidine (alpha agonists), may be helpful in situations such as nonresponse to stimulant medication, family preference, concerns about medication abuse or diversion, and coexisting tic or sleep problems. ADHD medication options are listed in Table 13-1. Common side effects include appetite suppression and sleep disturbance with stimulant medications, gastrointestinal tract symptoms with atomoxetine, and sedation with alpha agonists. These side effects usually can be managed by careful adjustment of medication dosage and timing. Screening (by history and exam) for cardiac disease and monitoring of cardiac status is prudent given concerns raised by a retrospective study suggesting extremely rare but slightly increased odds of sudden cardiac death in those taking stimulant medication.

## COMPLICATIONS

ADHD may be associated with academic underachievement, difficulties in interpersonal relationships, and poor self-esteem. These can have long-reaching effects (e.g., lower levels of educational, employment attainment). Adolescents with ADHD, particularly those who are untreated, are at increased risk for high-risk behaviors such as drug use, early sexual activity, and automobile accidents. Despite parental concerns of illicit drug use and addiction from stimulant medication, there is actually decreased risk of drug abuse in children and adolescents with ADHD who are appropriately medically managed.

## PREVENTION

Child-rearing practices including promoting calm environments and opportunities for age-appropriate activities that require increasing levels of focus may be helpful. Limited time spent watching television and playing rapid-response video games also may be prudent because these activities reinforce short attention span. Early implementation of behavior management techniques may assist in curtailing problematic behaviors before they result in significant impairment. Secondary disabilities can be prevented by educating medical professionals and teachers about the signs and symptoms of ADHD and the most appropriate behavioral and pharmacological interventions. Collaboration between health care providers, educational professionals, and mental health clinicians will enhance the early identification of and provision of services to children at risk for ADHD.

### Table 13-1: FDA-Approved Medications for Attention-Deficit/Hyperactivity Disorder

<table>
<thead>
<tr>
<th>GENERIC MEDICATION</th>
<th>BRAND NAME</th>
<th>INITIAL-MAXIMUM DOSE</th>
<th>DURATION (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STIMULANTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed amphetamine salts</td>
<td>Adderall®</td>
<td>2.5 mg–40 mg</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Adderall® XR®</td>
<td>5 mg–40 mg</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Vyvanse</td>
<td>20 mg–70 mg</td>
<td>10–12</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Concerta</td>
<td>18–54 mg (&lt;13 years)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Daytrana</td>
<td>18–72 mg (≥13 years)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Metadate CD</td>
<td>10 mg–15 mg</td>
<td>Apply for 9 h</td>
</tr>
<tr>
<td></td>
<td>Methyl ER</td>
<td>20 mg–60 mg</td>
<td>6–8</td>
</tr>
<tr>
<td></td>
<td>Methylin</td>
<td>10 mg–60 mg</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Ritalin®</td>
<td>5 mg–60 mg</td>
<td>3–5</td>
</tr>
<tr>
<td></td>
<td>Ritalin LA</td>
<td>5 mg–60 mg</td>
<td>3–5</td>
</tr>
<tr>
<td></td>
<td>Ritalin SR®</td>
<td>20 mg–60 mg</td>
<td>6–8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg–60 mg</td>
<td>2–6</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>Focalin®</td>
<td>2.5 mg–20 mg</td>
<td>3–5</td>
</tr>
<tr>
<td></td>
<td>Focalin® XR</td>
<td>5 mg–30 mg</td>
<td>8–12</td>
</tr>
<tr>
<td><strong>NOREPINEPHRINE-REUPTAKE INHIBITOR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Stratter</td>
<td>0.5 mg/kg/d then increase to 1.2 mg/kg with max 1.4 mg/kg 40 mg/d for adults and children weighing &gt;154 lb titrate up to 100 mg/d</td>
<td>At least 10–12</td>
</tr>
<tr>
<td><strong>ALPHA AGONISTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Kapvay</td>
<td>0.1 mg/d–0.4 mg/d</td>
<td>At least 10–12</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>Intuniv</td>
<td>1 mg/d–4 mg/d</td>
<td>At least 10–12</td>
</tr>
</tbody>
</table>

Adapted from AAP: Implementing the key action statements: an algorithm and explanation for process of care for the evaluation, diagnosis, treatment, and monitoring of ADHD in children and adolescents. Pediatrics 117–S21, 2011.

*Dosages for the dermal patch are not equivalent to those of the oral preparations.
NORMAL DEVELOPMENT OF ELIMINATION

Development of control of urination and defecation involves physical and cognitive maturation and is strongly influenced by cultural norms, socioeconomic status, and practices within the United States and throughout the world. In the first half of the twentieth century, toilet mastery by 18 months of age was the norm in the United States. Concern about harsh toilet training and possible later psychological distress led to professional endorsement of later toilet training. In 1962 Brazelton introduced the child-centered approach, which respects the child’s autonomy and pride in mastery. The invention of disposable diapers also facilitated later toilet training. Social changes, including increased maternal work outside of the home and group child care, also have influenced this trend. Some families choose to wait until the child is older because the duration of the training period may be shorter. Toilet training usually begins after the second birthday and is achieved at about 3 years of age in middle-class white U.S. populations. Toilet training between 12 and 18 months of age continues to be accepted in lower-income families.

Prerequisites for achieving elimination in the toilet include the child’s ability to recognize the urge for urination and defecation, to get to the toilet, to understand the sequence of tasks required, to avoid oppositional behavior, and to take pride in achievement. The entire process of toilet training can take 6 months and need not be hurried. Successful parent-child interaction around the goal of toilet mastery can set the stage for future active parental teaching and training (e.g., manners, kindness, rules and laws, and limit setting).

ENURESIS

Enuresis is urinary incontinence in a child who is adequately mature to have achieved continence. Enuresis is classified as diurnal (daytime) or nocturnal (nighttime). In the United States, daytime and nighttime dryness are expected by 4 and 6 years of age, respectively. Another useful classification of enuresis is primary (incontinence in a child who has never achieved dryness) and secondary (incontinence in a child who has been dry for at least 6 months).

Etiology

Enuresis is a symptom with multiple possible etiologic factors, including developmental difference, organic illness, or psychological distress. Primary enuresis often is associated with a family history of delayed acquisition of bladder control. A genetic etiology has been hypothesized, and familial groups with autosomal dominant phenotypic patterns for nocturnal enuresis have been identified. Although most children with enuresis do not have a psychiatric disorder, stressful life events can trigger loss of bladder control. Sleep physiology may play a role in the etiology of nocturnal enuresis, with a high arousal threshold commonly noted. In a subgroup of enuretic children, nocturnal polyuria relates to a lack of a nocturnal vasopressin peak. Another possible etiology is mal-function of the detrusor muscle with a tendency for involuntary contractions even when the bladder contains small amounts of urine. Reduced bladder capacity can be associated with enuresis and is commonly seen in children who have chronic constipation with a large dilated distal colon, which impinges on the bladder.

Epidemiology

Enuresis is the most common urologic condition in children. Nocturnal enuresis has a reported prevalence of 15% in 5-year-olds, 7% in 8-year-olds, and 1% in 15-year-olds. The spontaneous remission rate is reported to be 15% per year. The odds ratio of nocturnal enuresis in boys compared with girls is 1.4:1. The prevalence of daytime enuresis is lower than nocturnal enuresis but has a female predominance, 1.5:1 at 7 years of age. Of children with enuresis, 22% wet during the day only, 17% wet during the day and at night, and 61% wet at night only.

Clinical Manifestations

The history focuses on elucidating the pattern of voiding: How often does wetting occur? Does it occur during the day, night, or both? Are there any associated conditions with wetting episodes (e.g., bad dreams, consumption of caffeinated beverages, or exhausting days)? Has the child had a period of dryness in the past? Did a stressful event precede the change in wetting pattern? A review of systems should include a developmental history and detailed information about the neurologic, urinary, and gastrointestinal systems (including patterns of defecation). A history of sleep patterns also is important, including snoring, parasomnias, and timing of nighttime urination. A family history often reveals that one or both parents had enuresis as children. Although enuresis is rarely associated with child abuse, physical and sexual abuse history should be included as part of the psychosocial history. Many families have tried numerous interventions before seeking a physician’s help. Identifying these interventions and how they were carried out aids the understanding of the child’s condition and its role within the family.

The physical examination begins with observation of the child and the parent for clues about child developmental and parent-child interaction patterns. Special attention is paid to the abdominal, neurologic, and genital examination. A rectal examination is recommended if the child has constipation. Observation of voiding is recommended if a history of voiding problems, such as hesitancy or dribbling, is elicited. The lumbosacral spine should be examined for signs of spinal dysraphism or a tethered cord.

For most children with enuresis, the only laboratory test recommended is a clean catch urinalysis to look for chronic urinary tract infection (UTI), renal disease, and diabetes mellitus. Further testing, such as a urine culture, is based on...
the urinalysis. Children with complicated enuresis, including children with previous or current UTI, severe voiding dysfunction, or a neurologic finding, are evaluated with a renal sonogram and a voiding cystourethrogram. If vesicoureteral reflux, hydronephrosis, or posterior urethral valves are found, the child is referred to a urologist for further evaluation and treatment.

**Differential Diagnosis**
Commonly there is no identified cause of enuresis and, in most cases, enuresis resolves by adolescence without treatment. Children with primary nocturnal enuresis are most likely to have a family history and are least likely to have an identified etiology. Children with secondary diurnal and nocturnal enuresis are more likely to have an organic etiology, such as UTI, diabetes mellitus, or diabetes insipidus, to explain their symptoms. Children with primary diurnal and nocturnal enuresis may have a neurodevelopmental condition or a problem with bladder function. Children with secondary nocturnal enuresis may have a psychosocial stressor or a sleep disturbance as a predisposing condition for enuresis.

**Treatment**
Treatment begins with treating any diagnosed underlying organic causes of enuresis. Elimination of underlying chronic constipation is often curative. For a child whose enuresis is not associated with an identifiable disorder, all therapies must be considered in terms of cost in time, money, disruption to the family, the treatment’s known success rate, and the child’s likelihood to recover from the condition without treatment. The most commonly used treatment options are conditioning therapy and pharmacotherapy. The clinician can also assist the family in making a plan to help the child cope with this problem until it is resolved. Many children have to live with enuresis for months to years before a cure is achieved; a few children have symptoms into adulthood. A plan for handling wet garments and linens in a nonhumiliating and hygienic manner preserves the child’s self-esteem. The child should take as much responsibility as he or she is able, depending on age, development, and family culture.

The most widely used conditioning therapy for nocturnal enuresis is the enuresis alarm. Enuresis alarms have an initial success rate of 70% with a relapse rate of 10%. The alarm is worn on the wrist or clipped onto the pajama and has a probe that is placed in the underpants or pajamas in front of the urethra. The alarm sounds when the first drop of urine contacts the probe. The child is instructed to get up and finish voiding in the bathroom when the alarm sounds. After 3 to 5 months, 70% of children are dry through the night.

Pharmacotherapy for nighttime enuresis includes desmopressin acetate and, rarely, tricyclic antidepressants. Desmopressin decreases urine production and has proved to be safe in the treatment of enuresis. The oral medication is started at 0.2 mg per dose (one dose at bedtime) and on subsequent nights is increased to 0.4 mg and then to 0.6 mg if needed. This treatment must be considered symptomatic, not curative, and has a relapse rate of 90% when the medication is discontinued. Imipramine, now rarely used for enuresis, reduces the frequency of nighttime wetting. The initial success rate is 50%. Imipramine is effective during treatment only, with a relapse rate of 90% on discontinuation of the medication. The most important contraindication is risk of overdose (associated with fatal cardiac arrhythmia).

**Complications**
The psychological consequences can be severe. Families can minimize the impact on the child’s self-esteem by avoiding punitive approaches and ensuring that the child is competent to handle issues of their own comfort, hygiene, and aesthetics.

**Prevention**
Appropriate anticipatory guidance to educate parents that bed-wetting is common in early childhood helps alleviate considerable anxiety.

**FUNCTIONAL CONSTIPATION AND SOILING**
**Constipation** is decreased frequency of bowel movements usually associated with a hard stool consistency. The occurrence of pain at defecation frequently accompanies constipation. Although underlying gastrointestinal, endocrinologic, or neurologic disorders can cause constipation, *functional constipation* implies that there is no identifiable causative organic condition. Encopresis is the regular, voluntary or involuntary passage of feces into a place other than the toilet after 4 years of age. Encopresis without constipation is uncommon and may be a symptom of oppositional defiant disorder or other psychiatric illness. Soiling is the involuntary passage of stool and often is associated with fecal impaction. The normal frequency of bowel movements declines between birth and 4 years of age, beginning with greater than four stools per day to approximately one per day.

**Etiology**
The etiology of functional constipation and soiling includes a low-fiber diet, slow gastrointestinal transit time for neurologic or genetic reasons, and chronic withholding of bowel movements, usually because of past painful defecation experiences. Approximately 95% of children referred to a subspecialist for encopresis have no other underlying pathologic condition.

**Epidemiology**
In U.S. studies, 16% to 37% of children experience constipation between 5 and 12 years of age. Constipation with overflow soiling occurs in 1% to 2% of preschool children and 4% of school-age children. The incidence of constipation and soiling is equal in preschool girls and boys, whereas there is a male predominance during school age.

**Clinical Manifestations**

<table>
<thead>
<tr>
<th>Decision-Making Algorithms</th>
<th>Available @ StudentConsult.com</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Irritable Infant</td>
</tr>
</tbody>
</table>

**Available @ StudentConsult.com**
The presenting complaint for constipation with soiling is typically a complaint of uncontrolled defecation in the underwear. Parents may report that the child has diarrhea because of soiling of liquid stool. Soiling may be frequent or continuous. On further questioning, the clinician learns that the child is passing large-caliber bowel movements that may occasionally block the toilet. Children younger than 3 years of age often present with painful defecation, impaction, and withholding. The history should include a complete review of systems for gastrointestinal, endocrine, and neurologic disorders and a developmental and psychosocial history.

**Stool impaction** can be felt on abdominal examination in about 50% of patients at presentation. Firm packed stool in the rectum is highly predictive of fecal impaction. A rectal examination allows assessment of sphincter tone and size of the rectal vault. Evaluation of anal placement and existence of anal fissures also is helpful in considering etiology and severity. A neurologic examination, including lower extremity reflexes, anal wink, and cremasteric reflexes, may reveal underlying spinal cord abnormalities.

Abdominal x-ray is not required. It can be helpful to show to the family the degree of colonic distention and fecal impaction. In general further studies, such as barium enema and rectal biopsy, are indicated only if an organic cause for the constipation is indicated by history or physical examination (see Chapter 129). Similarly although endocrinologic conditions such as hypothyroidism can cause chronic constipation, laboratory studies are not indicated without history or physical examination suggesting such a disorder.

**Differential Diagnosis**
The differential diagnosis for functional constipation and soiling includes organic causes of constipation (e.g., neurogenic, anatomic, endocrinologic, gastrointestinal, and pharmacologic). A child with chronic constipation and soiling who had delayed passage of meconium and has an empty rectum and tight sphincter may have Hirschsprung disease (see Chapter 129). Chronic constipation may be a presenting sign of spinal cord abnormalities, such as a spinal cord tumor or a tethered cord. Physical examination findings of altered lower extremity reflexes, absent anal wink, or a sacral hairy tuft or sacral sinus may be a clue to these anomalies. Hypothyroidism can present with chronic constipation and typically is accompanied by poor linear growth and bradycardia. Anal stenosis may lead to chronic constipation. The use of opiates, phenothiazine, antidepressants, and anticholinergics also may lead to chronic constipation. Developmental problems, including mental retardation and autism, may be associated with chronic constipation.

**Treatment**
Treatment begins with education and demystification for the child and family about chronic constipation and soiling, emphasizing the chronic nature of this condition and the good prognosis with optimal management. Explaining the physiologic basis of constipation and soiling to the child and the family alleviates blame and enlists cooperation. Education may improve adherence to the long-term treatment plan (Table 14-1). One half to two thirds of children with functional constipation recover completely and no longer require medication.

<table>
<thead>
<tr>
<th>Table 14-1</th>
<th>Education about Chronic Constipation and Soiling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation affects 16% to 37% of children.</td>
<td></td>
</tr>
<tr>
<td>1% to 4% of children have functional constipation and soiling.</td>
<td></td>
</tr>
<tr>
<td>Functional constipation with/without soiling begins early in life due to a combination of factors:</td>
<td></td>
</tr>
<tr>
<td>Uncomfortable/painful stool passage</td>
<td></td>
</tr>
<tr>
<td>Withholding of stool to avoid discomfort</td>
<td></td>
</tr>
<tr>
<td>Diets higher in constipating foods and lower in fiber and fluid intake*</td>
<td></td>
</tr>
<tr>
<td>Use of medications that are constipating</td>
<td></td>
</tr>
<tr>
<td>Developmental features—increasing autonomy; perhaps toilet avoidance</td>
<td></td>
</tr>
<tr>
<td>Possible family genetic factors—slower colonic transit</td>
<td></td>
</tr>
<tr>
<td>When chronic impaction, physiologic changes at the rectum reduce a child’s bowel control.</td>
<td></td>
</tr>
<tr>
<td>Dilated rectal vault results in reduced sensation to standard fecal volume.</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation of rectal musculature and strength requires several months.</td>
<td></td>
</tr>
<tr>
<td>Until then, dilated rectal musculature may be less able to expel stool effectively.</td>
<td></td>
</tr>
<tr>
<td>Paradoxical anal sphincter contraction may occur when the urge to defecate is felt; it can lead to incomplete emptying of stool at defecation attempt.</td>
<td></td>
</tr>
<tr>
<td>Many children do not recognize their soiling accidents owing to olfactory accommodation.</td>
<td></td>
</tr>
<tr>
<td>Low self-esteem or other behavioral concerns are common on presentation.</td>
<td></td>
</tr>
<tr>
<td>Improve for most with education and management for the constipation and soiling.</td>
<td></td>
</tr>
<tr>
<td>Effective management of functional constipation requires a substantial commitment of the child/family, usually for 6–24 mo.</td>
<td></td>
</tr>
<tr>
<td>Degree of child and family adherence is likely a predictor of the child’s success.</td>
<td></td>
</tr>
</tbody>
</table>

*The common features of the transition to the toddler diet (decreased fluid intake, continued high dairy intake, and finicky eating patterns) make this a high-risk time during development for constipation problems.

The younger the child is when diagnosis and treatment begin, the higher the success rate. Treatment involves a combination of behavioral training and laxative therapy. Successful treatment requires 6 to 24 months. The next step is adequate colonic cleanout or disimpaction. Clean-out methods include enemas alone or combinations of enema, suppository, and oral laxatives. High-dose oral mineral oil is a slower approach to clean-out. Choice of disimpaction method depends on the age of the child, family choice, and the clinician’s experience with a particular method. Methods and side effects are summarized in Table 14-2. The child and family should be included in the process of choosing the clean-out method. Because enemas may be invasive and oral medication may be unpleasant, allowing points of choice and control for the child and praising all signs of cooperation are important.

**Behavioral training** is essential to the treatment of chronic constipation and soiling. The child and family are asked to monitor and document stool output. Routine toilet sitting is instituted for 5 to 10 minutes three to four times per day. The child is asked to demonstrate proper toilet sitting position with the upper body flexed forward slightly and feet on the floor.
### Table 14-2 | Clean-Out Disimpaction

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>SIDE EFFECTS/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFANTS</strong></td>
<td></td>
</tr>
<tr>
<td>Glycerin suppositories</td>
<td>No side effects</td>
</tr>
<tr>
<td>Enema—6 mL/kg up to 4.5 oz (135 mL)</td>
<td>If enemas are considered, administer first in physician’s office.</td>
</tr>
<tr>
<td><strong>CHILDREN</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rapid Cleanout</strong></td>
<td></td>
</tr>
<tr>
<td>Enema—6 mL/kg up to 4.5 oz (135 mL)</td>
<td>Invasive; risk of mechanical trauma</td>
</tr>
<tr>
<td></td>
<td>Large impaction: mineral oil enema followed 1–3 h later by normal saline or phosphate enema</td>
</tr>
<tr>
<td></td>
<td>Small impaction: normal saline or phosphate enema</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>Lubricates hard impaction; may not see return after administration</td>
</tr>
<tr>
<td>Normal saline</td>
<td>Abdominal cramping; may not be as effective as hypertonic phosphate</td>
</tr>
<tr>
<td>Hypertonic phosphate</td>
<td>Abdominal cramping; risk of hyperphosphatemia, hypokalemia, and hypocalcemia, especially with Hirschsprung or renal insufficiency or if retained. Some experts do not recommend phosphate enema for children &lt;4 yr, others for children &lt;2yr.</td>
</tr>
<tr>
<td>Milk of molasses: 1:1 milk:molasses</td>
<td>For difficult to clear impaction</td>
</tr>
<tr>
<td>Combination: enema, suppository, oral laxative</td>
<td></td>
</tr>
<tr>
<td>Day 1: Enema q12–24 h</td>
<td>See enemas above</td>
</tr>
<tr>
<td>Day 2: Bisacodyl suppository (10 mg) q12–24 h</td>
<td>Abdominal cramping, diarrhea, hypokalemia</td>
</tr>
<tr>
<td>Day 3: Bisacodyl tablet (5 mg) q12–24 h</td>
<td>Abdominal cramping, diarrhea, hypokalemia</td>
</tr>
<tr>
<td>Repeat 3-day cycle if needed × 1–2</td>
<td></td>
</tr>
<tr>
<td>Oral/nasogastric tube: Polyethylene glycol electrolyte solution (GoLYTELY or NuLYTELY)—25 mL/kg/h up to 1000 mL/h × 4 h/day</td>
<td>Nausea, cramping, vomiting, bloating, aspiration. Large volume. Usually requires nasogastric tube and hospitalization to administer</td>
</tr>
<tr>
<td><strong>Slower Cleanout</strong></td>
<td></td>
</tr>
<tr>
<td>Oral high-dose mineral oil—15–30 mL per year of age per day up to 8 oz × 3–4 days</td>
<td>Aspiration—lipoid pneumonia. Give chilled.</td>
</tr>
<tr>
<td>X-Prep (senna): 15 mL q12h × 3</td>
<td>Abdominal cramping. May not see output until dose 2 or 3</td>
</tr>
<tr>
<td>Magnesium citrate: 1 oz/yr of age to maximum of 10 oz per day for 2–3 days</td>
<td>Hypermagnesemia</td>
</tr>
<tr>
<td>Maintenance medications—also may be used for cleanout</td>
<td></td>
</tr>
</tbody>
</table>

or foot support. The child should be praised for all components of cooperation with this program, and punishment and embarrassment should be avoided. As symptoms resolve, toilet sitting is decreased to twice daily and finally to once a day.

When disimpaction is achieved, the child begins the maintenance phase of treatment. This phase promotes regular stool production and prevents reimpaction. It involves attention to diet, medications to promote stool regularity, and behavioral training. Increasing dietary fiber and fluid are recommended. For children with chronic constipation, the recommended daily dose of fiber is calculated as 10 grams plus the child’s age in years (e.g., a 10-year-old should take 20 grams of fiber per day). At least 2 oz of nondairy fluid intake per gram of fiber intake is recommended. Sorbitol-based juices, including prune, pear, and apple juice, increase the water content of bowel movements. Lubricants or osmotic laxatives are used to promote regular soft bowel movements. Maintenance medications, including side effects, are listed in Table 14-3. Polyethylene glycol powder is well tolerated because the taste and texture are palatable. Some children may require the use of a lubricant in addition to an osmotic laxative; children with severe constipation may require a stimulant laxative.

Treatment failure occurs in approximately one in five children secondary to problems with adherence or poor recognition of inadequate treatment resulting in reimpaction.

**Complications**
Chronic constipation and soiling interfere with social functioning and self-esteem. Discomfort and fear of accidents may distract children from their schoolwork and other important tasks. Children also may develop unusual eating habits in response to chronic constipation and their beliefs about this condition. Case reports of child abuse related to soiling have been published.

**Prevention**
The primary care physician can recommend adequate fiber intake in all children and encourage families to help their children institute regular toileting habits at an early age as preventive measures. Earlier diagnosis of chronic constipation can prevent much secondary disability and shorten the length of treatment required.
Table 14-3 | Maintenance Medications

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>SIDE EFFECTS/COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFANTS</td>
<td></td>
</tr>
<tr>
<td>Oral Medications/Other</td>
<td></td>
</tr>
<tr>
<td>Juices containing sorbitol</td>
<td>Pear, prune, apple</td>
</tr>
<tr>
<td>Lactulose or sorbitol: 1–3 mL/kg/day + doses bid</td>
<td>See below</td>
</tr>
<tr>
<td>Corn syrup (light or dark): 1–3 mL/kg/day + doses bid Per Rectum</td>
<td>Not considered risk for Clostridium botulinum spores</td>
</tr>
<tr>
<td>Glycerin suppository</td>
<td>No side effects</td>
</tr>
<tr>
<td>CHILDREN</td>
<td></td>
</tr>
<tr>
<td>Oral Medications</td>
<td></td>
</tr>
<tr>
<td>Lubricant</td>
<td>Softens stool and eases passage</td>
</tr>
<tr>
<td>Mineral oil: 1–3 mL/kg day as one dose or + bid</td>
<td>Aspiration—lipoid pneumonia</td>
</tr>
<tr>
<td>Osmotics</td>
<td>Retain water in stool, aiding bulk and softness</td>
</tr>
<tr>
<td>Lactulose: 10 g/15 mL, 1–3 cc/kg/day + doses bid</td>
<td>Synthetic disaccharide: abdominal cramping, flatus</td>
</tr>
<tr>
<td>Magnesium hydroxide (milk of magnesia): 400 mg/5 mL, 1–3 mL/kg/day + bid</td>
<td>Risk of hypermagnesemia, hypophosphatemia, secondary hypocalcemia with overdose or renal insufficiency</td>
</tr>
<tr>
<td>MiraLAX (polyethylene glycol powder): 17 g/240 cc water or juice stock, 1.0 g/kg/day + doses bid (approximately 15 cc/kg/day)</td>
<td>Titrate dose at 3-day intervals to achieve mushy stool consistency. May make stock solutions to administer over 1–2 days</td>
</tr>
<tr>
<td>Sorbitol: 1–3 mL/kg/day + doses bid</td>
<td>Excellent adherence</td>
</tr>
<tr>
<td>Stimulants†</td>
<td>Improve effectiveness of colonic and rectal muscle contractions</td>
</tr>
<tr>
<td>Senna: syrup—8.8 g sennoside/5 mL</td>
<td>Idiosyncratic hepatitis, melanosis coli, hypertrophic osteoarthropathy, analgesic nephropathy; abdominal cramping</td>
</tr>
<tr>
<td>2–6 yr: 2.5–7.5 cc/day + doses bid</td>
<td>Improvement of melanosis coli after medication stopped</td>
</tr>
<tr>
<td>6–12 yr: 5–15 cc/day + doses bid (Tablets and granules available)</td>
<td>Abdominal cramping, diarrhea, hypokalemia</td>
</tr>
<tr>
<td>Bisacodyl: 5-mg tablets, 1–3 tablets/dose 1–2 × daily</td>
<td>Abdominal cramping, diarrhea, hypokalemia</td>
</tr>
</tbody>
</table>

Per Rectum

| Glycerin suppository | No side effects |
| Bisacodyl: 10-mg suppositories, 0.5–1 suppository, 1–2 × daily | Abdominal cramping, diarrhea, hypokalemia |

*Single agent may suffice to achieve daily, comfortable stools.
†Stimulants should be reserved for short-term use.

Chapter 15

NORMAL SLEEP AND PEDIATRIC SLEEP DISORDERS

Sleep is a universal phenomenon that is critical to child health, development, and daily functioning. This complex behavioral and physiologic process is characterized by a reversible state of partial unresponsiveness and disengagement from the environment. Sleep is broadly categorized by polysomnographic patterns into rapid eye movement (REM) sleep and non-REM (NREM) sleep. REM sleep is characterized by an active, awake-like electroencephalography (EEG) pattern and muscle atonia. NREM sleep is further divided into three stages—from stage 1 (N1), which is the lightest sleep stage and consists of low-amplitude, high-frequency EEG activity, to stage 3 (N3), also known as deep or slow-wave sleep, characterized by low-frequency, high-amplitude delta waves. REM and NREM sleep alternate in cycles throughout the night.

Sleep architecture changes from fetal life through infancy and childhood. Sleep cycles last approximately 60 minutes in newborns and gradually lengthen to 90 minutes in children and adults. Neonates typically begin their sleep cycle in REM sleep, whereas older children and adults begin sleep in NREM sleep.
Sleep. REM sleep in neonates is termed active sleep, and frequent muscle twitches and facial grimaces are common. REM sleep comprises up to 50% of total sleep time in newborns and gradually decreases to 25% to 30% by adolescence. Slow-wave sleep is not seen before 3 to 6 months of age. Beginning from 6 to 12 months and continuing through adulthood, the amount of REM sleep shifts toward the last third of the night, while NREM sleep predominates during the first third of the night.

The timing and duration of sleep also change with age. Sleep patterns become more diurnal and total daily sleep time gradually decreases. Full-term infants sleep on average 16 to 18 hours per day in fragmented intervals throughout the day and night. One-year-old children sleep on average 10 to 11 hours per night and nap for 2 to 3 hours during the day. Naps decrease from two naps to one during the second year of life. In the United States, over 80% of 2-year-olds nap, decreasing to 50% by age 3. By 12 years old, the average child sleeps 9 to 10 hours per day. By adolescence, the average sleep duration has dropped to 7½ hours per day, even though adolescents need an average of 9 hours per day. Adolescents also develop a physiologically based shift toward later sleep-onset and wake times relative to those in middle childhood.

Cultural factors strongly influence multiple sleep practices, including whether children sleep independently (the norm in the United States) or with parents, other siblings, or grandparents (the norm in many other cultures). Awareness of the varying cultural practices regarding sleep is essential to respectful and effective intervention.

**SLEEP DISORDERS**

Sleep problems are one of the most frequent complaints in pediatric practice. Numerous sleep disorders exist, including behavioral insomnias (bedtime refusal, delayed sleep onset, nighttime awakenings), parasomnias, and circadian rhythm disorders (Table 15-1). Obstructive sleep apnea (OSA) and sleep disorders associated with mental and physical illness should also be considered.

**Epidemiology**

Sleep problems occur in 20% to 30% of children at some point during childhood. Behavioral sleep disorders are common and found across all age groups but are most prevalent from infancy through preschool age. Bedtime resistance occurs in 10% to 15% of toddlers, and 15% to 30% of preschool-aged children have difficulties achieving and/or maintaining sleep. Although generally benign, parasomnias occur commonly in young children, including sleep walking (15% to 40%) and sleep terrors (1% to 6%). OSA is reported in 1% to 4% of children. Circadian rhythm disorders occur in 7% to 16% of adolescents.

**Clinical Manifestations and Evaluation**

Sleep disorders may manifest in a variety of ways and often go unrecognized. Some children present with daytime behavioral problems, including inattentiveness, hyperactivity, or irritability rather than overt sleepiness. Screening for sleep disorders is recommended as part of primary care. Clinicians should inquire about bedtime problems, excessive daytime sleepiness, awakenings during the night, regularity and duration of sleep, and presence of snoring and sleep-disordered breathing.

The assessment of sleep complaints begins with a detailed history of sleep habits, including bedtime, sleep-onset, and wake times. A detailed description of the sleep environment can result in a dynamic understanding of the challenges to and resources for achieving normal sleep. The recommended history includes the type of bed, who shares it, the ambient light, noise, temperature, and the bedtime routine. Household structure, routines, and cultural practices may be important and influence the timing and ease of sleep (e.g., parental work patterns, evening activities, number of household members). Dietary practices influence sleep, including timing of meals and caffeine intake. A detailed history assessing for symptoms of OSA (gaspings, snorting noises, breathing pauses, and so on) should be obtained in all children who snore regularly. New-onset sleep disorders may be associated with a psychological trauma. When the history does not reveal the cause of the sleep disorder, a sleep diary can be helpful.

A complete physical examination is important to rule out medical causes of sleep disturbance, such as conditions that cause pain, neurologic conditions that could be associated with seizure disorder, and other central nervous system disorders. Children with genetic syndromes associated with developmental delay may have sleep disorders. Similarly children with attention-deficit/hyperactivity disorder and fetal alcohol syndrome are at higher risk for sleep disorders than other children. Careful attention to the upper airway and pulmonary examination may reveal enlarged tonsils or adenoids or other signs of obstruction.

A polysomnogram is used to detect OSA, excessive limb movements, and seizure disorder. This consists of an all-night observation and recording performed in a sleep laboratory. Polysomnography is not indicated in children with primary insomnia (difficulty initiating or maintaining sleep), circadian rhythm disorders, uncomplicated parasomnias, or behaviorally based sleep problems.

**Differential Diagnosis**

Behavioral insomnia of childhood is divided into two subtypes: Sleep-onset association subtype manifests as frequent or prolonged nighttime awakenings that occur in infants or young children. During periods of normal brief arousal with each sleep cycle, the child awakens under conditions different from those experienced as they fell asleep. Thus they are unable to return to sleep independently. Limit-setting subtype is most common in preschool-aged and older children and is characterized by bedtime resistance or refusal that stems from a caregiver's unwillingness or inability to enforce bedtime rules and expectations. Nighttime fears are also common causes of bedtime refusal.

Parasomnias include sleepwalking, sleep terrors, and confusional arousals. These occur during NREM sleep and are more likely during the first third of the night. They are most common in preschool children and are likely to resolve with time and developmental maturation. Sleepwalking is common and often benign but is sometimes associated with agitation or dangerous behaviors. Sleep terrors consist of an abrupt awakening with a loud scream, agitation, and unresponsiveness to caregivers’ attempts to console. Sleep terrors are differentiated
Children are at increased risk for OSA. In toddlers OSA often is associated with poor growth, which improves when the obstruction is relieved by a tonsillectomy or adenoidectomy. Many children with OSA experience cognitive difficulties and school problems. Hyperactivity is also more common in these children than in age-matched controls.

Primary sleep disorders must be differentiated from sleep disorders associated with psychiatric and medical disorders. Psychoses, anxiety disorders, and substance abuse can present with disordered sleep. The clinician should also consider sleep-related epilepsy and developmental disorders.

**Prevention and Treatment**

Establishing a baseline of healthy sleep habits is essential to both prevention and treatment of sleep disorders at all ages.
These include having a consistent and appropriate bedtime and bedtime routine, and close attention to sleep hygiene (see Table 15-2). A bedtime routine should consist of three or four soothing activities that help calm the child and signal that it is time for sleep. It should last no more than 30 minutes. Activities may include bathing, brushing teeth, reading a story, or singing a song. Even older children and adolescents require a consistent pre-bed routine. A transitional object such as a blanket or stuffed animal can be used to promote positive sleep associations and encourage self-soothing. The bedtime should be set early enough to allow for sufficient nighttime sleep, and both bedtime and morning wake time should be consistent, including on weekends. Televisions and other electronic devices should be removed from the bedroom because these can lead to delayed sleep onset and maladaptive sleep associations.

Sleep-onset association disorder in infancy usually can be prevented by parental understanding of infant sleep physiology, developmentally appropriate expectations, and planning the infant sleep environment to coincide with family needs. It is recommended that infants be put in bed drowsy, but still awake, after they have had a diaper change, food, and comfort. Some toleration of infant crying is required for the infant to achieve self-regulation of sleep. A safe sleep environment is essential. It is important for parents to understand that it is normal for their infant to wake frequently for the first 6 weeks before settling into a routine of waking every 3 to 4 hours for feeding. Infants typically do not sleep through the night before 6 months of age, and some do not sleep through the night before 12 to 18 months of age. Even though co-sleeping (mother and infant sleeping together) is common, it is not recommended because of increased risk of SIDS. Proactively considering the desirability of bed sharing allows parents to be in control rather than ceding control to the young child.

Behavioral interventions comprise the mainstay of treatment for behavioral sleep disorders. In addition to meticulous attention to sleep hygiene and bedtime practices, difficulty falling asleep and bedtime resistance in young children are treated by specific behavioral strategies. Systematic ignoring consists of not responding to a child’s demands for parental attention at bedtime. Unmodified extinction (“cry it out”) involves putting the child to bed and then ignoring the child’s demands until the next morning. Graduated extinction involves waiting successively longer periods of time before briefly checking on the child. Both methods are effective in decreasing bedtime resistance and enabling young children to fall asleep independently. Positive reinforcement strategies can also be used in preschool-aged and older children. These include rewards (e.g., stickers) for meeting a bedtime goal (e.g., staying in bed). Rewards should be provided immediately (first thing in the morning) to increase effectiveness and better link the reward with the positive behavior. Children with nighttime fears can benefit from behavioral therapy aimed at reinforcing feelings of safety.

Infrequent or nonintrusive parasomnias do not need treatment beyond education and reassurance. Ensuring a safe environment is important. Sleep terrors are best managed by minimal intervention, because conversation with the child is impossible during the episode. Anticipatory brief awakening of the child shortly before the typical occurrence of a parasomnia may be effective in aborting the event. Children with frequent or prolonged parasomnias may need a sleep study to evaluate for possible coexisting sleep disorders or nocturnal seizures. Medications that suppress slow-wave sleep may be indicated in severe cases.

Circadian rhythm disorders are also treated by ensuring sleep hygiene practices and gradual resetting of the biologic clock. Bedtime fading involves allowing the child to go to bed at the time he or she naturally feels tired, then gradually advancing the bedtime forward over the course of several weeks. Rarely children with insomnia are treated pharmacologically. Melatonin (dose, 2.5 to 10 mg) has soporific properties useful in treating delayed sleep phase syndrome. It has been used successfully in both children with normal development and those with developmental delays. Melatonin is available without prescription in stores that sell dietary supplements. The α2-agonist clonidine acts preferentially on presynaptic α2 neurons to inhibit noradrenergic activity. Somnolence is a side effect of clonidine, which can be used to treat refractory sleep difficulties; this is an off-label use in children. Clonidine is usually started with a dose of 0.05 mg at bedtime and increased to 0.1 mg if needed. There are data on treating children as young as 4 years old with clonidine. Weaning off clonidine is recommended at the end of treatment.

Complications
The most obvious and serious complication associated with childhood sleep disorders is impairment of cognitive ability and emotional regulation. This impairment puts children at risk for school failure, family difficulties, and social problems. It is likely that sleep-deprived children are at increased risk for acute illness and psychiatric disorders.

Suggested Reading
The somatoform disorders are groups of disorders in which physical symptoms (pain or loss of function) are inconsistent and cannot be explained by a medical condition (Table 16-1). While transient symptoms, as “signals of distress,” are responsible for up to 50% of outpatient visits in the pediatric age group, somatoform disorders represent only the severe end of this continuum. Somatization that occurs in the context of a physical illness is identified by symptoms that go beyond the expected pathophysiology, affecting the child’s school, home life, and peer relationships and becoming the focus of the patient and the family’s life. Somatization is often associated with psychosocial stress and often persists beyond the acute stressor, leading to the belief by the child and the family that the correct medical diagnosis has not yet been found.

A somatization disorder occurs in as many as 10% to 20% of first-degree relatives and has a higher concordance rate in monozygotic twin studies. Lifetime prevalence of somatoform disorders is 3%, and that of subclinical somatoform illness is as high as 10%. Adolescent girls tend to report nearly twice as many functional somatic symptoms as adolescent boys, whereas prior to puberty the ratio is equal.

Affected children are more likely to have difficulty expressing emotional distress, come from families with a history of marital conflict, child maltreatment (including emotional, sexual, physical abuse), or history of physical illness. In early childhood, symptoms often include recurrent abdominal pain (RAP). Later headaches, neurologic symptoms, insomnia, and fatigue are more common.

Explainable medical conditions and a somatoform disorder (e.g., seizures and pseudoseizures) can coexist in up to 50% of patients and present difficult diagnostic dilemmas. The list of systemic medical disorders that could present with unexplained physical symptoms includes chronic fatigue syndrome (CFS), multiple sclerosis, myasthenia gravis, endocrine disorders, chronic systemic infections, vocal cord dysfunction, periodic paralysis, acute intermittent porphyria, fibromyalgia, polymyositis, and other myopathies.

Depression is a common comorbid condition and frequently precedes the somatic symptoms. Anxiety disorders can present with somatic complaints.

DSM-IV classifies somatoform disorders as somatization disorder, undifferentiated somatoform disorder, somatoform disorder not otherwise specified, conversion disorder, pain disorder, body dysmorphic disorder (BDD), and hypochondriasis. The diagnostic criteria for somatoform disorders are established for adults and need additional study in pediatric populations.

Somatization disorder involves multiple unexplained physical complaints, including pain, gastrointestinal, sexual, and pseudoneurologic symptoms not caused by known mechanisms. The criteria used to diagnose this disorder are listed in Table 16-2. Given the requirement for at least one sexual or reproductive symptom, the diagnosis is unusual in children and the onset is common during adolescence. Prevalence estimates range from 0.2% to 2% in females and less than 0.2% in males. Early onset of somatization disorder is associated with poor prognosis.

Undifferentiated somatoform disorder (Table 16-3) includes one or more unexplained physical complaints accompanied by functional impairment that last for at least 6 months. Children and adolescents are more likely to meet DSM-IV criteria for an undifferentiated somatoform disorder than for a somatization disorder, and no evidence exists to predict which patients will go on to develop the full symptom criteria for somatization disorder.

Conversion disorder involves symptoms affecting voluntary motor or sensory function and is suggestive of a neurologic illness in the absence of a disease process (Table 16-4). Adjustment difficulties, recent family stress, unresolved grief reactions, and family psychopathology occur at a high frequency in conversion symptoms. A physical condition and a conversion disorder (e.g., epileptic and nonepileptic seizures) may coexist in the same patient. There are four subtypes of conversion disorder based on whether the symptoms presented are primarily motor, sensory, nonepileptic (seizures), or mixed.

Presenting symptoms follow the psychological stressor by hours to weeks and may cause more distress for others than for the patient. This seeming lack of concern regarding potentially serious symptoms is referred to as la belle indifference.
Table 16-1  Features of Somatoform Disorders of Children and Adolescents

<table>
<thead>
<tr>
<th>PSYCHOPHYSIOLOGIC DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting complaint is a physical symptom.</td>
</tr>
<tr>
<td>Physical symptom is caused by a known physiologic mechanism.</td>
</tr>
<tr>
<td>Physical symptom is stress induced.</td>
</tr>
<tr>
<td>Patient may recognize association between symptom and stress.</td>
</tr>
<tr>
<td>Symptom frequently responds to medication, biofeedback, and stress reduction.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CONVERSION REACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting complaint is physical (loss of function, pain, or both).</td>
</tr>
<tr>
<td>Physical symptom is not caused by a known physiologic mechanism.</td>
</tr>
<tr>
<td>Physical symptom is related to unconscious idea, fantasy, or conflict.</td>
</tr>
<tr>
<td>Patient does not recognize association between symptom and the unconscious.</td>
</tr>
<tr>
<td>Symptom responds slowly to resolution of unconscious factors.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOMATIZATION DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires more than 13 physical symptoms in girls, more than 11 in boys (see Table 16-2)</td>
</tr>
<tr>
<td>Physical symptoms are not caused by a known physiologic or pathologic mechanism.</td>
</tr>
<tr>
<td>Physical symptoms are related to need to maintain the sick role.</td>
</tr>
<tr>
<td>Patient convinced that symptoms are unrelated to psychological factors.</td>
</tr>
<tr>
<td>Symptoms tend to persist or change character despite treatment.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HYPOCHONDRIASIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting complaint is a physical sign or symptom.</td>
</tr>
<tr>
<td>Patient interprets physical symptom to indicate disease.</td>
</tr>
<tr>
<td>Conviction regarding illness may be related to depression or anxiety.</td>
</tr>
<tr>
<td>Symptom does not respond to reassurance.</td>
</tr>
<tr>
<td>Medication directed at underlying psychological problems often helps.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MALINGERING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting complaint is a physical symptom.</td>
</tr>
<tr>
<td>Physical symptom is under voluntary control.</td>
</tr>
<tr>
<td>Physical symptom is used to gain reward (e.g., money, avoidance of military service).</td>
</tr>
<tr>
<td>Patient consciously recognizes symptom as factitious.</td>
</tr>
<tr>
<td>Symptom may not lessen when reward is attained (need to retain reward).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FACTITIOUS DISORDER (AS IN MUNCHHAUSEN SYNDROME)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting complaint is symptom complex mimicking known syndrome.</td>
</tr>
<tr>
<td>Symptom complex is under voluntary control.</td>
</tr>
<tr>
<td>Symptom complex is used to attain medical treatment (including surgery).</td>
</tr>
<tr>
<td>Patient consciously recognizes symptom complex as factitious but is often psychologically disturbed so that unconscious factors also are operating.</td>
</tr>
<tr>
<td>Symptom complex often results in multiple diagnoses and multiple operations.</td>
</tr>
</tbody>
</table>

Table 16-2  Criteria for Diagnosis of Somatization Disorder

Each of the following criteria must be met. Individual symptoms may occur at any time during the course of disturbance.

1. Four pain symptoms: pain related to at least four different sites or functions (e.g., head, abdomen, back, joints, extremities, chest, rectum; during menstruation, sexual intercourse, or urination)

2. Two gastrointestinal symptoms: at least two gastrointestinal symptoms other than pain (e.g., nausea, bloating, vomiting, diarrhea, or intolerance of several foods)

3. One sexual symptom: at least one sexual or reproductive symptom other than pain (e.g., sexual indifference, erectile or ejaculatory dysfunction, irregular menses, excessive menstrual bleeding, vomiting throughout pregnancy)

4. One pseudoneurologic symptom: at least one symptom or deficit suggesting a neurologic condition not limited to pain (conversion symptoms such as impaired coordination or balance, paralysis or localized weakness, difficulty swallowing or lump in throat, aphonia, urinary retention, hallucinations, loss of touch or pain sensation, double vision, blindness, deafness, seizures; dissociative symptoms such as amnesia; or loss of consciousness other than fainting)

Table 16-3  Criteria for Diagnosis of Undifferentiated Somatoform Disorder

A. One or more physical complaints (e.g., fatigue, loss of appetite, gastrointestinal complaints)

B. Either (1) or (2)

1. After appropriate investigation, each of the symptoms is not fully explained by a known general medical condition or the direct effects of a substance (e.g., drug, medication).

2. When there is a related general medical condition, the physical complaints, social or occupational impairment are in excess of what is expected from the history, physical examination, or laboratory findings.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. At least 6 months of disturbance

E. The disturbance is not better accounted for by another mental disorder (e.g., another somatoform disorder, sexual dysfunction, mood disorder, anxiety disorder, sleep disorder, or psychotic disorder).

F. The symptom is not intentionally produced or feigned (factitious disorder, malingering).

Symptoms are often self-limited but may be associated with chronic sequelae, such as contractures or iatrogenic injury.

Falling out syndrome (falling down with altered consciousness) is common in several cultures throughout the world, including the United States. Stocking glove (nonanatomic) anesthesia is another common finding. Symptoms are
often inconsistent; patients may move a paralyzed extremity when they think that no one is watching.

Non-epileptic seizures, sometimes described as pseudoseizures, resemble epileptic seizures but are not associated with the electroencephalographic abnormalities or a clinical course characteristic of true epilepsy. Most cases resolve within 3 months of diagnosis. Referring to nonclassic presentations for seizures as spells can help avoid medicalization of these symptoms.

The course of the condition is often benign, although 20% to 25% of patients experience a recurrence. Good prognostic characteristics include symptoms of paralysis, aphonia, blindness; acute onset; above-average intelligence; presence of an identifiable stressor; and early diagnosis and psychiatric treatment. Poor prognostic characteristics include tremor and pseudoseizures. The rate of misdiagnosis of conversion symptoms averages 4%. Myasthenia gravis, multiple sclerosis, dystonias, and dyskinesias (abnormal movements) are conditions commonly mistaken for the symptoms. Prevalence of obsessive-compulsive disorder (OCD) is four times greater than in the general population. When the belief or preoccupation is limited to an imagined defect in appearance, the diagnosis is body dysmorphic disorder (BDD), not hypochondriasis.

Body dysmorphic disorder is a preoccupation with an imagined or slight defect in physical appearance that causes clinically significant distress or impairment in functioning. It is usually seen in adolescents (the male-to-female ratio being almost equal) and is distinguished from common developmental preoccupations with appearance by the presence of clinically significant distress and/or impairment in functioning. Any bodily area can be a focus, but excessive concerns about the skin (scars and acne) and body shape are common. Because BDD can be associated with shame and the need for secrecy, the diagnosis may be missed unless clinicians ask directly about symptoms. Parents of children with BDD report excessive mirror checking, grooming, attempts to camouflage a particular body area, and reassurance-seeking. Patients may cause self-injury as a consequence of attempts to fix the perceived flaw.

### Table 16-4 Criteria for Diagnosis of Conversion Disorder

| A. | One or more symptoms affect voluntary motor or sensory function, suggesting a neurologic or other general medical condition. |
| B. | Psychological factors are judged to be associated with the symptom or deficit because the initiation or exacerbation is preceded by conflicts or other stressors. |
| C. | The symptom is not intentionally produced or feigned (factitious disorder, malingering). |
| D. | After appropriate investigation, the symptom cannot be fully explained by a general medical condition, by the direct effects of a substance, or as a culturally sanctioned behavior or experience. |
| E. | The symptom causes clinically significant distress or impairment in social, occupational, or other function or warrants medical evaluation. |
| F. | The symptom is not limited to pain or sexual dysfunction, does not occur exclusively during the course of somatization disorder, and is not better accounted for by another mental disorder. |

### Table 16-5 Criteria for Diagnosis of Pain Disorder

| A. | Pain in one or more anatomic sites is the predominant focus and is of sufficient severity to warrant clinical attention. |
| B. | The pain causes clinically significant distress or impairment in social, occupational, or other important functions. |
| C. | Psychological factors have an important role in the onset, severity, exacerbation, or maintenance of the pain. |
| D. | The symptom or deficit is not intentionally produced or feigned (factitious disorder, malingering). |
| E. | The pain is not better accounted for by a mood, anxiety, or psychotic disorder and does not meet criteria for dyspareunia. |

Specify the following:

- Acute: duration <6 months
- Chronic: duration ≥6 months
Many of these patients have had consultations with surgeons and dermatologists and often seek interventions but are unlikely to be satisfied with the results.

BDD is considered to be related to OCD. The prevalence of BDD has been reported to be 0.7% in children, 2% in adolescents, and up to 5% in patients seeking cosmetic surgery. Many individuals with BDD report a history of childhood maltreatment; comorbid psychiatric disorders, including depression, OCD, social phobia, and anorexia nervosa; gender identity disorder; delusional disorder; and narcissistic personality disorder. BDD is also associated with high rates of suicidal ideation and attempts, with 28% of sufferers having attempted suicide.

Fatigue is a common physical complaint, affecting up to 50% of adolescents. CFS specifically refers to a condition characterized by at least 6 months of severe, disabling fatigue associated with self-reported limitations in concentration and short-term memory, sleep disturbance, and musculoskeletal aches and pains, where alternative medical and psychiatric explanations have been excluded. CFS is often associated with depression and can be incapacitating. CFS is rare in childhood and uncommon in adolescence, with prevalence below 1%. Onset typically follows an acute post-viral illness in approximately two thirds of pediatric cases. Treatment is nonspecific, unless a psychological or general medical cause is uncovered.

Screening tools for somatoform disorders include the Children’s Somatization Inventory (child and parent versions) and the Illness Attitude Scales and Soma Assessment Interview (parental interview questionnaires). The Functional Disability Inventory assesses the severity of symptoms.

Treatment for somatoform disorders should use an integrated medical and psychiatric approach. The goals are to identify concurrent psychiatric disorders, rule out concurrent physical disorders, improve overall functioning, and minimize unnecessary invasive tests and doctor shopping. This works when mental health consultation is presented as part of a comprehensive evaluation, thereby minimizing stigma and distrust.

Antidepressant medications (fluoxetine, sertraline, citalopram, and clomipramine) may be of benefit in the treatment of unexplained headaches, fibromyalgia, BDD, somatoform pain, irritable bowel syndrome, and functional gastrointestinal disorders. Tricyclic antidepressants (clomipramine and others) should be avoided in youth with functional abdominal pain (FAP) because they have no proven efficacy in either pain management or mood disorders and are very dangerous in overdose. In chronic fatigue syndrome with comorbid depression and anxiety, a more activating antidepressant, like bupropion, can be useful. Stimulants may also be helpful in CFS.

Cognitive-behavioral methods, which reward health-promoting behaviors and discourage disability and illness behaviors, help in the treatment of recurrent pain, CFS, fibromyalgia, and FAP. Interpersonal and expressive psychotherapies in the presence of psychological trauma are particularly useful. Self-management strategies, such as self-monitoring, relaxation, hypnosis, and biofeedback, provide some symptomatic relief and encourage more active coping strategies. Family therapy and family-based interventions can be very useful. Home schooling should be avoided, and school attendance and performance should be emphasized as important indicators of appropriate functioning. In dealing with pain symptoms (e.g., headaches, stomachaches) parents should remove or limit attention for pain behavior; strongly encourage sticking to schedule (e.g., going to school); help the child identify stress at home and school; provide attention and special activities on days when child does not have symptoms; and limit activities and interactions on sick days. Discussions about excessive discomfort or illness should be replaced with having the child practice relaxation techniques and educating personnel working with their child about these approaches.

**FACTITIOUS DISORDERS AND MALINGERING**

In contrast to somatoform disorders, patients intentionally simulate or create their problems in factitious disorders and malingering.

**Factitious disorder** is a condition in which physical or psychological symptoms are produced intentionally but for unconscious reasons to assume a sick role. This diagnosis is made either by direct observation or by eliminating other possible causes. Most patients are immature, passive, and hypochondriacal. They show improvement when confronted with their behavior or acknowledge the factitious nature of their symptoms. It has been associated with borderline personality traits and substance abuse disorders. Approximate answers (e.g., 20−3=13) reported during a mental status examination are most commonly found in factitious disorders.

**Munchausen syndrome by proxy (MBP)** is a form of factitious disorder by proxy, where a parent (usually mother) mimics symptoms in his or her child. The motivation is believed to be a psychological need to assume a sick role through the child. Of these mothers, more than 72% have a history of factitious disorder or a somatoform disorder, and up to 80% of involved parents have some health care background. MBP is a type of child abuse. Boys are more commonly abused in this way, and neonates and preschoolers are the most common victims. Both factitious disorder by proxy (diagnosis of the abuser) and pediatric condition falsification (diagnosis of the child) are needed for diagnosis.

Common presenting symptoms include vomiting, diarrhea, respiratory arrest, asthma, seizures, incoordination, fever, bleeding, failure to thrive, rash, hypoglycemia, and loss of consciousness. Simulation of psychiatric disorders is rare. Nearly 75% of the morbidity to the child occurs in hospitals from invasive procedures. Once confronted with negative test results or discharge planning, the perpetrators may become intensely enraged and acutely suicidal or may initiate legal action so the treatment team should take appropriate precautions. Mortality in MBP may be as high as 33%, and siblings of these children are also at risk. Virtually all children suffer serious psychological sequelae from this form of abuse. Treatment involves protecting the child from further abuse and reporting to child protective services.

**Malingering** is a condition in which a physical symptom that is under voluntary control is used to gain reward (e.g., money or avoidance of school, jail, or obtaining drugs). The patient has conscious intent in production of symptoms. Symptoms may not lessen when the reward is attained. Malingering is difficult to prove unless the patient is directly observed or confesses.
ANXIETY AND PHOBIAS

ANXIETY DISORDERS
Anxiety disorders are characterized by uneasiness, excessive rumination, and apprehension about the future. The conditions tend to be chronic, recurring, and vary in intensity over time. They affect 5% to 10% of children and adolescents (Table 17-1). Some common anxiety disorders are discussed in the following sections.

Panic disorder is the presence of recurrent, unexpected panic attacks. A panic attack is a sudden unexpected onset of intense fear associated with a feeling of impending doom in the absence of real danger. At least 1 month of persistent worrying about having another panic attack is required to make the diagnosis (Table 17-2). Panic disorder most often begins in adolescence or early adulthood. Symptom severity waxes and wanes. Characteristic symptoms include shortness of breath, palpitations, chest pain, a choking or smothering sensation, and a fear of losing control or going “crazy” (Table 17-3). Symptoms generally last approximately 15 minutes and are generally time-limited. It is common for patients to think that they are about to die of a heart attack. Panic attacks are classified as (1) spontaneous, (2) bound to situations (occur immediately on exposure), and (3) predisposed to situations (attacks occur while at school, but not every time). Agoraphobia is a condition describing fear of situations where escape is difficult or would draw unwanted attention to the person. Agoraphobia is often persistent and can leave people home-bound. Panic disorder is seen in 95% of patients with agoraphobia. The condition is more common in females. Consider the diagnosis of a specific phobia (as opposed to agoraphobia) if the avoidance is limited to one or a few specific situations or social phobia if avoidance is limited to social situations in general.

Generalized anxiety disorder (GAD) is characterized by 6 or more months of persistent, out of proportion worry and anxiety that includes a historical diagnosis of overanxious disorder of childhood. The worries should be multiple, not paroxysmal, and not focused on a single theme and should cause significant impairment (Table 17-4). The anxiety must be accompanied by at least three of the following symptoms: restlessness, easy fatigability, difficulty concentrating, irritability, muscle tension, and disturbed sleep. Physical signs of anxiety are often present,

<table>
<thead>
<tr>
<th>Table 17-1</th>
<th>Common Anxiety Disorders: Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEATURE</strong></td>
<td><strong>PANIC DISORDER</strong></td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Prevalence is 0.2%–10%; rates are similar in all racial groups. Half have agoraphobia.</td>
</tr>
<tr>
<td>Onset</td>
<td>Average age at onset is 15–19 years; earlier in 25%.</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Anxiety disorder due to a general medical condition. Substance-induced anxiety disorder due to caffeine or other stimulants.</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Separation anxiety disorder (common). Substance abuse, major depression, obsessive-compulsive disorder (OCD), and other anxiety disorders. Asthma patients have a high incidence of panic attacks.</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Frequently chronic with a relative high rate of suicide attempts and completions.</td>
</tr>
</tbody>
</table>

ADHD, Attention-deficit/hyperactivity disorder, PTSD, posttraumatic stress disorder.
including shakiness, trembling, and myalgias. Gastrointestinal symptoms (nausea, vomiting, diarrhea) and autonomic symptoms (tachycardia, shortness of breath) commonly coexist. In children and adolescents, the specific symptoms of autonomic arousal are less prominent, and symptoms are often related to school performance or sports. Children with GAD are often exceedingly self-conscious, exhibit behavioral inhibition, have low self-esteem, and have more sleep disturbance than patients with other kinds of anxiety disorder. Care must be taken to elicit internalizing symptoms of negative cognitions about the self (hopelessness, helplessness, worthless, suicidal ideation), as well as those concerning relationships (embarrassment, self-consciousness) and associated with anxieties. Inquiries about eating, weight, energy, and interests should also be carried out to eliminate a mood disorder.

**Posttraumatic stress disorder (PTSD)** is characterized by re-experiencing a traumatic event in which actual or threatened death or serious injury was possible. The reexperiencing of trauma is characterized in children by the sudden intrusive events seen in adults, and complaint of anticipation of unwanted visual imagery increases the risk of PTSD. Presentation often depends on the age group of the child. In preverbal children, there are changes in behavior: regressed clingy behaviour, increased aggression, unwillingness to explore the environment, alterations in feeding, sleeping behaviors, and difficulty soothing. Preschool children may display rapidly changing emotional states like anger, sadness, and excitement and play. Dissociative states lasting a few seconds to many hours, in which four or more of the following symptoms developed abruptly and reached a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control or going crazy; and paresthesias (numbness or tingling sensations). Chills or hot flashes is accompanied by avoidance of stimuli that remind the person of the trauma and by autonomic hyperarousal (Table 17-5). Type, severity, duration, and proximity of the traumatic event are the most likely predictors of PTSD. Presentation often depends on the age group of the child. In preverbal children, there are changes in behavior: regressed clingy behavior, increased aggression, unwillingness to explore the environment, alterations in feeding, sleeping behaviors, and difficulty soothing. Preschool children may display rapidly changing emotional states like anger, sadness, and excitement and play. Dissociative states lasting a few seconds to many hours, in which four or more of the following symptoms developed abruptly and reached a peak within 10 minutes: palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, lightheaded, or faint; derealization (feelings of unreality) or depersonalization (being detached from oneself); fear of losing control or going crazy; and paresthesias (numbness or tingling sensations). Chills or hot flashes

### Table 17-2 Criteria for Diagnosis of a Panic Disorder

<table>
<thead>
<tr>
<th>A. Both (1) and (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Recurrent unexpected panic attacks</td>
</tr>
<tr>
<td>2. At least one attack is followed by ≥1 month of one or more of the following:</td>
</tr>
<tr>
<td>a. Persistent concern about having additional attacks</td>
</tr>
<tr>
<td>b. Worry about the implications of the attack or its consequences (e.g., losing control, having a heart attack, “going crazy”)</td>
</tr>
<tr>
<td>c. A significant change in behavior related to the attacks</td>
</tr>
<tr>
<td>B. The presence of agoraphobia</td>
</tr>
<tr>
<td>C. The panic attacks are not due to direct physiologic effects of drugs or abuse or medication or a general medical condition (e.g., hyperthyroidism)</td>
</tr>
<tr>
<td>D. The panic attacks are not better accounted for by another mental disorder, such as social phobia, specific phobia, obsessive-compulsive disorder, posttraumatic stress disorder, or separation anxiety disorder.</td>
</tr>
</tbody>
</table>

### Table 17-3 Criteria for Diagnosis of a Panic Attack

A discrete period of intense fear or discomfort, in which four or more of the following symptoms developed abruptly and reached a peak within 10 minutes:

- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, lightheaded, or faint
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- Fear of losing control or going crazy
- Paresthesias (numbness or tingling sensations)
- Chills or hot flashes

### Table 17-4 Criteria for Diagnosis of Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about numerous events or activities.

B. The person finds it difficult to control the worry.

C. The anxiety and worry are associated with three or more of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months): Note: Only one symptom is required in children.

1. Restlessness or feeling keyed up or on edge
2. Being easily fatigued
3. Difficulty concentrating or mind going blank
4. Irritability
5. Muscle tension
6. Sleep disturbance (difficulty falling or staying asleep or restless, unsatisfying sleep)

D. The focus of the anxiety and worry is not confined to features of a disorder (e.g., panic disorder, social phobia, obsessive-compulsive disorder, separation anxiety disorder, anorexia nervosa, somatization disorder, hypochondriasis), and the anxiety and worry do not occur exclusively during posttraumatic stress disorder.

E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

F. The disturbance is not due to the direct physiologic effects of a drug or a general medical condition (e.g., hyperthyroidism) and does not occur exclusively during a mood disorder, a psychotic disorder, or a pervasive developmental disorder.
A. The person has been exposed to a traumatic event in which both of the following were present:

1. The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury or a threat to the physical integrity of self or others.

2. The person’s response involved intense fear, helplessness, or horror. Note: In children, this may be expressed instead by disorganized or agitated behavior.

B. The traumatic event is persistently reexperienced in one or more of the following ways:

1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: In young children, repetitive play may occur in which themes or aspects of the trauma are expressed.

2. Recurrent distressing dreams of the event. Note: In children, there may be frightening dreams without recognizable content.

3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including flashbacks that occur on awakening or when intoxicated). Note: In young children, trauma-specific re-enactment may occur.

4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

5. Physiologic reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three or more of the following:

1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma.

2. Efforts to avoid activities, places, or people that arouse recollections of the trauma.

3. Inability to recall an important aspect of the trauma.

4. Markedly diminished interest or participation in significant activities.

5. Feeling of detachment or estrangement from others.

6. Restricted range of affect (e.g., unable to have loving feelings).

7. Sense of a foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span).

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two or more of the following:

1. Difficulty falling or staying asleep.

2. Irritability or outbursts of anger.

3. Difficulty concentrating.

4. Hypervigilance.

5. Exaggerated startle response.

E. Duration of the disturbance (symptoms in criteria B, C, and D) is >1 month.

F. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify the following:

- Acute: if duration of symptoms is <3 months
- Chronic: if duration of symptoms is ≥3 months
- With delayed onset: if onset of symptoms is at least 6 mo after the stressor.
In the management of anxiety disorders, likely medical conditions, including hyperthyroidism, medication side effects, substance abuse, or other medical conditions, should be ruled out. The patient should be screened for comorbid psychiatric disorders, such as mood disorders, psychosis, eating disorders, tic disorders, and disruptive behavior disorders. A history from multiple sources is important because the child may be unable to effectively communicate symptoms. A detailed history that includes the nature of the anxiety triggers; psychosocial history; and family history of tics, anxiety disorders, depression, and other mood disorders should be taken. The younger child may better communicate his or her anxieties through drawings or play.

Treatment consists of psychotherapy and psychopharmacology. For mild to moderate anxiety, evidence-based psychotherapies and psychoeducation should be used first. Combined therapy usually has better efficacy than psychotherapy and psychopharmacology alone. Cognitive and behavioral therapy (including systematic desensitization, exposure, operant conditioning, modeling, and cognitive restructuring) can be beneficial in a variety of anxiety disorders. Patients with anxiety disorders are often less tolerant of medication side effects, and supportive therapy helps them maintain treatment regimens.

Family and individual psychotherapy and care coordination with a patient’s school is helpful. Reassurance that the patient does not have a life-threatening illness is important. Other psychosocial treatments include stress management, supportive therapies, and biofeedback. Emphasis is placed on decreasing morbidity through proper treatment. Panic disorder tends to be chronic but usually is responsive to treatment. In PTSD trauma-focused cognitive behavioral therapy has shown efficacy. Critical-incident stress debriefing and “psychological first aid,” soon after the event, greatly reduce distress and involve discussing the nature and impact of the trauma event in a group format.

Selective serotonin reuptake inhibitors (SSRIs) are the medication of choice. The SSRIs approved for children by the U.S. Food and Drug Administration (FDA) are fluoxetine, sertraline, and fluvoxamine. They can initially exacerbate anxiety or even panic symptoms. Clomipramine requires electrocardiographic and blood level monitoring but may be effective and is approved by the FDA for obsessive-compulsive disorder. Tricyclic antidepressants have also shown efficacy. Benzodiazepines (alprazolam and clonazepam) include a risk of causing disinhibition in children. Alpha-2a-agonists (guanfacine and...
DEPRESSION AND BIPOLAR DISORDERS

DEPRESSION

Major depressive disorder (MDD) requires a minimum of 2 weeks of symptoms, including either depressed mood or loss of interest or pleasure in nearly all activities. Four additional symptoms must also be present (Table 18-1). In children and adolescents, a new onset of irritability, restlessness, or boredom may be seen instead of depressed mood. A sudden drop in grades is often present. A change in appetite (usually decreased but can be increased) with carbohydrate craving with or without accompanying weight changes and sleep disturbance along with somatic complaints (fatigue, vague aches and pains) may also be present. Psychotic symptoms, seen in severe cases of major depression, are generally mood-congruent (e.g., derogatory auditory hallucinations, guilt associated delusional thinking). Suicidal thoughts and attempts are common and should be evaluated.

The prevalence of MDD in prepubertal children is 2% with 1:1 female-to-male ratio; in adolescents the prevalence is 6% to 8%, with a female-to-male ratio of 2:1 (similar to adults). If untreated, major depression can become chronic in 10% of patients.

Depression has a clear genetic predisposition, with family history as the strongest single factor for developing MDD. Twin studies show 40% to 65% heritability for depression. Family studies show a twofold to fourfold increased risk for depression in offspring of depressed parents. Other potential responsible factors for depression include dysregulation of central serotonergic and/or noradrenergic systems, hypothalamic-pituitary-adrenal axis dysfunction, and the influence of pubertal sex hormones. The stress-diathesis model relates to the interaction of genes and environment; for example, a less functional genetic variant of the serotonin receptor in presence of stressful life events could contribute to depression.

Dysthymic disorder disorder and anxiety disorders (prevalence 30% and 80%, respectively), substance abuse (20% to 30%), and disruptive behavior disorders (10% to 20%) are frequent comorbid disorders in depressed children and adolescents. Twenty percent of patients diagnosed with depression develop bipolar disorder (BD); this is more common in cases with a family history of mania or concurrent psychotic features.

The differential diagnoses for MDD are diverse and many. It is always prudent to rule out mood disorder due to a general medical condition or substance-induced mood disorders before considering MDD. Schizophrenia in its initial stages and the dysphoria related to untreated attention-deficit/hyperactivity disorder (ADHD) may also be mistakenly diagnosed as depression. Hypothyroidism, anemia, diabetes, and folate and B12 vitamin deficiencies need to be ruled out.

Dysthymic disorder (prevalence rate 0.6% to 1.7%) is a chronic, milder form of depression characterized by a depressed or irritable mood (subjectively or described by others) present for at least 1 year. Two of the following symptoms

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<table>
<thead>
<tr>
<th>Table 18-1 Criteria for Diagnosis of a Major Depressive Episode</th>
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</thead>
<tbody>
<tr>
<td>A. Five or more of the following symptoms present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Note: Do not include symptoms that are clearly due to a general medical condition or mood-incongruent delusions or hallucinations.</td>
</tr>
<tr>
<td>1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, mood can be irritable.</td>
</tr>
<tr>
<td>2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation by others).</td>
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<tr>
<td>3. Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.</td>
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<tr>
<td>4. Insomnia or hypersomnia nearly every day.</td>
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<tr>
<td>5. Psychomotor agitation or retardation nearly every day (observable by others).</td>
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<tr>
<td>6. Fatigue or loss of energy nearly every day.</td>
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<tr>
<td>7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not self-reproach or guilt about being sick).</td>
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<tr>
<td>8. Diminished ability to think, concentrate, or be decisive nearly every day (subjective account or as observed by others).</td>
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<tr>
<td>9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, a suicide attempt or a specific plan for committing suicide.</td>
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<tr>
<td>B. The symptoms do not meet criteria for a mixed manic episode.</td>
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<tr>
<td>C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.</td>
</tr>
<tr>
<td>D. The symptoms are not due to the direct physiologic effects of a drug or abuse, a medication, or a general medical condition (e.g., hypothyroidism).</td>
</tr>
<tr>
<td>E. The symptoms are not better accounted for by bereavement, and the symptoms persist &gt;2 mo or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.</td>
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</tbody>
</table>
are also required: changes in appetite; sleep difficulty, fatigue; low self-esteem; poor concentration or difficulty with making decisions; and feelings of hopelessness. About 70% of children and adolescents with dysthyemic disorder eventually develop major depression. The development of MDD after dysthymia is often referred to as double depression.

Atypical depression is MDD characterized by hypersomnia, increased appetite with carbohydrate craving, weight gain, interpersonal rejection sensitivity, and mood reactivity.

Adjustment disorder with depressed mood is the most common depressive disorder in children and adolescents. Symptoms start within 3 months of an identifiable stressor (e.g., loss of a relationship), with distress in excess of what would be expected and interference with social, occupational, or school functioning. Symptoms should not meet criteria for another psychiatric disorder, should not be caused by bereavement, and should not last longer than 6 months after the stressor has stopped.

Seasonal affective disorder is a condition common in northern or extreme southern latitudes, in which depressive symptoms occur in the late fall and early winter when the hours of daylight are shortening.

Depressive disorder not otherwise specified is a diagnosis used when patients have functionally impairing depressive symptoms that do not meet criteria for another condition.

Treatment of depression involves psychopharmacy and psychotherapy. First line antidepressant selective serotonin reuptake inhibitors (SSRIs) have response rates of 50% to 70% despite high-placebo response rate. Fluoxetine is the only agent approved by the U.S. Food and Drug Administration (FDA) for treatment of youth. Citalopram, escitalopram, paroxetine, and venlafaxine have positive clinical trial results as well. An antidepressant should be given an adequate trial (6 weeks at therapeutic doses) before switching or discontinuing unless there are serious side effects. For a first episode of depression in children and adolescents, treatment for 6 to 9 months after remission of symptoms is recommended. Patients with recurrent or chronic depression may need to take antidepressants for extended periods (years or even a lifetime). If a patient does not respond to adequate trials of two or more antidepressants, a child psychiatrist should be consulted. The psychiatrist’s evaluation should focus on diagnostic clarity and psychosocial issues that might be preventing a full response. The psychiatrist may use augmentation strategies that may include lithium, thyroid hormone, lamotrigine, or bupropion.

For acute depression, more frequent visits are indicated, and the risks of medication (including suicidal and self-destructive behavior) should be discussed with parents, guardians, and patients. Higher frequency of monitoring can include phone calls or collaborative care with a psychotherapist. Parents and patients should also be educated about warning signs and to call immediately if these new symptoms occur. Notable side effects are thoughts of suicide, increased agitation, or restlessness. Other side effects include headache, dizziness, gastrointestinal symptoms, sleep cycle disturbance, sexual dysfunction, akathisia, serotonin syndrome, and risk of increased bruising (due to platelet inhibition.) There is also a risk of SSRIs-induced mania.

In 2004 the FDA issued warnings for all antidepressants regarding suicidal thinking or behavior. The data suggest that antidepressants pose a 4% risk, versus a 2% risk in placebo. An increase in suicides in children and adolescents since that year has many experts believing that it might be related to low prescription of antidepressants and resultant untreated depression. Substance use, concomitant conduct problems, and impulsivity increase the risk of suicide.

Psychotherapy appears to have good efficacy in mild to moderate depression. In moderate to severe depression, combined treatment with psychotherapy and medication has the greatest rate of response, although in severe cases the efficacy was equivalent to medication alone. Cognitive-behavioral therapy and interpersonal therapies are the empirically supported psychotherapies. Cognitive behavioral therapy and its derivative, dialectic behavioral therapy (for borderline personality disorder), involve techniques and skills-building to mitigate cognitive distortions and maladaptive processing; whereas interpersonal therapy focuses on collaborative decisions between the therapist and patient and is based on the exploration and recognition of precipitants of depression. Family therapy is often used as an adjunct to other treatments for depression.

Light therapy has been shown to be beneficial for seasonal affective disorder and in MDD with a seasonal component. Electroconvulsive therapy is used in refractory and life-threatening depression.

Depression is a chronic and debilitating illness that often starts in childhood or adolescence. It increases risk for future suicide, substance use, and other psychiatric sequelae. Adolescent depressive disorders are more likely to be recurrent into adulthood than childhood onset depression.

Suicide is a fatal complication of MDD and surpasses motor vehicle accidents as a cause of death in adolescents. It has high prevalence among high school students with 20% having contemplated suicide and 8% having attempted each year. While the risk of suicide during an MDD episode is high, it can be paradoxically higher during start of treatment as energy and motivation improve with cognitive recovery from depression.

Treatment is targeted toward decreasing morbidity and suicide. Along with treatments mentioned previously, modalities such as hospitalization, partial hospital, therapeutic after-school programs, or psychoeducation may be needed.

BIPOLAR DISORDERS

Bipolar disorder consists of distinct periods of mania (elevated, expansive, or irritable moods and distractibility) that may alternate with periods of severe depression (Table 18-2).

To diagnose mania associated with BD, euphoria (elevated or expansive mood) and three additional symptoms; or irritability and four additional manic symptoms are required. Children and adolescents with euphoric mood are bubbly, giggly, and “over-the-top” happy, to a degree that is socially unacceptable to others. Grandiosity in children is often dramatic. Children act as if they are superior even when it is obvious that it is not true, and they behave as if the laws of nature do not apply to them. Racing thoughts are common in BD. Periods of extreme rage also are common. Children with BD often present with rapid or ultra-rapid cycling with multiple shifts between euthymia, mania, and depression.

A decreased need for sleep is a hallmark of mania. There are no other diagnoses where a child has a greatly decreased amount of total sleep (compared with age-appropriate norms) and is not fatigued. Sleep deprivation, substance abuse, and antidepressants may trigger mania. BD onset often begins with an episode of depression. It is estimated that 33% of youth will develop BD
Table 18-2 | Mania Symptoms

<table>
<thead>
<tr>
<th>Mania Symptoms</th>
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<tbody>
<tr>
<td>A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)</td>
</tr>
<tr>
<td>B. During the period of mood disturbance, three or more of the following symptoms have persisted (four if the mood is only irritability) and are present to a significant degree:</td>
</tr>
<tr>
<td>1. Inflated self-esteem or grandiosity</td>
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<tr>
<td>2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)</td>
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<tr>
<td>3. More talkative than usual or pressure to keep talking</td>
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<tr>
<td>4. Flight of ideas or subjective experience that thoughts are racing</td>
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<tr>
<td>5. Distractibility (i.e., easily drawn to unimportant or irrelevant external stimuli)</td>
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<tr>
<td>6. Increased goal-directed activity (socially, at work or school, or sexually) or psychomotor agitation</td>
</tr>
<tr>
<td>C. Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., unrestrained buying sprees, sexual indiscretions, or foolish investments)</td>
</tr>
<tr>
<td>D. The symptoms do not meet criteria for a mixed episode.</td>
</tr>
<tr>
<td>E. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning, usual social activities or relationships with others or to necessitate hospitalization to prevent harm to self or others, or with psychotic features.</td>
</tr>
<tr>
<td>F. The symptoms are not due to the direct physiologic effects of a substance or a general medical condition. Note: Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy) should not count toward a diagnosis of bipolar I disorder.</td>
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</table>

Within 5 years of a depressive episode. Features associated with switching include early-onset depression, psychomotor retardation, psychosis, mood lability, seasonal pattern, family history of BD or mood disorders, and antidepressant-induced hypomania. A mixed episode requires 1 week of symptoms of both a manic and major depressive episode. Dysphoric mania is another term used to describe periods of mania that are accompanied by “bad feelings.” Hypomania is used to describe a period of more than 4 but fewer than 7 days of manic symptoms. It also is used less specifically to describe less intense mania. The prevalence of psychosis in adolescence (often auditory hallucinations) is 16% to 60%. Although high, it is still less than its prevalence in adult BD.

Bipolar II disorder includes at least one full major depressive episode and at least one period of hypomania. Bipolar disorder not otherwise specified is used to describe prominent symptoms of BD that do not meet full diagnostic criteria or when historical information is unclear.

Cyclothymic disorder is characterized by 2 years or more (1 year in children) of numerous periods of hypomania and depression that do not meet full criteria for either a manic or a major depressive episode.

BD occurs in up to 4% of the general population. It is estimated that 1% of children and adolescents meet diagnostic criteria for BD. According to retrospective studies, 60% of BD onset occurs before 20 years of age. Although BD in adults tends to be gender neutral, it is estimated that prepubertal BD is almost four times more frequently diagnosed in boys. This may be because aggression is the main reason for referral for psychiatric services.

The etiology of BD is multifactorial. Studies in BD point to a highly familial etiology with family history of mental illness, including major depression, BD, schizophrenia, or ADHD. A first-degree relative with BD leads to a 10-fold increase in a child’s chance of developing BD. An earlier onset of BD in a parent increases the risk of early onset BD in offspring with a more chronic and debilitating course that may be less responsive to treatment.

The differential diagnosis for BD includes ADHD, major depression, conduct disorder (CD), mood disorder due to a general medical condition, substance-induced mood disorder, pervasive developmental disorder, and schizophrenia.

Patients with BD often have concurrent conditions that warrant treatment. ADHD occurs in approximately 60% to 90% of children with BD. Anxiety disorders also commonly occur with BD and do not respond to antimanic agents. Substance abuse can precipitate and perpetuate mania and depression. The alteration between highs and lows related to some types of substance abuse often mimics BD. Patients with BD may also self-medicate in attempts to alleviate symptoms. Many patients with BD may commit crimes and meet criteria for CD due to aggression and impulsivity. Prominent symptoms of mania assist in differentiating between CD and BD. Patients with BD generally exhibit reactive aggression, whereas those with CD are more likely to preplan and develop a typical pattern of crimes.

No laboratory or imaging studies can diagnose BD. Physical examination, careful history, review of systems, and laboratory testing are done to rule out suspected medical etiologies, including neurologic and substance-induced disorders.

Treatment of BD includes decreasing acute symptoms. The FDA has approved lithium, divalproex sodium, carbamazepine, olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole for adults with BD. Lithium is the oldest proven treatment for mania in adults and has been used effectively in children and adolescents for years. Common side effects of lithium include hypothyroidism, polyuria, and acne. Divalproex is also a first-line agent (preferable for mixed or rapid cycling cases) for adults. It has been used effectively for decades in youth, but it is not FDA-approved. Periodic monitoring of blood levels for select medications (lithium and divalproex sodium) can help ensure both treatment safety and the receipt of therapeutic amounts of the medication. Antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone) have had positive results in youth with BD. It is likely that newer antipsychotics will also be effective in BD.

Treating comorbid psychiatric disorders must be done carefully. Stimulants may be used to treat ADHD once the patient has been stabilized on a mood stabilizer. Antidepressants should be avoided; if the youth is depressed or has significant anxiety and is not responsive to other pharmacotherapy, cautious use of antidepressants may be necessary. Careful monitoring for manic reactivation, cycling, and suicidality is needed.

Cognitive and behavioral therapies are aimed at improving adherence to medication treatments and ameliorating anxiety and depressive symptoms. Psychoeducation and family therapy are needed to stabilize the patient’s environment and improve prognosis. There should be continuous ongoing safety assessment. Because developmental delays are also common in young children with BD due to poor learning while symptomatic, collaboration with school regarding behavioral management, special educational needs, and an appropriate individualized educational plan is also needed.
OBSESSIVE-COMPULSIVE DISORDER

Obsessive-compulsive disorder (OCD) is characterized by obsessions, compulsions, or both, in the absence of another psychiatric disorder that better explains the symptoms (Table 19-1). Obsessions are persistent intrusive thoughts, images, or impulses. Compulsions are non-gratifying repeated behaviors aimed at reducing or preventing distress or anxiety. Usually the compulsions are performed to offset anxiety created by the obsessions. In children, due to low level of insight, rituals or compulsive symptoms may predominate over worries or obsessions. Symptoms are usually recognized as being excessive or unreasonable. Common examples of obsessions in children are fears of contamination, repeated doubts, need for orderliness, and aggressive or horrific impulses. Common compulsions are hand washing, ordering, checking, requesting or demanding reassurance, praying, counting, repeating words silently, and hoarding.

Prevalence of OCD in children and adolescents ranges from 1% to 4%, increasing with age. It is more common in boys at a younger age and in girls during adolescence.

At least 50% of youth with OCD have at least one other psychiatric illness. Psychiatric comorbidities include tics (20% to 30%), mood and anxiety disorders (up to 75%), disruptive behavior disorders (attention-deficit/hyperactivity disorder [ADHD] and oppositional defiant disorder), developmental disorders, body dysmorphic disorder, hypochondriasis, and obsessive-compulsive personality disorder.

Twin studies suggest that obsessive-compulsive symptoms are moderately heritable, with genetic factors accounting for 45% to 65% of variance. Strepococcal infection causing inflammation in the basal ganglia may account for 10% of childhood-onset OCD and is a part of a condition referred to as pediatric autoimmune neuro-psychiatric disorders associated with streptococcal (also known as PANDAS) infection. Antistreptolysin O, antistreptococcal DNAase B titers, and a throat culture assist in diagnosing a group A beta-hemolytic streptococcal infection. Early antibiotic therapy may help treat these cases.

OCD has been linked to a disruption in the brain's serotonin, glutamate, and dopamine systems. Overactivity in neural pathways involving orbital frontal cortex and the caudate nucleus has been implicated in OCD.

Physical examination may reveal rough, cracked skin as evidence of excessive hand washing. The Yale-Brown Obsessive-Compulsive Scale (also known as Y-BOCS) is regarded as the gold standard measure of obsessive-compulsive symptom severity. Although somewhat lengthy, it can be helpful in the clinical setting.

Cognitive-behavioral therapy (CBT) involving exposure and response prevention is considered the treatment of choice in milder cases. CBT provides durability of symptom reduction and response prevention is considered the treatment of choice in milder cases. CBT provides durability of symptom relief and avoidance of potential pharmacotherapy-associated side effects. As with other anxiety disorders, CBT is at least

<table>
<thead>
<tr>
<th>Table 19-1</th>
<th>Criteria for Diagnosis of Obsessive-Compulsive Disorder</th>
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<tbody>
<tr>
<td>A. Either obsessions or compulsions</td>
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</tr>
<tr>
<td>Obsessions are defined by (1), (2), (3), and (4).</td>
<td></td>
</tr>
<tr>
<td>1. Recurrent and persistent thoughts, impulses, or images experienced at some time during the disturbance as intrusive and inappropriate and causing marked anxiety or distress</td>
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<tr>
<td>2. Thoughts, impulses, or images are not simply excessive worries about real-life problems.</td>
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<tr>
<td>3. The person attempts to ignore or suppress such thoughts, impulses, or images or to neutralize them with some other thought or action.</td>
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<tr>
<td>4. The person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion).</td>
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</tr>
<tr>
<td>Compulsions are defined by (1) and (2).</td>
<td></td>
</tr>
<tr>
<td>1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession or according to rigidly applied rules.</td>
<td></td>
</tr>
<tr>
<td>2. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts are not unrealistically connected with what they are designed to neutralize/prevent or are clearly excessive.</td>
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<tr>
<td>B. At some point, the person recognizes that the obsessions or compulsions are excessive or unreasonable. Note: This is not required for children.</td>
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<tr>
<td>C. The obsessions or compulsions cause marked distress; are time-consuming (taking &gt;1 hour a day); or significantly interfere with a normal routine, occupational (or academic) functioning, or usual social activities or relationships.</td>
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<tr>
<td>D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an eating disorder).</td>
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<tr>
<td>E. The disturbance is not due to the direct physiologic effects of a drug of abuse, a medication, or a general medical condition.</td>
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<tr>
<td>Specify the following:</td>
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<tr>
<td>With poor insight: if, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable</td>
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</table>
Pervasive developmental disorders, also known as autism spectrum disorders (ASDs), consist of five disorders: autism, Asperger syndrome, childhood disintegrative disorder, Rett syndrome, and pervasive developmental disorder not otherwise specified.

Autism

Asperger syndrome, childhood disintegrative disorder, Rett syndrome, consist of five disorders: autism, Pervasive developmental disorders, also known as psychoses.

Chapter 20 Pervasive Developmental Disorders and Psychoses

Onset of these disorders is in infancy and preschool years. Hallmarks of these disorders include impaired communication and impaired social interaction as well as stereotypic behaviors, interests, and activities. Mental retardation is common, with a few children showing remarkable isolated abilities (savant or splinter skills).

ASDs are seen in less than 1% of the population with equal prevalence among all racial and ethnic groups. The prevalence is greater in boys (except for Rett syndrome), but girls with the disorders tend to be more severely affected.

Differentiating features of the pervasive developmental disorders are listed in Table 20-1.

Treatment of ASD is symptomatic and multimodal. At present there are no treatments for the core symptoms of ASDs. Antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, paliperidone, haloperidol, thioridazine) are used for aggression, agitation, irritability, hyperactivity, and self-injurious behavior. Anticonvulsants and lithium can be used for aggression. Naltrexone has been used to decrease self-injurious behavior, presumably by blocking endogenous opioids. Selective serotonin reuptake inhibitors are given for anxiety, perseveration, compulsions, depression, and social isolation. Stimulants are useful for hyperactivity and inattention (better response with Asperger syndrome). There are reports of significant worsening of irritability and aggression in some patients treated with stimulants. Alpha-2 agonists (guanfacine, clonidine) are used for hyperactivity, aggression, and sleep dysregulation, although melatonin is first-line medication for sleep dysregulation. Behavioral management training for parents is useful in teaching protocols to help their child learn appropriate behavior. Special educational services should be individualized for the child. Occupational, speech, and physical therapy are often required. Referral for disability services and support is often warranted. Potentially useful therapies tailored to the individual include applied behavioral analysis, discrete trial training, and structured teaching. There is a need for family support groups and individual supportive counseling for parents. The prognosis for autism is guarded. There are no known methods of primary prevention. Treatment and educational interventions are aimed at decreasing morbidity and maximizing function.

Autism

Autism, the prototypic pervasive developmental disorder, is characterized by lifelong marked impairment in reciprocal social interaction, communication, and a restricted range of activities and interests (Table 20-2). Approximately 20% of parents report relatively normal development until 1 or 2 years of age, followed by a steady or sudden decline. If no clinical manifestations of the disorder are present by 3 years of age, Rett syndrome or childhood disintegrative disorder need to be considered. As an infant, there is delayed or absent social smiling. The young child may spend hours in solitary play and be socially withdrawn with indifference to attempts at communication. Patients with autism often are not able to understand nonverbal communication (eye contact, facial expressions) and do not interact with people as significantly different from objects. Speech often is delayed and, when present, it is frequently dominated by echolalia (sometimes mistaken as a sign of obsessive-compulsive disorder [OCD]), perseveration (confused with psychosis or
OCD), pronoun reversal, nonsense rhyming, and other abnormalities. Intense absorbing interests, ritualistic behavior, and compulsive routines are characteristic, and their disruption often invokes tantrum or rage reactions. Head banging, teeth grinding, rocking, diminished responsiveness to pain and external stimuli, and self-mutilation may be noted.

Although the etiology of autistic disorder is unknown, there is an increased risk of autistic disorder in siblings compared to the general population. Twin studies have revealed high levels of concordance for monozygotic twins. Family studies reveal prevalence rates of between 2% and 10% in siblings, and, when absent, there may be increased risk for language, learning, and social development problems.

It is proposed that the brain connectivity is adversely affected. Abnormalities in the limbic system, temporal, and frontal lobes have been suggested. Some postmortem studies reveal abnormalities in the brain microarchitecture, size, and neuronal packing. Functional magnetic resonance imaging (MRI) studies show hypoactivity of the fusiform gyrus of the amygdala, a location involved in face processing tasks and facial expression recognition involved in social and affective judgments.

The American Academy of Pediatrics recommends screening for autism at 18 and 24 months of age. Comprehensive testing should be done if there is an affected sibling or parental, other caregiver, or pediatric concern.

There are no definitive laboratory studies for autistic disorder, but they can help rule out other diagnoses. A hearing test may account for the language deficits, chromosomal testing (to identify fragile X syndrome, tubular sclerosis, and genetic polymorphisms), congenital viral infections, and metabolic disorders (phenylketonuria) should be performed. Electroencephalography abnormalities may be seen in 20% to 25% of children with autism but are not diagnostic. Psychological tests in children with autism often show strengths in nonverbal tasks (e.g., puzzles) and marked deficiency in verbal cognitive abilities. IQ is usually low, though savant skills and hyperlexia (a precocious interest in letters and numbers) are sometimes observed. Speech pathology consultation can be helpful in evaluating the communication difficulties.

Common comorbidities are mental retardation (in up to 80%), seizure disorder (in 25%), anxiety disorders, OCD, and attention-deficit/hyperactivity disorder. Seizures often start around the onset of puberty. Higher IQ and better language skills are related to improved prognosis. Good communication by the age of 6 years and average nonverbal cognitive skills predict the likelihood of living independently or in a less structured group living situation.

The earliest studies of autism suggested a relatively poor prognosis, with only a small number of individuals (1% to 2%) being able to function independently as adults. Recent research reveals major gains, but not a cure, with early diagnosis and treatment.

### SCHIZOPHRENIA

Schizophrenia generally presents in adolescence or early adulthood. The same diagnostic criteria are applied as in adults but must be interpreted in terms of the developmental stage of the child (Table 20-3).

Childhood-onset schizophrenia is a rare disorder (<1 in 10,000 children) and usually indicates a more severe form of schizophrenia. The frequency increases between 13 and 18 years of age. Boys tend to be affected about twice as often as girls, regardless of ethnic or other cultural factors. The etiology of schizophrenia is unknown. Numerous studies have shown genetic predisposition and linkages for the disorder. In addition, family studies consistently show a higher risk in monozygotic twins compared with dizygotic twins and siblings. First-degree relatives of patients with schizophrenia have a 10-fold higher risk.

The symptoms of schizophrenia typically fall into four broad categories:

- **Positive symptoms** include hallucinations and delusions. Hallucinations are auditory or visual misperceptions that occur without external stimuli. Delusions are fixed false beliefs that are unreasonable, difficult to change, and may be formed despite evidence to the contrary.

- **Negative symptoms** refer to the absence of normal brain functions, such as motivation, communication, and social interaction. These symptoms can include social withdrawal, reduced facial expression, and reduced speech.

- **Disorganized symptoms** involve disordered speech and thinking, such as disorganized thinking, flat affect, and poverty of speech. These symptoms may include magical ideation, chaotic behavior, and disorganized speech.

- **Neutral signs** refer to abnormalities in the physical examination, such as hyperreflexia or abnormal posturing. These signs may indicate abnormalities in the brain's structure or function.

<table>
<thead>
<tr>
<th>Table 20-1</th>
<th>Pervasive Developmental Disorder: Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEATURE</strong></td>
<td><strong>AUTISM</strong></td>
</tr>
<tr>
<td>Epidemiology</td>
<td>10 cases per 10,000; 5:1 male-to-female ratio</td>
</tr>
<tr>
<td>Onset</td>
<td>Before age 3 yr</td>
</tr>
<tr>
<td>Language/communication impairment</td>
<td>Marked</td>
</tr>
<tr>
<td>Motor issues</td>
<td>Poor; May be preserved previously</td>
</tr>
<tr>
<td>Restricted interests</td>
<td>Marked, mannerisms, trouble with change, occasionally savant ability</td>
</tr>
</tbody>
</table>

CDD, Childhood disintegrative disorder; PDD-NOS, pervasive developmental disorder—not otherwise specified.
beliefs and can be bizarre or non-bizarre, depending on cultural norms.

- **Negative symptoms** include a lack of motivation and social interactions and flat effect. Negative symptoms are most frequent in early childhood and later adolescence. Children with high IQs often show more positive and fewer negative symptoms than children with low IQs.

- **Disorganization of thoughts and behavior** can cause significant impairment.

- **Cognitive impairment** is common and is perhaps the most disabling feature of schizophrenia, causing marked social and functional impairment.

### Table 20-2 Criteria for Diagnosis of Autistic Disorder

<table>
<thead>
<tr>
<th>A. Six or more items from (1), (2), and (3), with at least two from (1) and one each from (2) and (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Qualitative impairment in social interaction, as manifested by at least two of the following:</td>
</tr>
<tr>
<td>a. Marked impairment in the use of multiple nonverbal behaviors, such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction</td>
</tr>
<tr>
<td>b. Failure to develop peer relationships appropriate to developmental level</td>
</tr>
<tr>
<td>c. A lack of spontaneously seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)</td>
</tr>
<tr>
<td>d. Lack of social or emotional reciprocity</td>
</tr>
<tr>
<td>2. Qualitative impairments in communication as manifested by at least one of the following:</td>
</tr>
<tr>
<td>a. Delay in, or total lack of, the development of spoken language (not accompanied by attempts to compensate through alternative modes of communication, such as gesture or mime)</td>
</tr>
<tr>
<td>b. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others</td>
</tr>
<tr>
<td>c. Stereotyped and repetitive use of language or idiosyncratic language</td>
</tr>
<tr>
<td>d. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level</td>
</tr>
<tr>
<td>3. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:</td>
</tr>
<tr>
<td>a. Encompassing preoccupation with stereotypes and restricted patterns of interest that is abnormal either in intensity or focus</td>
</tr>
<tr>
<td>b. Apparently inflexible adherence to specific, nonfunctional routines or rituals</td>
</tr>
<tr>
<td>c. Stereotyped and repetitive motor mannerisms (e.g., hand-or finger-flapping or twisting or complex whole body movements)</td>
</tr>
<tr>
<td>d. Persistent preoccupation with parts of objects</td>
</tr>
<tr>
<td>B. Delays or abnormal functioning in at least one of the following areas, with onset before age 3 yr</td>
</tr>
<tr>
<td>1. Social interaction</td>
</tr>
<tr>
<td>2. Language as used in social communication</td>
</tr>
<tr>
<td>3. Symbolic or imaginative play</td>
</tr>
<tr>
<td>C. The disturbance is not better accounted for by Rett syndrome or childhood disintegrative disorder.</td>
</tr>
</tbody>
</table>

### Table 20-3 Criteria for Diagnosis of Schizophrenia

<table>
<thead>
<tr>
<th>A. Characteristic symptoms: two of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Delusions</td>
</tr>
<tr>
<td>2. Hallucinations</td>
</tr>
<tr>
<td>3. Disorganized speech (e.g., frequent derailment or incoherence)</td>
</tr>
<tr>
<td>4. Grossly disorganized or catatonic behavior</td>
</tr>
<tr>
<td>5. Negative symptoms (i.e., affective flattening, alogia, or avolition)</td>
</tr>
</tbody>
</table>

Note: Only one criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person’s behavior or thoughts or two or more voices conversing with each other.

- **B. Social/occupational dysfunction:** for a significant portion of the time since the onset of the disturbance, major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved before the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

- **C. Duration:** continuous signs of the disturbance persist for at least 6 months with at least 1 month of symptoms (or less if successfully treated) that meet criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During prodromal or residual periods, signs of disturbance may be manifested by only negative symptoms or symptoms listed in criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

- **D. Schizoaffective and mood disorder exclusion:** schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or hypomanic episodes have occurred concurrently with the active-phase symptoms or (2) if mood episodes have occurred during active-phase symptoms, the total duration has been brief relative to the duration of the active and residual periods.

- **E. The disturbance is not due to the direct physiologic effects of a drug abuse, a medication, or a general medical condition.**

- **F. If there is a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations also are present for at least 1 month (or less if successfully treated).**

Classification of longitudinal course (can be applied only after at least 1 year has elapsed since the initial onset of active-phase symptoms):

- Episodic with inter-episode residual symptoms (episodes are defined by the reemergence of prominent psychotic symptoms); also specify if: with prominent negative symptoms.

- Episodic with no inter-episode residual symptoms

- Continuous (prominent psychotic symptoms are present throughout the period of observation); also specify if: with prominent negative symptoms.

There are five subtypes of schizophrenia: paranoid, disorganized, catatonic, undifferentiated, and residual.

- **Paranoid type:** prominent hallucinations and delusions with relatively normal cognition. The delusions are often persecutory, but other types of delusions also may occur.

- **Disorganized type:** disorganized speech, disorganized behavior, and flat or inappropriate affect.
• **Catatonic type**: prominent psychomotor abnormalities that may include extreme inactivity or excessive motor activity. Cataplexy (waxy flexibility) is rare in children and adolescents.

• **Undifferentiated type**: case in which a patient meets the diagnostic criteria for schizophrenia but not paranoid, disorganized, or catatonic type.

• **Residual type**: clinical situation in which full diagnostic criteria have been met previously but no current, prominent, positive symptoms.

To meet criteria for diagnosing schizophrenia, clinical symptoms should be present for at least 6 months. If symptoms are present for less than 1 month, the condition is called a brief psychotic disorder. If symptoms are present for more than 1 month but less than 6 months, a diagnosis of schizophréniform disorder is made. Psychotic symptoms that do not meet full diagnostic criteria for schizophrenia but are clinically significant are diagnosed as **psychotic disorder not otherwise specified**.

There are several disorders that have to be distinguished from schizophrenia. These include the following:

**Schizoaffective disorder** is diagnosed when a person has clear symptoms of schizophrenia for at least 2 weeks without active symptoms of depression or mania. These affective syndromes occur at other times, even when psychotic symptoms are present.

**Major depression with psychotic features** and **bipolar disorder with psychotic features** are diagnoses made when psychotic symptoms occur during the course of depression or mania only. Psychotic disorder due to a general medical condition describes psychotic symptoms that are judged to be the direct result of a general medical condition.

**Substance-induced psychotic disorders** have psychotic symptoms related to drug or alcohol ingestion.

**Shared psychotic disorder, folie à deux**, occurs when delusional symptoms from one person influence delusions, with similar content, in another person.

Other disorders in the differential diagnoses are autism, childhood disintegrative disorder (Heller syndrome), Asperger syndrome, drug-induced psychosis, and organic brain disorders.

No diagnostic tests or imaging studies are specific for schizophrenia. It is a clinical diagnosis of exclusion. Obtaining a family history with attention to mental illness is critical. The workup of schizophrenia includes physical and neurologic examinations, MRI, electroencephalography (to rule out epilepsy, especially temporal lobe epilepsy), drug screening, and metabolic screening for endocrinopathies. Evaluation to rule out Wilson disease and delirium is also indicated. Psychotic symptoms in younger children must be differentiated from manifestations of normal vivid fantasy life or abuse-related symptoms. Youth with posttraumatic stress disorder often have vivid recollections and nightmares related to abuse but sometimes are less specific and can include nightmares with other negative topics. Psychological testing can be helpful in identifying psychotic thought processes.

Treatment is based on a multimodal approach, including use of antipsychotic medications. First-line drugs are atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, and paliperidone). Second-line medications are typical antipsychotics (e.g., haloperidol, thiothixene, chlorpromazine, trifluoperazine, loxapine, and molindone). It is likely that the newer antipsychotics approved for adults will also work in youth. However, these are not yet approved in youth by the U.S. Food and Drug Administration. Antipsychotics can be augmented with lithium or another mood stabilizer. Clozapine or electroconvulsive therapy is generally reserved for resistant cases.

Psychosocial treatments, including skills training, supportive psychotherapy, behavior modification, and cognitive-behavioral therapy, are all appropriate and should be considered as needed for individual patients. Attention should be paid to psychoeducation for parents and the child about the disease and its treatments. School interventions are needed to ensure that any special learning needs are addressed.

The course of illness for schizophrenia varies in exacerbations and remissions of psychotic symptoms. The poorest prognosis is seen if the onset is at an age younger than 13 years, with poor premorbid function, when marked negative symptoms are present, and when a family history of schizophrenia exists.

### Suggested Reading


Failure to thrive (FTT) is a descriptive term given to malnourished infants and young children who fail to meet expected standards of growth. FTT is most often used to describe malnutrition related to environmental or psychosocial causes. In many children with inadequate growth, however, organic and environmental contributors coexist, underscoring the importance of assessing potential medical, nutritional, developmental, psychosocial, and environmental contributors in all cases.

FTT is often diagnosed by weight that falls or remains below the 3rd percentile for age; decreases, crossing two major percentile lines on the growth chart over time; or is less than 80% of the median weight for the height of the child. Caveats to these definitions exist. According to growth chart standards, 3% of the population naturally falls below the 3rd percentile. These children, who typically have short stature or constitutional delay of growth, usually are proportional (normal weight for height). Additionally in the first few years of life, large fluctuations in percentile position can occur in normal children. Changes in weight should be assessed in relation to height (length) and head circumference.

Weight that decreases from a disproportionately high percentile to one that is proportional causes no concern, but weight that decreases to a disproportionately low percentile is of concern. Allowances must be made for prematurity; weight corrections are needed until 24 months of age, height corrections until 40 months of age, and head circumference corrections until 18 months of age. Although some growth variants can be difficult to distinguish from FTT, growth velocity and height-for-weight determinations can be useful in distinguishing the cause. In children with FTT, malnutrition initially results in wasting (deficiency in weight gain). Stunting (deficiency in linear growth) generally occurs after months of malnutrition, and head circumference is spared except with chronic, severe malnutrition. FTT that is symmetric (proportional weight, height/length, and head circumference) suggests long-standing malnutrition, chromosomal abnormalities, congenital infection, or teratogenic exposures. FTT is a common problem in pediatrics, affecting 5% to 10% of young children, 3% to 5% of children admitted to hospitals, and 15% of children living in poverty and foster care.

ETIOLOGY
Because possible causes of growth failure are diverse and often multifactorial, the management of FTT begins with a careful search for its etiology (Table 21-1). The common causes of FTT vary by age, which should be reflected in the evaluation (Table 21-2). In most cases, a comprehensive history and physical examination are sufficient to suggest or eliminate medical disease as the primary cause of FTT. Medical diseases are diagnosed in fewer than 50% of children hospitalized for growth failure and even less frequently in children managed in the outpatient setting. Growth failure is often a manifestation of more extensive family problems. It is clinically useful to categorize the causes of malnutrition into inadequate nutritional intake, inadequate nutrient absorption, or increased metabolic demand.

DIAGNOSIS AND CLINICAL MANIFESTATIONS
A medical history should include prenatal history prematurity, birth size (weight, length, and head circumference), as well as family and travel history. Indicators of medical diseases, such as vomiting, diarrhea, fever, respiratory symptoms, and fatigue, should be noted. A careful diet history is essential. Lactation problems in breastfed infants and improper formula preparation are frequent causes of growth failure early in infancy. It is crucial to evaluate intake of solid foods and liquids for older infants and children. Due to parental dietary beliefs, some children have inappropriately restricted diets; others drink excessive amounts of fruit juice, leading to malabsorption or anorexia. The child’s daily meal schedule (timing, frequency, location) should also be noted. Mealtime practices, especially distractions that interfere with completing meals, can influence growth. A complete psychosocial assessment of the child and family is required. Child factors (temperament, development), parental factors (depression, domestic violence, social isolation, mental retardation, substance abuse), and environmental and societal factors (poverty, unemployment, illiteracy, lead toxicity) all may contribute to growth failure.

A complete physical examination and developmental screening should assess signs of inflicted injury; oral or dental problems; indicators of pulmonary, cardiac, or gastrointestinal
Section 5  •  Psychosocial Issues

Table 21-1  Causes of Failure to Thrive

<table>
<thead>
<tr>
<th>ENVIRONMENTAL (COMMON)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional deprivation</td>
</tr>
<tr>
<td>Rumination</td>
</tr>
<tr>
<td>Child maltreatment</td>
</tr>
<tr>
<td>Maternal depression</td>
</tr>
<tr>
<td>Poverty</td>
</tr>
<tr>
<td>Poor feeding techniques</td>
</tr>
<tr>
<td>Improper formula preparation</td>
</tr>
<tr>
<td>Improper mealtime environment</td>
</tr>
<tr>
<td>Unusual parental nutritional beliefs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GASTROINTESTINAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis and other causes of pancreatic insufficiency</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Other malabsorption syndromes</td>
</tr>
<tr>
<td>Gastrointestinal reflux</td>
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</tbody>
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<table>
<thead>
<tr>
<th>CONGENITAL/ANATOMIC</th>
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<tbody>
<tr>
<td>Chromosomal abnormalities, genetic syndromes</td>
</tr>
<tr>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>Gastrointestinal abnormalities (e.g., pyloric stenosis, malrotation)</td>
</tr>
<tr>
<td>Vascular rings</td>
</tr>
<tr>
<td>Upper airway obstruction</td>
</tr>
<tr>
<td>Dental caries</td>
</tr>
<tr>
<td>Congenital immunodeficiency syndromes</td>
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<table>
<thead>
<tr>
<th>INFECTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Urinary tract infection, chronic sinusitis, parasitic infection</td>
</tr>
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<table>
<thead>
<tr>
<th>METABOLIC</th>
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<tbody>
<tr>
<td>Thyroid disease</td>
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<tr>
<td>Adrenal or pituitary disease</td>
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<tr>
<td>Aminoaciduria, organic aciduria</td>
</tr>
<tr>
<td>Galactosemia</td>
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<table>
<thead>
<tr>
<th>NEUROLOGIC</th>
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</thead>
<tbody>
<tr>
<td>Cerebral palsy</td>
</tr>
<tr>
<td>Hypothalamic and other central nervous system tumors</td>
</tr>
<tr>
<td>Hypotonia syndromes</td>
</tr>
<tr>
<td>Neuromuscular diseases</td>
</tr>
<tr>
<td>Degenerative and storage diseases</td>
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<table>
<thead>
<tr>
<th>RENAL</th>
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<tbody>
<tr>
<td>Chronic renal failure</td>
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<tr>
<td>Renal tubular acidosis</td>
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<tr>
<td>Urinary tract infection</td>
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<table>
<thead>
<tr>
<th>HEMATOLOGIC</th>
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<tbody>
<tr>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
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</tbody>
</table>

Table 21-2  Common Causes of Malnutrition in Early Life

<table>
<thead>
<tr>
<th>Table 21-2  Common Causes of Malnutrition in Early Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEONATE</td>
</tr>
<tr>
<td>Failed breastfeeding</td>
</tr>
<tr>
<td>Improper formula preparation</td>
</tr>
<tr>
<td>Congenital syndromes</td>
</tr>
<tr>
<td>Prenatal infections</td>
</tr>
<tr>
<td>Teratogenic exposures</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>EARLY INFANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal depression</td>
</tr>
<tr>
<td>Improper formula preparation</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Poverty</td>
</tr>
<tr>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Neurologic abnormalities</td>
</tr>
<tr>
<td>Child neglect</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>LATER INFANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Food intolerance</td>
</tr>
<tr>
<td>Child neglect</td>
</tr>
<tr>
<td>Delayed introduction of age-appropriate foods</td>
</tr>
<tr>
<td>Juice consumption</td>
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<table>
<thead>
<tr>
<th>AFTER INFANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired diseases</td>
</tr>
<tr>
<td>Highly distractible child</td>
</tr>
<tr>
<td>Juice consumption</td>
</tr>
<tr>
<td>Autonomy struggles</td>
</tr>
<tr>
<td>Inappropriate mealtime environment</td>
</tr>
<tr>
<td>Inappropriate diet</td>
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</tbody>
</table>

disease; and dysmorphic features that may suggest a genetic or teratogenic cause for growth failure. A complete neurologic examination may reveal spasticity or hypotonia, which can have untoward effects on feeding and growth. Physical findings related to malnutrition include decreased subcutaneous fat, decreased muscle mass, dermatitis, hepatomegaly, cheilosisis, or edema (see Chapter 30). Additionally children with FTT have more otitis media, respiratory, and gastrointestinal infections than age-matched controls; severely malnourished children are at risk for a variety of serious infections.

The history and physical examination findings should guide the laboratory evaluation. Simple screening tests are recommended to identify common illnesses that cause growth failure and to search for medical problems resulting from malnutrition. Initial tests may include a complete blood count; screening for iron deficiency anemia and lead toxicity; urinalysis, urine culture, and serum electrolytes to assess renal infection or dysfunction; thyroid stimulating hormone; liver function tests; and a protein purified derivative test to screen for tuberculosis. Human immunodeficiency virus testing may also be indicated. For children with diarrhea, abdominal pain, or malodorous stools, a stool sample for culture and ova and parasites may be
indicated. A review of the child’s newborn screen may also be warranted. Observation during feeding and home visitation, if possible, is of great diagnostic value in assessing feeding problems, food preferences, mealtime distractions, unusual or disruptive parent-child interactions, and the home environment.

**TREATMENT**

Treatment must address the child’s nutritional requirements and the social issues of the family. Initial treatment should focus on the nutritional and medical management of the child while engaging the family in the treatment plan. Parents of malnourished children may feel personally responsible and threatened by the diagnosis of FTT. Parents may be so depressed or dysfunctional they cannot focus on their child’s needs; they may not recognize the psychosocial and family contributors to the malnutrition. These issues can have a profound effect on the success of treatment, and they need to be addressed.

Children with mild malnutrition whose cause is easily identified can be managed by the primary care physician and family. In more challenging cases, a multidisciplinary team, including pediatricians, nutritionists, developmental specialists, nurses, and social workers, improves nutritional outcome in children with FTT. Most children with FTT can be treated in the outpatient setting. Children with severe malnutrition, underlying diagnoses that require hospitalization for evaluation or treatment, or whose safety is in jeopardy because of maltreatment require hospitalization. Admitting children to the hospital to induce and document weight gain is not recommended unless intensive outpatient evaluation and intervention has failed or the social circumstances are a contraindication for attempting outpatient management.

Nutritional management is the cornerstone of treatment, regardless of the etiology. Children with FTT may require more than 1.5 times the expected calorie and protein intake for their age for catch-up growth. Children with FTT who are anorexic and picky eaters may not be able to consume this amount in volume and require calorically dense foods. For formula-fed infants, the concentration of formula can be adjusted appropriately (Table 21-3). For toddlers dietary changes should include increasing the caloric density of favorite foods by adding butter, oil, sour cream, peanut butter, or other high-calorie foods. High-calorie oral supplements (30 cal/oz) are often well tolerated by toddlers. In some cases, specific carbohydrate, fat, or protein additives are used to boost calories by increasing calories without increasing volume requirements. Additionally vitamin and mineral supplementation is needed, especially during catch-up growth. In general the simplest and least costly approach to dietary change is warranted.

Depending on the severity of the malnutrition, initiation of catch-up growth may take 2 weeks. Initial weight gain two to three times normal growth can be seen. Weight improvement precedes improvement in stature. For children with chronic, severe malnutrition, many months are needed to reverse all trends in growth. Although many children with FTT eventually reach normal size, they remain at risk for developmental, learning, and behavioral problems.

**COMPLICATIONS**

Malnutrition causes defects in host defenses. Children with FTT may suffer from a malnutrition-infection cycle, in which recurrent infections exacerbate malnutrition, leading to greater susceptibility to infection. Children with FTT must be evaluated and treated promptly for infection and followed closely.

During starvation, the body slows metabolic processes and growth to minimize the need for nutrients and uses its stores of glycogen, fat, and protein to maintain normal metabolic requirements. The body also generally maintains homeostasis and normal serum concentrations of electrolytes. With the rapid reinstitution of feeding after starvation, fluid and electrolyte homeostasis may be lost. Changes in serum electrolyte concentrations and the associated complications are collectively termed the refeeding syndrome. These changes typically affect phosphorus, potassium, calcium, and magnesium and can result in life-threatening cardiac, pulmonary, or neurologic problems. Infants and children with marasmus, kwashiorkor, and anorexia nervosa and those who have had prolonged fasting are at risk for refeeding syndrome. Refeeding syndrome can be avoided by slow institution of nutrition, close monitoring of serum electrolytes during the initial days of feeding, and prompt replacement of depleted electrolytes.

Occasionally children who live in psychological deprivation develop short stature with or without concomitant FTT or delayed puberty, a syndrome called psychosocial short stature. The signs and symptoms include polyphagia, polydipsia, hoarding and stealing of food, gorging and vomiting, drinking from toilet bowls, and other notable behaviors. Affected children are often shy and passive and are typically depressed and socially withdrawn. Endocrine dysfunction is often identified in affected children, who may have decreased growth hormone secretion and a muted response to exogenous growth hormone. Removal of the child from the adverse environment typically results in rapid improvement in endocrine function and subsequent rapid somatic and pubertal growth of the child. The prognosis for children with psychosocial short stature depends on the age at diagnosis and the degree of psychosocial trauma. Early identification and removal from the environment portends a healthy prognosis. Those diagnosed in later childhood or adolescence may not reach their genetic potential for growth and have a poorer psychosocial prognosis.

### Table 21-3  Infant Formula Preparation

<table>
<thead>
<tr>
<th>AMOUNT OF POWDER/ LIQUID</th>
<th>AMOUNT OF WATER (OZ)</th>
<th>FINAL CONCENTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 cup powdered formula</td>
<td>29</td>
<td>20 kcal/oz</td>
</tr>
<tr>
<td>4 scoops powdered formula</td>
<td>8</td>
<td>20 kcal/oz</td>
</tr>
<tr>
<td>13 oz liquid concentrate</td>
<td>13</td>
<td>20 kcal/oz</td>
</tr>
<tr>
<td>1 cup powdered formula</td>
<td>24</td>
<td>24 kcal/oz</td>
</tr>
<tr>
<td>5 scoops powdered formula</td>
<td>8</td>
<td>24 kcal/oz</td>
</tr>
<tr>
<td>13 oz liquid concentrate</td>
<td>9</td>
<td>24 kcal/oz</td>
</tr>
<tr>
<td>1 cup powdered formula</td>
<td>21</td>
<td>27 kcal/oz</td>
</tr>
<tr>
<td>5.5 scoops powdered formula</td>
<td>8</td>
<td>27 kcal/oz</td>
</tr>
<tr>
<td>13 oz liquid concentrate</td>
<td>6</td>
<td>27 kcal/oz</td>
</tr>
</tbody>
</table>

*Final concentrations are reached by adding formula to water. One scoop of powdered formula = one measuring tablespoon. For healthy infants, formulas are prepared to provide 20 kcal/oz.

Chapter 22

CHILD ABUSE AND NEGLECT

Few social problems have as profound an impact on the well-being of children as child abuse and neglect. Each year in the United States, 3 million reports of suspected maltreatment are made to child welfare agencies. Approximately 1 million of these reports are substantiated after investigation by Child Protective Services (CPS). These reports represent only a small portion of the children who suffer from maltreatment. Parental surveys indicate that several million adults admit to physical violence against their children each year, and many more adults report abusive experiences as children. Federal and state laws define child abuse and neglect. Each state determines the process of investigating abuse, protecting children, and holding perpetrators accountable for their actions or inactions. Adverse childhood events, such as child abuse and neglect, increase the risk of the individual’s developing behaviors in adolescence and adulthood that predict adult morbidity and early mortality. The ability to recognize child maltreatment and effectively advocate for the protection and safety of a child is a great challenge in pediatric practice that can have a profound influence on the health and future well-being of a child.

Child abuse is parental behavior destructive to the normal physical or emotional development of a child. Because personal definitions of abuse vary according to religious and cultural beliefs, individual experiences, and family upbringing, various physicians have different thresholds for reporting suspected abuse to CPS. In every state, physicians are mandated by law to identify and report all cases of suspected child abuse and neglect. It is the responsibility of CPS to investigate reports of suspected abuse to ensure the ongoing safety of the child. State laws also define intentional or reckless acts that cause harm to a child as crimes. Law enforcement investigates crimes such as sexual abuse and serious physical abuse or neglect for possible criminal charges against a perpetrator.

Child abuse and neglect are often considered in broad categories that include physical abuse, sexual abuse, emotional abuse, and neglect. Neglect is the most common, accounting for approximately half of the reports made to child welfare agencies. Child neglect is defined by omissions that prevent a child's basic needs from being met. These needs include adequate food, clothing, supervision, housing, health care, education, and nurturance. Child abuse and neglect result from a complex interaction of individual, family, and societal risk factors. Although some risk factors, such as parental substance abuse, maternal depression, and domestic violence, are strong risk factors for maltreatment, they are better considered as broadly defined markers to alert a physician to a potential risk, rather than determinants of specific abuse and neglect.

The ability to identify victims of child abuse varies by the age of the patient and the type of maltreatment sustained. Children who are victims of sexual abuse are often brought for medical care after the child makes a disclosure, and the diagnosis is straightforward. Physically abused infants may be brought for medical evaluation of irritability or lethargy, without a disclosure of trauma. If the infant's injuries are not severe or visible, the diagnosis may be missed. Approximately one third of infants with abusive head trauma initially are misdiagnosed by unsuspecting physicians, only to be identified after sustaining further injury. Although physicians are inherently trusting of parents, a constant awareness of the possibility of abuse is needed.

The physical abuse of children by parents affects children of all ages. It is estimated that 1% to 2% of children are physically abused during childhood and that approximately 1500 children are fatally injured each year. Although mothers are the most frequently reported as the perpetrators of physical abuse, serious injuries, such as head or abdominal trauma, are more likely to be inflicted by fathers or maternal boyfriends. The diagnosis of physical abuse can be made easily if the child is battered, has obvious external injuries, or is capable of providing a history of the abuse. In many cases, the diagnosis is not obvious. The history provided by the parent is often inaccurate because the parent is unwilling to provide the correct history or is a nonoffending parent who is unaware of the abuse. The child may be too young or ill to provide a history of the assault. An older child may be too scared to do so or may have a strong sense of loyalty to the perpetrator.

A diagnosis of physical abuse initially is suggested by a history that seems incongruent with the clinical presentation of the child (Table 22-1). Although injury to any organ system can occur from physical abuse, some injuries are more common. Bruises are universal findings in healthy ambulatory children but also are among the most common injury identified in abused children. Bruises suggestive of abuse include those that are patterned, such as a slap mark on the face or looped extension cord marks on the body (Fig. 22-1). Bruises

<table>
<thead>
<tr>
<th>Table 22-1</th>
<th>Clues to the Diagnosis of Physical Abuse</th>
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<tbody>
<tr>
<td>A child presents for medical care with significant injuries, and a history of trauma is denied, especially if the child is an infant or toddler.</td>
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<tr>
<td>The history provided by the caregiver does not explain the injuries identified.</td>
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<tr>
<td>The history of the injury changes significantly over time.</td>
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<tr>
<td>A history of self-inflicted trauma does not correlate with the child’s developmental abilities.</td>
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<tr>
<td>There is an unexpected or unexplained delay in seeking medical care.</td>
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<tr>
<td>Multiple organ systems are injured, including injuries of various ages.</td>
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<tr>
<td>The injuries are pathognomonic for child abuse.</td>
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in healthy children generally are distributed over bony prominences; bruises that occur in an unusual distribution, such as isolated to the torso, ears or neck, should raise concern. Bruises in nonambulatory infants are unusual, occurring in less than 2% of healthy infants seen for routine medical care. Occasionally a subtle bruise may be the only external clue to abuse and can be associated with significant internal injury.

Burns are common pediatric injuries and usually represent preventable unintentional trauma (see Chapter 44). Approximately 10% of children hospitalized with burns are victims of abuse. Inflicted burns can be the result of contact with hot objects (irons, radiators, or cigarettes) but more commonly the result of scalding injuries (Fig. 22-2). Hot tap water burns in infants and toddlers are sometimes the result of intentional immersion injuries, which often occur around toilet training issues. These burns have clear lines of demarcation, uniformity of burn depth, and characteristic pattern.

Inflicted fractures occur more commonly in infants and young children. Although diaphyseal fractures are most common in abuse, they are nonspecific for inflicted injury. Fractures that should raise suspicion for abuse include fractures that are unexplained; occur in young, nonambulatory children; or involve multiple bones. Certain fractures have a high specificity for abuse, such as rib, metaphyseal, scapular, vertebral, or other unusual fractures (Fig. 22-3). Some metabolic diseases can be confused with abuse and should be considered in the differential diagnosis when appropriate.

Abdominal injury is an uncommon but serious form of physical abuse. Blunt trauma to the abdomen is the primary mechanism of injury, and infants and toddlers are the most common victims. Injuries to solid organs, such as the liver or pancreas, predominate and hollow viscus injury occurs more commonly with inflicted trauma than accidental. Even

**Figure 22-1** Multiple looped cord marks on a 2-year-old abused child who presented to the hospital with multiple untreated burns to the back, arms, and feet.

**Figure 22-2** A 1-year-old child brought to the hospital with a history that she sat on a hot radiator. Suspicious injuries such as this require a full medical and social investigation, including a skeletal survey to look for occult skeletal injuries and a child welfare evaluation.

**Figure 22-3** A, Metaphyseal fracture of the distal tibia in a 3-month-old infant admitted to the hospital with severe head injury. There also is periosteal new bone formation of that tibia, perhaps from a previous injury. B, Bone scan of same infant. Initial chest x-ray showed a single fracture of the right posterior fourth rib. A radionuclide bone scan performed 2 days later revealed multiple previously unrecognized fractures of the posterior and lateral ribs. C, Follow-up radiographs 2 weeks later showed multiple healing rib fractures. This pattern of fracture is highly specific for child abuse. The mechanism of these injuries is usually violent squeezing of the chest.
in severe cases of trauma, there may be no bruising to the abdominal wall. The lack of external trauma, along with the usual inaccurate history, can cause delay in diagnosis. A careful evaluation often reveals additional injuries. Abdominal trauma is the second leading cause of mortality from physical abuse, although the prognosis is generally good for children who survive the acute assault.

Abusive head trauma is the leading cause of mortality and morbidity from physical abuse. Most victims are young; infants predominate. Shaking and blunt impact trauma cause injuries. The perpetrators are most commonly fathers and boyfriends, and the trauma typically is precipitated by the perpetrator's intolerance to a crying, fussy infant. Victims present with neurologic symptoms ranging from lethargy and irritability to seizures, apnea, and coma. Unsuspecting physicians misdiagnose approximately one third of infants, and of these, more than 25% are reinjured before diagnosis. A common finding on presentation is subdural hemorrhage, often associated with progressive cerebral edema (Fig. 22-4). Hypoxic-ischemic injury is a significant contributor to the pathophysiology of the brain injury. Associated findings include retinal hemorrhages (seen in many, but not all, victims) and skeletal trauma, including rib and classic metaphyseal fractures. At the time of diagnosis, many head-injured infants have evidence of previous injury. Survivors are at high risk for permanent neurologic sequelae.

The extensive **differential diagnosis** of physical abuse depends on the type of injury (Table 22-2). For children who present with pathognomonic injuries to multiple organ systems, an exhaustive search for medical diagnoses is warranted. Children with unusual medical diseases have been incorrectly diagnosed as victims of abuse, emphasizing the need for careful, objective assessments of all children. All infants and young toddlers who present with suspicious

**Figure 22-4** Acute subdural hemorrhage in the posterior interhemispheric fissure in an abused infant.

**Table 22-2** Differential Diagnosis of Physical Abuse

<table>
<thead>
<tr>
<th>BRUISES</th>
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<tbody>
<tr>
<td>Accidental injury (common)</td>
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<tr>
<td>Dermatologic disorders</td>
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<tr>
<td>Mongolian spots</td>
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<tr>
<td>Erythema multiforme</td>
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<tr>
<td>Phytophotodermatitis</td>
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<tr>
<td>Hematologic disorders</td>
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<tr>
<td>Idiopathic thrombocytopenic purpura</td>
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<tr>
<td>Leukemia</td>
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<td>Hemophilia</td>
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<tr>
<td>Vitamin K deficiency</td>
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<td>Disseminated intravascular coagulopathy</td>
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<tr>
<td>Cultural practices</td>
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<tr>
<td>Cao gio (coining)</td>
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<tr>
<td>Quat sha (spoon rubbing)</td>
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<td>Infection</td>
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<td>Sepsis</td>
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<td>Purpura fulminans (meningococcemia)</td>
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<td>Genetic diseases</td>
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<tr>
<td>Ehlers-Danlos syndrome</td>
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<tr>
<td>Familial dysautonomia (with congenital indifference to pain)</td>
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<tr>
<td>Vasculitis</td>
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<tr>
<td>Henoch-Schönlein purpura</td>
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<table>
<thead>
<tr>
<th>BURNS</th>
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<tbody>
<tr>
<td>Accidental burns (common)</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Staphylococcal scalded skin syndrome</td>
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<tr>
<td>Impetigo</td>
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<tr>
<td>Dermatologic</td>
<td></td>
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<tr>
<td>Phytophotodermatitis</td>
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<tr>
<td>Stevens-Johnson syndrome</td>
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<tr>
<td>Fixed drug eruption</td>
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<tr>
<td>Epidermolysis bullosa</td>
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<tr>
<td>Severe diaper dermatitis, including Ex-Lax ingestion</td>
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<tr>
<td>Cultural practices</td>
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<tr>
<td>Cupping</td>
<td></td>
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<tr>
<td>Moxibustion</td>
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<table>
<thead>
<tr>
<th>FRACTURES</th>
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<tbody>
<tr>
<td>Accidental injury</td>
<td></td>
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<tr>
<td>Birth trauma</td>
<td></td>
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<tr>
<td>Metabolic bone disease</td>
<td></td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td></td>
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<tr>
<td>Copper deficiency</td>
<td></td>
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<tr>
<td>Rickets</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
</tr>
<tr>
<td>Congenital syphilis</td>
<td></td>
</tr>
<tr>
<td>Osteomyelitis</td>
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injuries should undergo a skeletal survey looking for occult or healing fractures. One third of young infants with multiple fractures, facial injuries, or rib fractures may have occult head trauma. Brain imaging may be indicated for these infants.

**SEXUAL ABUSE**

Child sexual abuse is the involvement of children in sexual activities that they cannot understand, for which they are developmentally unprepared and cannot give consent to, and that violates societal taboos. Sexual abuse can be a single event, but more commonly it is chronic. Most perpetrators are adults or adolescents who are known to the child and who have real or perceived power over the child. Most sexual abuse involves manipulation and coercion and does not involve physical violence. Although assaults by strangers occur, they are infrequent. Perpetrators are more often male than female and include parents, relatives, teachers, family friends, members of the clergy, and other individuals who have access to children. All perpetrators strive to keep the child from disclosing the abuse and often do so with coercion or threats.

Approximately 80% of victims are girls, although the sexual abuse of boys is underrecognized and underreported. Children generally come to attention after they have made a disclosure of their abuse. They may disclose to a nonoffending parent, sibling, relative, friend, or teacher. Children commonly delay disclosure for many weeks, months, or years after their abuse, especially if the perpetrator has ongoing access to the child. Sexual abuse also should be considered in children who have behavioral problems, although no behavior is pathognomonic. Hypersexual behaviors should raise the possibility of abuse, although some children with these behaviors are exposed to inappropriate sexual behaviors on television or videos or by witnessing adult sexual activity. Sexual abuse occasionally is recognized by the discovery of an unexplained vaginal, penile, or anal injury or by the discovery of a sexually transmitted infection.

In most cases, the diagnosis of sexual abuse is made by the history obtained from the child. In cases in which the sexual abuse has been reported to CPS or the police (or both), and the child has been interviewed before the medical visit, a complete, forensic interview at the physician’s office is not needed. Many communities have systems in place to ensure quality investigative interviews of sexually abused children. However if no other professional has spoken to the child about the abuse, or the child makes a spontaneous disclosure to the physician, the child should be interviewed with questions that are open-ended and non-leading. In all cases, the child should be questioned about medical issues related to the abuse, such as timing of the assault and symptoms (bleeding, discharge, or genital pain).

The **physical examination** should be complete, with careful inspection of the genitals and anus. Most sexually abused children have a normal genital examination at the time of the medical evaluation. Genital injuries are seen more commonly in children who present for medical care within 72 hours of their most recent assault and in children who report genital bleeding, but they are diagnosed in only 5% to 10% of sexually abused children. Many types of sexual abuse (fondling, vulvar coitus, oral genital contact) do not injure genital tissue, and genital mucosa heals so rapidly and completely that injuries often heal by the time of the medical examination. For children who present within 72 hours of the most recent assault, special attention should be given to identifying acute injury and the presence of blood or semen on the child. Injuries to the oral mucosa, breasts, or thighs should not be overlooked. Forensic evidence collection is needed in a few cases and has the greatest yield when collected in the first 24 hours after an acute assault. Few findings are diagnostic of sexual assault, but findings with the most specificity include acute, unexplained lacerations or ecchymoses of the hymen, posterior fourchette or anus, complete transection of the hymen, unexplained anogenital scarring, or pregnancy in an adolescent with no other history of sexual activity.

The **laboratory evaluation** of a sexually abused child is dictated by the child’s age, history, and symptoms. Universal screening for sexually transmitted infections for prepubertal children is unnecessary because the risk of infection is low in asymptomatic young children. The type of assault, identity and known medical history of the perpetrator, and the epidemiology of sexually transmitted infections in the community also are considered. Many clinicians use nucleic acid amplification testing to screen for sexually transmitted infections in sexually abused children because these tests have excellent sensitivity while maintaining good specificity for STIs in children and adolescents. The diagnosis of most sexually transmitted infections in young children requires an investigation for sexual abuse (see Chapter 116).

**MANAGEMENT**

The management of child abuse includes medical treatment for injuries and infections, careful medical documentation of verbal statements and findings, and ongoing advocacy for the safety and health of the child (Fig. 22-5). Parents always should be informed of the suspicion of abuse and the need to report to CPS, focusing on the need to ensure the safety and well-being of the child. Crimes that are committed against children also are investigated by law enforcement, so the police become involved in some, but not all, cases of suspected abuse. Physicians occasionally are called to testify in court hearings regarding civil issues, such as dependency and

<table>
<thead>
<tr>
<th>Table 22-2</th>
<th>Differential Diagnosis of Physical Abuse*—cont’d</th>
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<tbody>
<tr>
<td><strong>HEAD TRAUMA</strong></td>
<td></td>
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<tr>
<td>Accidental head injury</td>
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<tr>
<td>Hematologic disorders</td>
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<tr>
<td>Vitamin K deficiency (hemorrhagic disease of the newborn)</td>
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<tr>
<td>Hemophilia</td>
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<tr>
<td>Intracranial vascular abnormalities</td>
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<tr>
<td>Infection</td>
<td></td>
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<tr>
<td>Metabolic diseases</td>
<td></td>
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<tr>
<td>Glutaric aciduria type I, Menkes kinky hair syndrome</td>
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*The differential diagnosis of physical abuse varies by the type of injury and organ system involved.

custody, or criminal issues. Careful review of the medical records and preparation for court are needed to provide an educated, unbiased account of the child’s medical condition and diagnoses.

The prevention of child maltreatment is a great challenge. There are a few partially successful primary prevention programs. Visiting home nursing programs that begin during pregnancy and continue through early childhood may reduce the risk of abuse and neglect. Physician training in screening for risk factors in parents has shown to be supportive of families and reduce child maltreatment in some populations. Ultimately physicians always need to remain cognizant of the diagnosis, aware of their professional mandates, and willing to advocate on behalf of these vulnerable patients.

Figure 22-5 A, Approach to initiating the civil and criminal investigation of suspected abuse. B, Reporting to Child Protective Services (CPS) or law enforcement or both in child abuse cases. CPS reports are required when a child is injured by a parent, by an adult acting as a parent, or by a caregiver of the child. The police investigate crimes against children committed by any person, including parents or other caregivers. (From Christian CW: Child abuse. In Schwartz MW, editor: Clinical Handbook of Pediatrics, ed 3, Baltimore, 2003, Lippincott Williams & Wilkins, pp 192−193.)
HOMOSEXUALITY AND GENDER IDENTITY

The development of sexuality occurs throughout a child’s life. Sexuality includes gender roles, gender identity, sexual orientation, and sexual behaviors. It is influenced by biologic and social factors and individual experience. Pediatricians are likely to be consulted if parents have a concern about their child’s sexual development. A pediatrician who provides an open and nonjudgmental environment may be a valuable resource for an adolescent with questions about heterosexual behaviors, homosexuality, or gender identity (Table 23-1).

DEVELOPMENT OF SEXUAL IDENTITY

Sexual behaviors occur throughout childhood. Early in life, male infants can have erections and female infants are capable of vaginal lubrication. During the preschool period, masturbation occurs in both sexes. Between 2 and 3 years of age, children identify themselves as a boy or a girl, but the understanding that one is always a male or always a female may not develop until 4 to 5 years of age. Stating that one wants to be a member of the opposite sex and pretending to be a member of the opposite sex are not unusual behaviors in this age group. Preschool children need to begin to learn that genitals and sexual behaviors are private; it is common for preschool children to touch their genitals in public, show their genitals to others, or undress in public. It would be highly unusual for a preschool child to imitate intercourse or other adult sexual behaviors. If this behavior is occurring, the child should be evaluated for exposure to inappropriate sexual material and possible sexual abuse (see Chapter 22).

Most elementary school-age children show a strong and consistent gender identity, and their behaviors (gender roles) reflect this. If a child this age is engaging in cross-sex gender role behaviors, parents may be concerned about teasing and the possibility of their child having a homosexual sexual orientation. This concern is particularly likely if a boy is engaged in effeminate behaviors that are generally viewed as less socially acceptable than a girl acting as a “tomboy.” By this age, dressing as a member of the opposite sex and, particularly, stating a desire to be the opposite sex are uncommon, but playing with toys designed for the opposite sex remains common. In assessing parental concerns about atypical gender role behaviors, the type of behavior exhibited and its consistency should be considered. Reassurance that the behavior is consistent with typical development is appropriate when these behaviors are part of a flexible repertoire of male and female gender role behaviors. Reassurance is appropriate if the behaviors occur in response to a stress, such as the birth of an infant of the opposite sex or divorce of the parents. In contrast if these behaviors occur as a consistent and persistent pattern of nearly exclusive interest in behaviors typical of the gender role opposite that of the child’s anatomic sex, referral for evaluation for gender identity disorder (GID) would be appropriate.

The biologic, social, and cognitive changes during adolescence place a focus on sexuality. Becoming comfortable with one’s sexuality is one of the principal developmental tasks of this period and is likely to include questioning and experimentation. Almost half of high school students report that they have had sexual intercourse. Ten to 25% have at least one homosexual experience, with this behavior being reported more commonly by boys than girls. Although many adolescents have sexual experiences with a same-sex partner, only a few have a homosexual sexual orientation by late adolescence. When adolescents develop a consistent sexual orientation is probably affected by many different factors (societal, family, individual). Some adolescents report that they are certain of their sexual orientation in the early teenage years, whereas for others this does not develop until later. By 18 years of age, only a small proportion of individuals report being uncertain of their sexual orientation.

GENDER IDENTITY DISORDER

GID is characterized by intense and persistent cross-gender identification and discomfort with one’s own sex. In children these feelings may be manifested by behaviors such as cross-dressing, stating that one wants to be or is the opposite sex, and a strong and almost exclusive preference for cross-sex roles, games, and playmates. The onset of these behaviors often can be traced back to the preschool period. However referral for evaluation typically occurs at school age or later, when it becomes clear that the behaviors do not represent a transient phase, and the behaviors may begin to interfere with social relationships. Forty to 80% of children with GID will have a bisexual or homosexual sexual orientation as adults. However there is no reliable way to predict adult sexual orientation, and there is no evidence that parental behavior would alter the developmental pathway toward homosexual or heterosexual behavior.

In adults GID may be characterized by a belief that one was born the wrong sex and by a persistent desire to live and be treated as the opposite sex. Adults may request hormones or surgical procedures to alter sexual characteristics to simulate the other sex, but, when these procedures are done in individuals who have completed puberty, they often fail to fully achieve the appearance of the desired gender. Long-term follow-up studies of children with GID suggest that only 2% to 20% have GID as adults, but gender dysphoria that intensifies with the onset of puberty is likely to persist. In 2009 the Endocrine Society published guidelines that recommended

<table>
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<tr>
<th>Table 23-1</th>
<th>Terminology</th>
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<tr>
<td>Gender identity</td>
<td>Perception of oneself as male or female</td>
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<tr>
<td>Gender role</td>
<td>Behaviors and appearance that signal to others of being male or female</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>Sexual attraction to members of the opposite sex with weak attraction to members of the same sex</td>
</tr>
<tr>
<td>Homosexual</td>
<td>Sexual attraction to members of the same sex with weak attraction to members of the opposite sex</td>
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considering reversible suppression of puberty using gonadotropin releasing hormone analogs at Tanner stages 2 through 3 for individuals with GID because this allows the adolescent more time to decide whether to begin cross-sex hormone treatment.

HOMOSEXUALITY

Identical twins (even twins raised in separate families) show a higher concordance rate for sexual orientation than would be expected by chance alone, but nowhere near 100%, as would be expected if genetics alone determined sexual orientation. Some studies have found differences in the size of certain brain regions in homosexual individuals, but the findings are inconsistent. The levels of androgens and estrogens have not been found to differ in homosexual and heterosexual adults. Although it is well documented that parents tend to treat boys and girls differently, if, or how, these interactions affect sexual orientation is unknown.

It is currently estimated that about 1% to 4% of adults identify themselves as homosexual. Given the prevalent negative societal attitudes toward homosexuality, these children are at high risk for having a negative self-esteem, being isolated, being verbally harassed, and often being physically assaulted. Although sexual behaviors, not sexual orientation, determine risk of sexually transmitted infections, homosexual male adolescents engage in high-risk behaviors despite the threat of infection from the human immunodeficiency virus (HIV). For medical and psychosocial reasons, health care providers need to provide an environment in which adolescents feel comfortable discussing their sexual orientation (Table 23-2).

Acknowledging that one is homosexual and disclosing it to one's parents is often extremely stressful. Although many parents come to accept their child's homosexuality, some parents, particularly those who view this behavior as immoral, may reject their child. Homosexual youth are at a high risk for homelessness. Adolescents need to be made aware that even parents who eventually come to accept their child's homosexuality initially may be shocked, fearful about their child's well-being, or upset about the loss of the adulthood they had expected for their child. Parents may need to be reassured that they did not cause their child to have a homosexual orientation. Likewise they may need to be informed that therapies designed to change sexual orientation not only are unsuccessful, but also often lead to the child having more feelings of guilt and a lower self-esteem. The health care provider should have knowledge of support groups and counselors who can discuss these issues with the adolescent or his or her parents when the information the health care provider offers is not sufficient.

The homosexual youth is affected by how homosexuality is addressed in schools, by peers, and by other community groups. Unbiased information about homosexuality is often not available in these settings, and homophobic jokes, teasing, and violence are common. It is not surprising that homosexual youth and adults have higher rates of anxiety and mood disorders than are found in the general population. Increased rates of substance abuse and suicide are reported. Health care providers have an important role in detecting these problems.

Although education about safe sexual practices should be part of all adolescent well-child visits, health care providers should be aware that certain sexual behaviors of homosexual males increase the risk of certain types of sexually transmitted infections. Anal intercourse is an efficient route for infection by hepatitis B virus, cytomegalovirus, and HIV. Proctitis caused by gonorrhea, chlamydia, herpes simplex virus, syphilis, or human papillomavirus may occur (see Chapter 116).

### Table 23-2
Providing Supportive Health Care Environments for Homosexual Youth

<table>
<thead>
<tr>
<th>Ensure confidentiality</th>
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<tbody>
<tr>
<td>Implement policies against homophobic jokes and remarks</td>
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<tr>
<td>Ensure that information-gathering forms use gender-neutral language (e.g., partner as opposed to husband/wife)</td>
</tr>
<tr>
<td>Ensure that one uses gender-neutral questions when asking about dating or sexual behaviors</td>
</tr>
<tr>
<td>Display posters, brochures, and information that show concern for issues important to homosexual youth and their families</td>
</tr>
<tr>
<td>Provide information about support groups and other resources for homosexual youth and their families</td>
</tr>
</tbody>
</table>

A family is a dynamic system of interactions among biologically, socially, or legally related individuals; families have a unique power to promote or interfere with health and development. When a family functions well, interactions support the physical and emotional needs of all family members, and the family serves as a resource for an individual member who is having difficulty. Alternatively the problems of an individual member or the interactions among members may prevent the family from meeting the physical or emotional needs of one or more family members or, in the worst-case scenario, may cause physical or emotional harm to a member of the family. These situations are often referred to as family dysfunction.

### FAMILY FUNCTIONS

The functions that families carry out in support of their children can be categorized broadly as providing for physical needs, emotional support, education, and socialization (Table 24-1). Within these categories, all families have strengths and weaknesses. The amount of support that an individual child needs in these categories varies with the child's development, personality, temperament, health status, experiences, and stressors. Too much and too little support can interfere with optimal child health and development. Most cases of child abuse involve the failure of the family to provide a safe environment for the child and, in cases of neglect, inappropriate
support for the child’s physical, emotional, or social development. At the other extreme, overprotective parents may limit friendships and other growth-promoting experiences or seek excessive health care, as may occur in the vulnerable child syndrome. Parental perfectionism may create intense pressure on children related to achievement that may contribute to problems such as anxiety disorders.

**FAMILY STRUCTURE**
The traditional family consists of a married mother and father and their biologic children. The diversity in the structure of the family in the United States has increased dramatically; less than half of children now live in the traditional nuclear family. Today children may live with unmarried parents, single parents of either gender, a parent and a stepparent, grandparents, parents living as a same-sex couple, or foster care families. There is little evidence that family structure alone is a significant predictor of child health or development. Regardless of family structure, the presence of a loving adult or other adults serving as a parent or parents committed to fulfilling a child’s physical, emotional, and socialization needs is the best predictor of good health and development. Different family structures create different types of family stresses.

**Single-Parent Families**
At any one point in time, approximately 30% of children are living in single parent families, and more than 40% of children are born to unmarried mothers. In some cases this is the mother’s choice, but often times this results from a young woman’s unplanned pregnancy. Children may also live in single-parent families because of divorce or the death of a parent (see Chapter 26). Although most single parent families are still headed by mothers, single-father families are increasing and in 2009 nearly 5% of children lived in single-father families.

Single parents often have limited financial resources and social supports. For households headed by single mothers, the median income is only 40% of the income of two-parent families and for single fathers it is only 60% of the income of two parent families. Thus the frequency of children living in poverty is three to five times higher in single-parent families. These parents must also rely to a greater extent on other adults for child care. Although these adults may be sources of support for the single parent, they also may criticize the parent, decreasing confidence in parenting skills. Fatigue associated with working and raising a child may also make consistent parenting difficult. Single parents are likely to have less time for a social life or other activities, which may increase their isolation. When the increased burdens of being a single parent are associated with exhaustion, isolation, and depression, developmental and behavioral problems in the child are more likely.

When the parent is a teenage mother, problems of parenting may be exacerbated further (see Section 12). Being a teenage parent is associated with lower educational attainment, lower paying jobs without much opportunity for autonomy or advancement, and lower self-esteem. They are even less likely than other single mothers to have any support from the child’s father. Children of adolescent mothers are at high risk for cognitive delays, behavioral problems, and difficulties in school. Referral to early intervention services or Head Start programs is important in these situations.

When a single parent has good social supports, is able to collaborate well with other care providers, and has sufficient financial resources, he or she is likely to be successful in raising a child. Pediatricians can improve parental confidence through education about child development and behavior and validation of parenting behaviors. Empathetic understanding of the difficulties of being a single parent can have a healing effect or help a parent discuss difficulties that may suggest the need for a referral to other professionals.

**Children Living with Homosexual Parents**
Many children with a gay or lesbian parent were conceived in the context of a heterosexual relationship. Some parents were unaware of their homosexuality at the time that they married, whereas others may view themselves as bisexual or marry despite the recognition that they are homosexual. Gay men and lesbian women also become parents on their own or in the context of an already established relationship with a same-sex partner through adoption, insemination, or surrogacy. Children living with homosexual parents may encompass many possible family structures.

Parents in these families are likely to have concerns about how disclosure of the homosexuality and the associated social stigma will affect the child. In general earlier disclosure of a parent’s homosexuality to children, especially before adolescence, is associated with better acceptance. Most children of homosexual parents experience some social stigma associated with having a gay or lesbian parent; this may occur in the form of teasing by peers, disapproval from adults, and stress or isolation related to keeping the parent’s homosexuality a secret.

Evidence suggests that having a homosexual parent does not cause increased problems in the parent-child relationship or the child’s social-emotional development. Gender and gender role behaviors are typical for the child’s age. Nonetheless distress related to teasing or maintaining the parent’s secret may be great for some children, especially in early adolescence.

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**Table 24-1 Important Roles Families Play in Supporting Children**

<table>
<thead>
<tr>
<th>PHYSICAL NEEDS</th>
</tr>
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<tbody>
<tr>
<td>Safety</td>
</tr>
<tr>
<td>Food</td>
</tr>
<tr>
<td>Shelter</td>
</tr>
<tr>
<td>Health and health care</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EMOTIONAL SUPPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affection</td>
</tr>
<tr>
<td>Stimulation</td>
</tr>
<tr>
<td>Communication</td>
</tr>
<tr>
<td>Guidance/discipline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EDUCATION AND SOCIALIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values</td>
</tr>
<tr>
<td>Relationships</td>
</tr>
<tr>
<td>Community</td>
</tr>
<tr>
<td>Formal schooling</td>
</tr>
</tbody>
</table>
when issues of peer acceptance, sexual identity, and separation from one’s parents are especially strong.

Adoption

Adoption is a legal and social process that provides full family membership to a child not born to the adoptive parents. Approximately 2% of children in the United States are adopted. A significant proportion of legal and informal adoptions are by stepparents or relatives of the child. Most adoptions in the United States involve U.S. parents adopting U.S. children, but shifting cultural trends have increased the diversity in the ways in which adoptions occur (e.g., international adoptions, single-parent adoptions, privately arranged adoptions, and the use of a surrogate parent). These types of adoption each raise unique issues for families and health care providers. Open adoptions in which the biologic parents and birth parents agree to interact are occurring with increased frequency and create new issues for the adoption triad (biologic parent, adoptive parent, and child).

Pediatricians are in an ideal position to help adoptive parents obtain and evaluate medical information, consider the unique medical needs of the adopted child, and provide a source of advice and counseling from the preadooption period through the issues that may arise when the child is an adolescent. A preadooption visit may allow discussion of medical information that the prospective parents have received about the child and identify important missing information such as the medical history of the biologic family and the educational and social history of the biologic parents. The preadooption period is the time that families are most likely to be able to obtain this information. Depending on the preadoption history, there may be risks of infections, in utero substance exposure, poor nutrition, or inadequate infant care that should be discussed with adoptive parents.

When the adopted child is first seen, screening for medical disorders beyond the typical age-appropriate screening tests should be considered. If the child has not had the standard newborn screening tests, the pediatrician may need to obtain these tests. Documented immunizations should be reviewed and, if needed, a plan developed to complete the needed immunizations (see Chapter 94). Children may be at high risk for infection based on the biologic mother’s social history or the country from which the child was adopted, including infection with human immunodeficiency virus, hepatitis B, cytomegalovirus, tuberculosis, syphilis, and parasites. A complete blood count may be needed to screen for iron deficiency.

A knowledgeable pediatrician also can be a valuable source of support and advice about psychosocial issues. The pediatrician should help the adoptive parents think about how they will raise the child while helping the child to understand the fact that he or she is adopted. Neither denial of nor intense focus on the adoption is healthy. Parents should use the term adoption around their children during the toddler years and explain the simplest facts first. Children’s questions should be answered honestly. Parents should expect the same or similar questions repeatedly, and that during the preschool period the child’s cognitive limitations make it likely the child will not fully understand the meaning of adoption. As children get older, they may have fantasies of being reunited with their biologic parents, and there may be new challenges as the child begins to interact more with individuals outside of the family. Families may want advice about difficulties created by school assignments such as creating a genealogic chart or teasing by peers. During the teenage years, the child may have questions about his or her identity and a desire to find his or her biologic parents. Adoptive parents may need reassurance that these desires do not represent rejection of the adoptive family but the child’s desire to understand more about his or her life. In general adopted adolescents should be supported in efforts to learn about their past, but most experts recommend encouraging children to wait until late adolescence before deciding to search actively for the biologic parents.

Although adopted children have a higher rate of school, learning, and behavioral problems, much of this increase is likely to be related to biologic and social influences before the adoption. The pediatrician can play an important role in helping families distinguish developmental and behavioral variations from problems that may require recommendations for early intervention, counseling, or other services.

Foster Care

Foster care is a means of providing protection for children who require out-of-home placement, most commonly because of homelessness, parental inability to care for the child, parental substance abuse, or child neglect or abuse. From the late 1990s through 2005, over half a million children were in foster care, but between 2005 and 2010, the number of children living in foster care decreased by about 20%. These decreases were associated with changes in federal and state policies that have emphasized shortened stays in foster care, promoted more rapid adoptions, and expanded efforts to support troubled families.

The 400,000 children in foster care are at extremely high risk for medical, nutritional, developmental, behavioral, and mental health problems. At the time of placement in foster care, most of these children have received incomplete medical care and have had multiple detrimental life experiences. Comprehensive assessments at the time of placement reveal many untreated acute medical problems, and nearly half of the children have a chronic illness. Developmental delays and serious behavioral or emotional disorders are common.

Ideally foster care provides a healing service for these children and families, leading to reunification or adoption. Too often children experience multiple changes in placement within the foster care system, further exacerbating the problems foster children may have in forming a secure relationship with adult caregivers. Children may manifest this difficulty by resisting foster parents’ attempts to develop a close relationship. This detachment from the foster parent may be difficult for the foster parent to endure, which may perpetuate a cycle of placement failures. The trauma or neglect experienced that led to the need for foster care in combination with instability of placements causes enduring long-term difficulties. Foster care alumni report rates of anxiety disorders, depression, substance abuse, and posttraumatic stress disorder that are two to six times higher than in the general population. Furthermore although the protections of the foster care system often end at 18 years of age, these adolescents rarely have the skills and maturity needed to allow them to be successful living independently. Thus the Fostering Connections to Success
and Increasing Adoptions Act of 2008 mandates that effective transition to adulthood planning be done with youth in foster care.

The challenges for the foster care system are great. However when children are placed with competent and nurturing foster parents and provided coordinated care from skilled professionals, significant improvements in a child’s health status, development, and academic achievement usually occur.

**FAMILY DYSFUNCTION**

**Physical Needs**

Failure to meet a child’s physical needs for protection or nutrition results in some of the most severe forms of family dysfunction (see Chapters 21 and 22). There are many other ways in which parental behaviors can interfere with a child having a healthy and safe environment, such as prenatal and postnatal substance abuse. Prenatal use of alcohol can damage the fetus resulting in spectrum disorders known as *fetal alcohol spectrum disorders* (FASD). At the most severe end of the spectrum, this teratogen causes *fetal alcohol syndrome* (FAS) characterized by in utero and postnatal growth retardation, microcephaly, intellectual disability, and a characteristic dysmorphic facial appearance. Other manifestations of FASD include birth defects and problems with coordination, attention, hyperactivity, impulsivity, learning, or behavior. Children with these difficulties may be diagnosed with *alcohol-related neurodevelopmental disorder, alcohol-related birth defects, or partial FAS*.

Other substances also may affect the fetus, but investigation of these effects is complicated by the fact that often more than one substance is used, and nutrition and prenatal care are not optimal. Cigarette smoking during pregnancy is associated with lower birth weight and increased child behavioral problems. Use of cocaine in the perinatal period has been associated with prematurity, intracranial hemorrhages, and abruptio placentae. Exposure to opiates in utero can result in prematurity and a neonatal withdrawal syndrome. Investigations of the effects of cocaine and opiates on cognitive development have produced mixed results.

Parental substance abuse after the child’s birth is associated with increased family conflict, decreased organization, increased isolation, and increased family stress related to marital and work problems. Family violence may be more frequent. Despite the fact that these parents often have difficulty providing discipline and structure, they may expect their children to be competent at a variety of tasks at a younger age than non-substance–abusing parents. This sets the children up for failure and contributes to increased rates of depression, anxiety, and low self-esteem. The parents’ more accepting attitude toward alcohol and drugs seems to increase the chance that their children will use substances during adolescence.

Parents also may expose children directly to the harmful effects of other substances, such as exposure to *second hand cigarette smoke*, which is consistently associated with increased rates of childhood respiratory illnesses, otitis media, and sudden infant death syndrome. Despite these effects, only a few parents restrict smoking in their homes. There are many other ways in which parents may not physically protect their children. Failing to immunize children, to childproof the home adequately, and to provide adequate supervision are other examples.

Parents’ attempts to provide too much protection for their child also can cause problems. One example of this is the *vulnerable child syndrome* in which a child who is ill early in life continues to be viewed as vulnerable by the parents despite that the child has fully recovered. Behavioral difficulties may result if parents are overindulgent and fail to set limits. Parental reluctance to leave the child may contribute to the child having separation anxiety. Parents may be particularly attentive to minor variations in bodily functions, leading them to seek excess medical care. If the physician does not recognize this situation, the child may be exposed to unnecessary medical procedures.

**Emotional Support, Education, and Socialization**

Failure to meet a child’s emotional or educational needs can have a severe and enduring negative impact on child development and behavior. Infants need a consistent adult who learns to understand their signals and meets the infant’s needs for attention as well as food. As the adult caregiver learns these signals, he or she responds more rapidly and appropriately to the infant’s attempts at communication. Through this process, often referred to as *attachment*, the special relationship between parent and child develops. When affectionate and responsive adults are not consistently available, infants often are less willing to explore the environment and may become unusually clingy, angry, or difficult to comfort.

Appropriate stimulation also is vital for a child’s cognitive development. Children whose parents do not read to them and do not play developmentally appropriate games with them have lower scores on intelligence tests and more school problems. In these situations, early intervention has been shown to be particularly effective in improving skill development and subsequent school performance. At the other extreme, there are increasing concerns that some parents may provide too much stimulation and scheduling of the child’s day. There may be such emphasis on achievement that children come to feel that parental love is contingent on achievement. There are concerns that this narrow definition of success may contribute to problems with anxiety and self-esteem for some children.

**VIOLENCE**

**INTIMATE PARTNER VIOLENCE AND CHILDREN**

Intimate partner violence (IPV) is a pattern of purposeful coercive behaviors aimed at establishing control of one partner over the other that may include inflicted physical injury, psychological abuse, sexual assault, progressive social isolation, stalking, deprivation, intimidation, and threats. Such violence between adults affects the lives of millions of children each year. Children experience IPV by seeing or hearing the violence and its aftermath. Children who live in households with
IPV often develop psychological and behavioral problems that interfere with their ability to function normally in school, at home, and with peers. They may be injured during violent outbursts, sometimes while attempting to intervene on behalf of a parent. Many children are victims of abuse themselves. It is estimated that there is at least a 50% concurrence rate between IPV and child abuse. Children who grow up in violent households learn that violence is appropriate in intimate relationships. A history of having witnessed IPV as a child is a strong predictor for becoming a batterer in adulthood. In addition to sporadic outbursts of violence, children who live in households with IPV experience disruptive events that can overtly or subtly affect the child’s development. Although partner violence often occurs between male perpetrators and female victims, it may also occur bi-directionally and may be better conceptualized as family or interpersonal-violence. Violence may escalate during the perinatal period.

There is no particular behavioral consequence or disturbance that is specific to children who witness IPV. Some children are traumatized by fear for their caregiver’s safety and feel helpless. Others may blame themselves for the violence. Children may have symptoms of posttraumatic stress disorder, depression, anxiety, aggression, or hypervigilance. Older children may have conduct disorders, poor school performance, low self-esteem, or other nonspecific behaviors. Infants and young toddlers are at risk for disrupted attachment and routines around eating and sleeping. Preschoolers may show signs of regression, irritable behavior, or temper tantrums. During school-age years, children may show both externalizing (aggressive or disruptive) and internalizing (withdrawn and passive) behaviors. Because of family isolation, some children have no opportunity to participate in extracurricular activities at school and do not form friendships. Adolescents in homes where IPV is present have higher rates of school failure, substance abuse, and risky sexual behaviors. These adolescents are more likely than their peers to enter into a violent dating relationship.

Because of the high concurrence of IPV and child abuse, asking about IPV is part of the screening for violence against children. Recognizing the importance of IPV screening in pediatric practice, the American Academy of Pediatrics has endorsed universal screening in this setting and suggests that intervening on behalf of battered women may be one of the most effective means of preventing child abuse. Without standardized screening, pediatricians may underestimate the IPV prevalence in their practices. Parents should not be screened together. Questions about family violence should be direct, nonjudgmental, and done in the context of child safety and anticipatory guidance (Table 25-1).

Intervention is needed for caregivers who disclose IPV. It is appropriate to show concern and to provide available community resources. It is important to assess for the safety of the victim and the children. In some states, physicians are mandated to report IPV. Information for families that provides details about community resources and state laws is helpful.

**YOUTH VIOLENCE**

Youth violence is a leading cause of pediatric mortality in the United States. Homicide is the second leading cause of death for all children 1 to 19 years of age. Each year nearly 6000 children, primarily adolescents, are victims of homicide, and 4000 more commit suicide. Youth violence is a problem in urban, suburban, and rural communities and affects children across race and gender. Surveys of adolescents show that 30% to 40% of boys and 15% to 30% of girls report having committed a serious violent offense during childhood, including robbery, rape, aggravated assault, or homicide. Most of these crimes are not reported to the police, and the perpetrator is arrested in a few cases only. Although boys commit more crimes than girls, this gap has narrowed. Boys are much more likely to be arrested for their crimes. Self-reported violent events do not differ much between white and minority adolescents; the latter are more likely to be arrested for their crimes.

Most violent youth begin to exhibit their violent behaviors during early adolescence. Bullying, which peaks in middle school, is a form of aggression in which a child repeatedly and intentionally intimidates, harasses, or physically harms another child. Technology-assisted bullying behavior or cyber-bullying has become a major concern. Psychosocial consequences of being bullied include depression and suicidal ideation. Children who bully others are more likely to be involved with other problem behaviors, such as smoking and alcohol use. Bullying and being bullied are both associated with higher rates of weapon carriage and fighting. Although most bullies

<table>
<thead>
<tr>
<th>Table 25-1</th>
<th>Questions for Adults and Children Related to Family Violence</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOR THE CHILD</td>
<td></td>
</tr>
<tr>
<td>How are things at home and at school?</td>
<td></td>
</tr>
<tr>
<td>Who lives with you?</td>
<td></td>
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<tr>
<td>How do you get along with your family members?</td>
<td></td>
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<tr>
<td>What do you like to do with them?</td>
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<tr>
<td>What do you do if something is bothering you?</td>
<td></td>
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<tr>
<td>Do you feel safe at home?</td>
<td></td>
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<tr>
<td>Do people fight at home? What do they fight about? How do they fight?</td>
<td></td>
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<tr>
<td>ADDITIONAL QUESTIONS FOR THE ADOLESCENT</td>
<td></td>
</tr>
<tr>
<td>Do your friends get into fights often? How about you?</td>
<td></td>
</tr>
<tr>
<td>When was your last physical fight?</td>
<td></td>
</tr>
<tr>
<td>Have you ever been injured during a fight?</td>
<td></td>
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<tr>
<td>Has anyone you know been injured or killed?</td>
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<tr>
<td>Have you ever been forced to have sex against your will?</td>
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<tr>
<td>Have you ever been threatened with a gun or a knife?</td>
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<tr>
<td>How do you avoid getting in fights?</td>
<td></td>
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<tr>
<td>Do you carry a weapon for self-defense?</td>
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<tr>
<td>FOR THE PARENT</td>
<td></td>
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<tr>
<td>Do you have any concerns about your child?</td>
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<tr>
<td>Who helps with your child?</td>
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<tr>
<td>How do you feel about your neighborhood?</td>
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<tr>
<td>Do you feel safe at home?</td>
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<tr>
<td>Is there any fighting or violence at home?</td>
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<tr>
<td>Does anyone at home use drugs?</td>
<td></td>
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<tr>
<td>Have you been frightened by your partner?</td>
<td></td>
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<tr>
<td>Does your partner ever threaten you or hurt you?</td>
<td></td>
</tr>
</tbody>
</table>

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**Psychosocial Issues**

Bullying, which peaks in middle school, is a form of aggression in which a child repeatedly and intentionally intimidates, harasses, or physically harms another child. Technology-assisted bullying behavior or cyber-bullying has become a major concern. Psychosocial consequences of being bullied include depression and suicidal ideation. Children who bully others are more likely to be involved with other problem behaviors, such as smoking and alcohol use. Bullying and being bullied are both associated with higher rates of weapon carriage and fighting. Although most bullies
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**Table 25-2  Risk and Protective Factors for Serious Youth Violence by Age of Onset**

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>EARLY ONSET (&lt;12 yr)</th>
<th>LATER ONSET (&gt;12 yr)</th>
<th>PROTECTIVE FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance use*</td>
<td>General offenses</td>
<td>Intolerance toward deviance</td>
<td></td>
</tr>
<tr>
<td>General offenses</td>
<td>Aggression†</td>
<td>High IQ</td>
<td></td>
</tr>
<tr>
<td>Being male</td>
<td>Being male</td>
<td>Being female</td>
<td></td>
</tr>
<tr>
<td>Antisocial behavior</td>
<td>Physical violence</td>
<td>Positive social orientation</td>
<td></td>
</tr>
<tr>
<td>Aggression**</td>
<td>Antisocial attitudes</td>
<td>Perceived sanctions for transgressions</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>Crimes against persons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to TV violence</td>
<td>Low IQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low IQ</td>
<td>Substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisocial attitudes</td>
<td>Risk-taking behaviors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dishonesty†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low SES/poverty</td>
<td>Poor parent-child relations</td>
<td>Supportive parents or other adults</td>
<td></td>
</tr>
<tr>
<td>Antisocial parents</td>
<td>Low parent involvement</td>
<td>Parental monitoring</td>
<td></td>
</tr>
<tr>
<td>Poor parent-child relations</td>
<td>Antisocial parents</td>
<td>Parents’ positive evaluation of peers</td>
<td></td>
</tr>
<tr>
<td>Broken home</td>
<td>Broken home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abusive, neglectful</td>
<td>Low SES/poverty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>parents</td>
<td>Abusive parents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor attitude</td>
<td>Poor attitude</td>
<td>Commitment to school</td>
<td></td>
</tr>
<tr>
<td>Poor performance</td>
<td>Poor performance; academic failure</td>
<td>Recognition for involvement in school activities</td>
<td></td>
</tr>
<tr>
<td>Peer</td>
<td>Weak social ties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisocial peers</td>
<td>Weak social ties</td>
<td>Friends who engage in conventional behavior</td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>Gang membership</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neighborhood crime</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neighborhood drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neighborhood disorganization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Bold = factors with strongest effect.
†Males only.

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do not progress into serious violent offenders, violent behavior that continues into high school years indicates the potential for severe violent behavior in adulthood. Another subset of violent youth begins at a very young age. These children tend to be more serious offenders, perpetrate more crimes, and more often continue their violence into adulthood. Most adolescent violence ends by young adulthood. Most violent youth are only intermittently violent. Frequent acts of violence are committed more commonly by youth who start their violence before the onset of puberty. These violent youth need to be evaluated for cognitive impairments or mental illness.

Serious youth violence is not an isolated problem but usually coexists with other adolescent risk-taking behaviors, such as drug use, truancy and school dropout, early sexual activity, and gun ownership. Risk factors for youth violence are slightly different for children who begin their violence early in life compared with youth who begin during adolescence. Often these risk factors exist in clusters, and they tend to be additive. Although understanding risk factors for violence is crucial for developing prevention strategies, the risk factors do not predict whether a particular individual will become violent. For children who begin their violence early in life, the strongest risk factors are early substance abuse (<12 years of age) and perpetration of nonviolent, serious crimes during childhood. Additional risk factors include poverty, male gender, and antisocial behavior. For children who begin their violence during adolescence, individual risk factors are less important, whereas factors related to peer groups are most important. Gang membership, associating with antisocial or delinquent friends, being unpopular in school, and having weak ties to conventional peer groups are important risk factors for adolescent-onset violence (Table 25-2). The strength of the listed risk factors is not uniform, and some factors show a small effect only. Table 25-2 also lists protective factors that seem to buffer the effects of risk factors. One important protective factor is the child’s level of school connectedness, such as involvement in class and extracurricular activities, and how positively the child regards the school’s personnel. Another protective factor is the support of nonviolent family members and close friends.

Violence prevention efforts that target risk and protective factors need to be developmentally appropriate. Education about the dangers of substance abuse should begin before the onset of puberty, whereas adolescent programs must consider the importance of peer group identification. Many violence prevention programs fail to show long-term effects. Effective violence prevention programs must address simultaneously...
individual, family, and environmental (school, peer group, social) risk factors; capitalize on the child's strengths; involve family and other supports; and be implemented over an extended period.

**DATING VIOLENCE AND DATE RAPE**

Dating violence and date rape are common. It is estimated that 15% to 40% of adolescents have experienced violence in a dating relationship. Adolescent women experience higher rates of sexual assault than any other age group. An acquaintance or partner of the victim perpetrates most adolescent sexual assaults. Risk factors for date rape include initiating dating at a young age, initiating early sexual activity, and having a history of past sexual abuse or victimization. A history of child abuse by parents or siblings increases the risk of dating violence. Adolescent boys who believe that it is appropriate to strike a girl if she insults or embarrasses him or intentionally tries to make him jealous are at risk for becoming perpetrators. Date-specific factors put some teens at risk for date rape, including who initiated the date, the date activities, which person drove, and who paid.

Alcohol use is common in episodes of adolescent sexual assault, occurring in approximately 50% of cases. Drugs such as benzodiazepines, cocaine, and marijuana may also contribute. Flunitrazepam (Rohypnol) and gamma hydroxybutyrate are two commonly implicated drugs that cause sedation and amnesia, especially when used in conjunction with alcohol.

Relatively few victims of date rape report the assault to law enforcement. Reporting rates are even lower when the victim knows the perpetrator. Women who report assaults to the police are more likely to receive timely medical care; it is likely that many sexually assaulted adolescents do not receive medical attention, putting them at risk for physical and mental health consequences. Routine adolescent health care should screen for adolescent dating violence, provide routine sexually transmitted infection evaluation, and be able to identify counseling resources for teens who are victims or perpetrators of dating violence (see Chapter 116).

**DIVORCE, SEPARATION, AND BEREAVEMENT**

The family is the child's principal resource for meeting needs for protection, emotional support, education, and socialization. A variety of different disruptions may cause the child to be separated from his or her parents. At times these separations may be relatively brief but unexpected (e.g., a parent's acute illness or injury). The separation may occur in the context of significant parental discord, as often occurs with a divorce. The death of a parent results in a permanent separation that may be anticipated or unanticipated. All of these disruptions cause significant stress for the child, with the potential for long-term adverse consequences. The child's adaptation to these stresses is affected by the reasons for the separation and the child's age, temperament, and available support systems.

**DATING VIOLENCE AND DATE RAPE**

Approximately 40% to 50% of first marriages end in divorce. About half of these divorces occur in the first 10 years of marriage, so there are often young children in the family when the parents divorce. At least 25% of children experience the divorce or separation of their parents. Few events in childhood are as dramatic and challenging for the child as divorce.

Divorce is likely to be accompanied by changes in behavioral and emotional adjustment. In the immediate post-divorce period, many children exhibit anger, noncompliance, anxiety, and depression. Children from divorced families require psychological help two to three times more frequently than children with married parents. Long-term studies suggest that in the absence of ongoing stressors, most children demonstrate good adjustment a few years after the divorce, but some have enduring difficulties.

Divorce is not a single event, but a process that occurs over time. In most cases, marital conflict begins long before the physical or legal separation, and the divorce brings about permanent changes in the family structure. Multiple potential stressors for the child are associated with divorce, including parental discord before and after the divorce, changes in living arrangements and sometimes location, and changes in the child's relationship with both parents.

The child's relationship with each parent is changed by the divorce. In the short-term, the parent is likely to experience new burdens and feelings of guilt, anger, or sadness that may disrupt parenting skills and family routines. Contact with the noncustodial parent may decline greatly. Parents may be perceived by their children as being unaware of the child's distress around the time of the divorce. Pediatricians can help parents understand things they can do that will be reassuring to the child. Maintaining contact with both parents, seeing where the noncustodial parent is living, and, in particular, maintaining familiar routines are comforting to the child in the midst of the turmoil of a separation and divorce. The child should attend school and continue to have opportunities to interact with friends. Given the parents' distress, assistance from the extended family can be helpful, but these family members may not offer to help for fear of “interfering.” It may be helpful for pediatricians to encourage parents to ask for this assistance. Pediatricians should look for maladaptive coping responses. Some parents may respond to their increased burdens and distress by treating their children as friends with whom they share their distress. Alternatively they may place excessive responsibilities on the child or leave the child unsupervised for longer periods of time. Responses such as these increase the chance that the child will develop behavioral or emotional problems.

**Reactions to Divorce at Different Ages**

The child's reaction to the divorce is influenced by the child's age and developmental level. Although infants do not react directly to the divorce, they require special considerations...
in relation to custody and visitation because infants need a stable daily routine and regular contact with a primary caregiver to develop secure attachment. Separations from a primary caregiver should be brief. Increased infant irritability or listlessness and withdrawal may be signs of distress for an infant. Preschool children are characterized by having magical beliefs about cause and effects and an egocentric view of the world. They may believe that something they did caused the divorce, leading them to be particularly upset. They may engage in unusual behaviors that they believe will bring the parents back together again. At this age, parents need to deliver a clear message that the divorce was related to disagreements between the parents, that nothing the child did caused the divorce, and that nothing the child could do would bring the parents back together again. Preschool children may reason that if the parents left each other they also might leave the child. To counteract this fear of abandonment, children may need to be reassured that although parents separated, they will not abandon the child and that the child's relationship with both parents will endure.

School-age children have a concrete understanding of cause and effect; if something bad happened, they understand that something caused it to happen. However, they are not likely to understand fully the subtleties of parental conflict or the idea that multiple factors contribute to a conflict. Children at this age may still worry that something they did caused the divorce. They may express more anger than younger children and often feel rejected. Many young school-age children worry about what will happen to one or both parents. School performance often deteriorates. Older elementary school-age children may believe that one parent was wronged by the other. This belief, in conjunction with their concrete understanding of cause and effect, allows children to be easily co-opted by one parent to take sides against the other. Parents need to understand this vulnerability and resist the temptation to support their child in taking sides.

Adolescents may respond to the divorce by acting out, becoming depressed, or experiencing somatic symptoms. Adolescents are developing a sense of autonomy, a sense of morality, and the capacity for intimacy, and divorce may lead them to question previously held beliefs. They may be concerned about what the divorce means for their future and whether they too will experience marital failure. Questioning of previous beliefs in conjunction with decreased supervision may set the stage for risk-taking behaviors, such as truancy, sexual behaviors, and alcohol or drug use.

Outcome of Divorce
One of the best predictors of children's adaptation to divorce is whether the physical separation is associated with a decrease in the child's exposure to parental discord. In most cases, divorced parents still must interact with each other around the child's schedule, child custody and support, and other parenting issues. These types of issues create the potential for the child to have ongoing exposure to significant discord between the parents. For example if one parent tends to keep the child up much later than the bedtime at the other parent's house, sleep problems may develop. When children feel caught in the middle of ongoing conflicts between their divorced parents, behavior or emotional problems are much more likely. Regardless of how angry parents are with each other, the parents should be counseled that they must shield their child from this animosity. Clear rules about schedules, discipline, and other parenting roles is ideal, but in cases of conflict it can also be helpful for the pediatrician to help a parent accept that he or she can only control his or her actions and decisions related to the child. When parents have trouble resolving these issues, mediation may be helpful. Pediatricians need to be wary of parents' attempts to recruit them into custody battles to substantiate claims of poor parenting, unless the pediatrician has first-hand knowledge that the concerns are valid.

Although the primary physical residence for most children is still with the mother, the court's bias toward preferring mothers in custody decisions has decreased, and there is more emphasis on including both parents in the child's life. In the early 1980s, 50% of children had no contact with their fathers 2 or 3 years after a divorce, whereas today only 20% to 25% of children have no contact with their father. Most states now allow joint physical or legal custody. In joint physical custody, the child spends a significant amount of time with each parent, and in joint legal custody, parents share authority in decision making. Although joint custody arrangements may promote the involvement of both parents in the child's life, they also can be a vehicle through which parents continue to express their anger at each other. When parents have severe difficulty working together, joint custody is an inappropriate arrangement and has been associated with deterioration in the child's psychological and social adjustment.

Divorce often creates financial difficulties. Family income usually declines in the first year after the divorce. Only about half of mothers who have child support awards receive the full amount, and one fourth receive no money at all. These financial changes may have multiple adverse affects on the child. A move to a new house may require the child to attend a new school disrupting peer relationships and other potential supports. The child may spend more time in child care if one or both parents have to increase work hours.

Role of the Pediatrician
Pediatricians may be confronted with issues related to marital discord before the divorce, may be consulted around the time of the divorce, or may be involved in helping the family to manage issues in the years after the divorce. The pediatrician can be an important voice in helping the parents understand and meet the child's needs (Table 26-1). Before the divorce, parents may wonder what they should tell their children. Children should be told of the parents' decision before the physical separation. The separation should be presented as a rational step in resolving marital conflict and should prepare the child for the changes that will occur. Parents should be prepared to answer children's questions, and they should expect that the questions will be repeated over the next months. Once parents have told children of the separation, it may be confusing to the child if the parents continue to appear to live together and may raise false hopes that the parents will not divorce.

Many parents report not feeling like their life had stabilized until 2 to 3 years or more after the divorce, and for some the divorce remains a painful issue 10 years later. The child's emotional adjustment to divorce is closely predicted by the parents' adjustment so parents should be encouraged to get help for themselves if they are struggling emotionally after a divorce.
Although most children ultimately show good adjustment to the divorce, some have significant acting-out behaviors or depression that requires referral to a mental health professional. Some parents need the assistance of a mediator or family therapist to help them stay focused on their child's needs. In the most contentious situations, a guardian ad litem may need to be appointed by the court. This individual is usually a lawyer or mental health professional with the power to investigate the child and family's background and relationships to make a recommendation to the court as to what would be in the best interests of the child.

### SEPARATIONS FROM PARENTS

Children experience separations from their primary caregiver for a variety of reasons. Brief separations, such as those to attend school, camp, or other activities, are nearly a universal experience. Many children experience longer separations for a variety of reasons, including parental business trips, military service, or hospitalization. Child adjustment to separation is affected by child factors, such as the age of the child and the child's temperament; factors related to the separation, such as the length of and reason for the separation, whether the separation was planned or unplanned; and factors related to the caregiving environment during the separation, such as how familiar the child is with the caregiver and whether the child has access to friends and familiar toys and routines.

Children between 6 months and 3 to 4 years of age often have the most difficulty adjusting to a separation from their primary caregiver. Older children have cognitive and emotional skills that help them adjust. They may be better able to understand the reason for the separation, communicate their feelings, and comprehend the passage of time, allowing them to anticipate the parent's return. For older children, the period immediately before a planned separation may be particularly difficult if the reason for the separation causes significant family tension, as it may in the case of hospitalization or military service.

If parents anticipate a separation, they should explain the reason for the separation and, to the extent possible, give concrete information about when they will be in contact with the child and when they will return home. If the child can remain at home with a familiar and responsive caregiver, this is likely to help adjustment. If children cannot remain at home, they should be encouraged to take with them transitional objects, such as a favorite blanket or stuffed animal, familiar toys, and important objects such as a picture of the parent. Maintenance of familiar family routines and relationships with friends should be encouraged.

### DEATH OF A PARENT OR FAMILY MEMBER AND BEREAVEMENT

Death of a close family member is a sad and difficult experience. When a child loses a parent, it is a devastating experience. This experience is not rare. By 15 years of age, 4% of children in the United States experience the death of a parent. This experience is likely to alter forever the child's view of the world as a secure and safe place. Similar to the other separations, a child's cognitive development and temperament along with the available support systems affect the child's adjustment after the death of a parent. Many of the recommendations in Table 26-1 are helpful. The death of a parent or close family member also brings up some unique issues.

### Explaining Death to a Child

Children's understanding of death changes with their cognitive development and experiences (see Chapter 4). Preschool children often do not view death as permanent and may have magical beliefs about what caused death. As children become older, they understand death as permanent and inevitable, but the concept that death represents the cessation of all bodily functions and has a biologic cause may not be fully appreciated until adolescence.

Death should not be hidden from the child. It should be explained in simple and honest terms that are consistent with the family's beliefs. The explanation should help the child to understand that the dead person's body stopped functioning and that the dead person will not return. Preschool children should be reassured that nothing they did caused the individual to die. One should be prepared to answer questions about where the body is and let the child's questions help determine what information the child is prepared to hear. False or misleading information should be avoided. Comparisons of death to sleep may contribute to sleep problems in the child.

There are many possible reactions of children to the death of a parent or close relative. Sadness and a yearning to be with the dead relative are common. Sometimes a child might express a wish to die so that he or she can visit the dead relative, but a plan or desire to commit suicide is uncommon and would need immediate evaluation. A decrease in academic functioning, lack of enjoyment with activities, and changes in appetite and sleep can occur. About half of children have their most severe symptoms about 1 month after the death, but for many the most severe symptoms in reaction to the death do not occur until 6 to 12 months after the death.

<table>
<thead>
<tr>
<th>Table 26-1 General Recommendations for Pediatrists to Help Children During Separation, Divorce, or Death of a Close Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acknowledge and provide support for grief that the parent/caregiver is experiencing.</td>
</tr>
<tr>
<td>Help parent/caregiver consider child's needs.</td>
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<tr>
<td>Encourage parent/caregiver to maintain routines familiar to the child.</td>
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<tr>
<td>Encourage continued contact between child and his or her friends.</td>
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<tr>
<td>If primary residence changes, the child should take transitional objects, familiar toys, and other important objects to the new residence.</td>
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<tr>
<td>Minimize frequent changes in caregivers, and for infants keep brief the times spent away from primary caregiver.</td>
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<tr>
<td>Have parent/caregiver reassure the child that he or she will continue to be cared for.</td>
</tr>
<tr>
<td>Have parent/caregiver reassure the child that he or she did not cause the separation, divorce, or death (especially important in preschool children).</td>
</tr>
<tr>
<td>Encourage parent/caregiver to create times or rituals that allow the child to discuss questions and feelings if the child wishes.</td>
</tr>
</tbody>
</table>

### Death of a Child

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Should the Child Attend the Funeral?
Children often find it helpful to attend the funeral. It may help the child to understand that the death occurred and provide an opportunity to say good-bye. Seeing others express their grief and sadness may help the child to express these feelings. Going to the funeral helps prevent the child from having fears or fantasies about what happened at the funeral. If the child is going to attend the funeral, he or she should be informed of what will happen. If a preschool-age child expresses a desire not to attend the funeral, he or she should not be encouraged to attend. For older children, it may be appropriate to encourage attendance, but a child who feels strongly about not wanting to go to the funeral should not be required to attend.

Suggested Readings
Chapter 27

DIET OF THE NORMAL INFANT

Proper nutrition in infancy is essential for normal growth, resistance to infections, long-term adult health, and optimal neurologic and cognitive development. Healthy nutrition is especially important during the first 6 months, a period of exceptionally accelerated growth and high nutrient requirements relative to body weight (see Chapter 5). Breastfeeding is associated with a reduced risk of many diseases in infants, children, and mothers (for more details visit http://www.nutrition.gov/).

BREASTFEEDING

Human milk and breastfeeding are the ideal and normative standards for infant feeding and nutrition. The American Academy of Pediatrics (AAP) recommends human milk as the sole source of nutrition for the first 6 months of life, with continued intake for the first year, and as long as desired thereafter. Breastfeeding has short- and long-term advantages for infant neurodevelopment. Pediatric health care providers should approach breastfeeding at multiple levels (individual, community, social, and political) to reach the goals of “Healthy People in 2020”; its targets include 82% of infants with any breastfeeding, 23.7% of infants with exclusive breastfeeding for the first 6 months of life, and lactation support at work of 38%. In collaboration with national and global organizations, including the AAP, World Health Organization (WHO), UNICEF, the Centers for Disease Control and Prevention (CDC), and the Joint Commission, hospitals are asked to promote and facilitate breastfeeding.

The first 2 days of breastfeeding, and perhaps the first hour of life, may determine the success of breastfeeding. The current rate of breastfeeding initiation for the total U.S. population is 75% (Figure 27-1). There is greater emphasis to improve and standardize hospital practices with “Baby Friendly” programs for breastfeeding support.

The Department of Health and Human Services and the CDC recognize that breastfeeding offers infants, mothers, and society compelling advantages in industrialized and developing countries. Human milk feeding decreases the incidence and severity of diarrhea, respiratory illnesses, otitis media, bacteremia, bacterial meningitis, and necrotizing enterocolitis.

There are beneficial effects of feeding preterm infants with human milk on long-term neurodevelopment (IQ) in preterm infants. Preterm breastfed infants also have a lower readmission rate in the first year of life.

Mothers who breastfeed experience both short- and long-term health benefits. Decreased risk of postpartum hemorrhages, more rapid uterine involution, longer period of amenorrhea, and decreased postpartum depression have been observed. Similarly, there is an association between a long lactation of 12 to 23 months (cumulative lactation of all pregnancies) and a significant reduction of hypertension, hyperlipidemia, cardiovascular disease, and diabetes in the mother. Cumulative lactation of more than 12 months also correlates with reduced risk of ovarian and breast cancer.

Adequacy of milk intake can be assessed by voiding and stooling patterns of the infant. A well-hydrated infant voids six to eight times a day. Each voiding should soak, not merely moisten, a diaper, and urine should be colorless. By 5 to 7 days, loose yellow stools should be passed at least four times a day. Rate of weight gain provides the most objective indicator of adequate milk intake. Total weight loss after birth should not exceed 7%, and birth weight should be regained by 10 days. The mean feeding frequency during the early weeks postpartum is 8 to 12 times per day. An infant may be adequately hydrated while not receiving enough milk to achieve adequate energy and nutrient intake. Telephone follow-up is valuable during the interim between discharge and the first doctor visit to monitor the progress of lactation. A follow-up visit should be scheduled by 3 to 5 days of age, and again by 2 weeks of age.

In the newborn period, elevated concentrations of serum bilirubin are present more often in breastfed infants than in formula-fed infants (Chapter 62). Feeding frequency during the first 3 days of life of breastfed infants is inversely related to the level of bilirubin; frequent feedings stimulate meconium passage and excretion of bilirubin in the stool. Infants who have insufficient milk intake and poor weight gain in the first week of life may have an increase in unconjugated bilirubin secondary to an exaggerated enterohepatic circulation of bilirubin. This is known as breastfeeding jaundice. Attention should be directed toward improved milk production and intake. The use of water supplements in breastfed infants has no effect on bilirubin levels and is not recommended.
After the first week of life in a breastfed infant, prolonged elevated serum bilirubin may be due to presence of an unknown factor in milk that enhances intestinal absorption of bilirubin. This is termed breast milk jaundice, which is a diagnosis of exclusion and should be made only if an infant is otherwise thriving, with normal growth and no evidence of hemolysis, infection, biliary atresia, or metabolic disease (Chapter 62). Breast milk jaundice usually lasts no more than 1 to 2 weeks. The American Academy of Pediatrics recommends vitamin D supplementation (400 IU/day starting soon after birth), and, when needed, fluoride after 6 months for breastfed infants.

Common Breastfeeding Problems
Breast tenderness, engorgement, and cracked nipples are the most common problems encountered by breastfeeding mothers. Engorgement, one of the most common causes of lactation failure, should receive prompt attention because milk supply can decrease quickly if the breasts are not adequately emptied. Applying warm or cold compresses to the breasts before nursing and hand expression or pumping of some milk can provide relief to the mother and make the areola easier to grasp by the infant. Nipple tenderness requires attention to proper latch-on and positioning of the infant. Supportive measures include nursing for shorter periods, beginning feedings on the less sore side, air drying the nipples well after nursing, and applying lanolin cream after each nursing session. Severe nipple pain and cracking usually indicate improper latch-on. Temporary pumping, which is well tolerated, may be needed. Meeting with a lactation consultant may help minimize these problems and allow the successful continuation of breastfeeding.

If a lactating woman reports fever, chills, and malaise, mastitis should be considered. Treatment includes frequent and complete emptying of the breast and antibiotics. Breastfeeding usually should not be stopped because the mother’s mastitis commonly has no adverse effects on the breastfed infant.

Untreated mastitis may also progress to a breast abscess. If an abscess is diagnosed, treatment includes incision and drainage, antibiotics, and regular emptying of the breast. Nursing from the contralateral breast can be continued with a healthy infant. If maternal comfort allows, nursing can continue on the affected side.

Maternal infection with human immunodeficiency virus (HIV) is considered a contraindication for breastfeeding in developed countries. When the mother has active tuberculosis, syphilis, or varicella, restarting breastfeeding may be considered after therapy is initiated. If a woman has herpetic lesions on her breast, nursing and contact with the infant on that breast should be avoided. Women with genital herpes can breastfeed. Proper hand-washing procedures should be stressed.

There are limited numbers of medical contraindications for breastfeeding, including pediatric metabolic disorders such as galactosemia, and infants with phenylketonuria, although infants with the latter may alternate breastfeeding with special protein-free or modified formulas. Maternal contraindications are shown in Table 27-1.
Maternal Drug Use

Any drug prescribed therapeutically to newborns usually can be consumed via breast milk without ill effect. The factors that determine the effects of maternal drug therapy on the nursing infant include the route of administration, dosage, molecular weight, pH, and protein binding. Few therapeutic drugs are absolutely contraindicated; these include radioactive compounds, antimetabolites, lithium, and certain antithyroid drugs. The mother should be advised against the use of unprescribed drugs, including alcohol, nicotine, caffeine, or “street drugs.”

Maternal use of illicit or recreational drugs is a contraindication to breastfeeding. If a woman is unable to discontinue drug use, she should not breastfeed. Expression of milk for a feeding or two after use of a drug is not acceptable. Breastfed infants of mothers taking methadone (but no alcohol or other drugs) as part of a treatment program generally have not experienced ill effects.

FORMULA FEEDING

Cow's milk–based formulas are the vast majority of commercial formulas. Most milk-based formulas have added iron, which the AAP recommends, and parents should use only iron-fortified formula unless advised otherwise by the primary health care provider. Infant formula manufacturers have begun to examine the benefits of adding a variety of nutrients and biological factors to infant formula to mimic the composition and quality of breast milk. These include long-chain polyunsaturated fatty acids, nucleotides, prebiotics, and probiotics. Soy-based formulas, which sometimes have added iron, may be used for newborns who may be allergic to cow's milk. However, some newborns allergic to cow's milk are also allergic to the protein in soy formulas. There are hypoallergenic formulas for infants who can't tolerate the basic formulas, such as those with allergies to milk or soy proteins. The proteins in these hypoallergenic formulas are broken down to their basic components and are therefore easier to digest (Table 27-2). Specialized formulas are designed for premature, low birth weight babies. The carbohydrate is generally lactose, although lactose-free cow's milk–based formulas are available. The caloric density of formulas is 20 kcal/oz (0.67 kcal/mL), similar to that of human milk. A relatively high-fat and calorically dense diet (human milk or formula) is needed to deliver adequate

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>BREAST MILK</th>
<th>BREAST MILK AFTER FREEZING AND PASTEURIZING</th>
<th>STANDARD FORMULA</th>
<th>SOY FORMULA</th>
<th>HYPOALLERGENIC FORMULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>1.1 per dL</td>
<td>Reduced</td>
<td>1.5 per dL</td>
<td>1.7 per dL</td>
<td>1.9 per dL</td>
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<td>Fat</td>
<td>4.0 per dL</td>
<td>4.0 per dL</td>
<td>3.6 per dL</td>
<td>3.6 per dL</td>
<td>3.8–3.3 per dL</td>
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<tr>
<td>Carbohydrate</td>
<td>7.2 per dL</td>
<td>7.2 per dL</td>
<td>6.9–7.2 per dL</td>
<td>6.8 per dL</td>
<td>6.9–7.3 per dL</td>
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<tr>
<td>Calcium</td>
<td>290 mg/L</td>
<td>290 mg/L</td>
<td>420–550 mg/L</td>
<td>700 mg/L</td>
<td>635–777 mg/L</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>140 mg/L</td>
<td>140 mg/L</td>
<td>280–390 mg/L</td>
<td>500 mg/L</td>
<td>420–500 mg/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>8.0 mg/L</td>
<td>8.0 mg/L</td>
<td>6.5–8.3 mg/L</td>
<td>13 mg/L</td>
<td>14 mg/L</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Variable</td>
<td>Variable</td>
<td>400 per dL</td>
<td>400 per dL</td>
<td>400 per dL</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osmolality</td>
<td>253 mOsm/L</td>
<td>253 mOsm/L</td>
<td>230 mOsm/L</td>
<td>200–220 mOsm/L</td>
<td>290 mOsm/L</td>
</tr>
<tr>
<td>Renal solute load</td>
<td>75 mOsm/L</td>
<td>75 mOsm/L</td>
<td>100–126 mOsm/L</td>
<td>126–150 mOsm/L</td>
<td>125–175 mOsm/L</td>
</tr>
<tr>
<td>IgA and SlgA</td>
<td>Present</td>
<td>Reduced 30%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IgM</td>
<td>Present</td>
<td>Present</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IgG</td>
<td>Present</td>
<td>Reduced 30%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>Present</td>
<td>Reduced 30%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Present</td>
<td>Reduced 25%</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lipases</td>
<td>Present</td>
<td>Present</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
</tr>
<tr>
<td>Monoglycerides</td>
<td>Present</td>
<td>Present</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
</tr>
<tr>
<td>Free fatty acids</td>
<td>Present</td>
<td>Present</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Present</td>
<td>Present</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
</tr>
<tr>
<td>Alpha-linoleic acid</td>
<td>Present</td>
<td>Present</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
<td>Added to some formulas</td>
</tr>
<tr>
<td>Bifidus factor</td>
<td>Present</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligosaccharides</td>
<td>Present</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Recommended to take full advantage of the child's development. At 2 months it is important to set the stage by making distinctions between sleeping and feeding time. At 4 to 6 months of age, children should be encouraged to self-feed with appropriate finger foods. The choice of foods to meet micronutrients. Children should get two to three servings of vegetables, with a strong family history of food allergy, foods with high allergic potential, such as fish, peanuts, tree nuts, dairy products, and eggs, should probably be avoided. All foods with the potential to obstruct the young infant's main airway should be avoided in general until 4 years of age or older. Because of the risk of infant botulism, honey should not be given before 1 year of age.

Complementary foods help meet the nutritional needs of the infant. If the introduction of solid foods is delayed, nutritional deficiencies can develop, and oral sensory issues (texture and oral aversion) may occur. General signs of readiness include the ability to hold the head up, maturity (around double the birth weight), opening their mouths wide, showing eager anticipation of eating food and interest in foods, sitting unassisted, bringing objects to the mouth, and the ability to track a spoon. The choice of foods to meet micronutrient needs is less critical for formula. Complementary feeding of semisolid foods is suggested. By this age, an exclusively breastfed infant requires additional sources of several nutrients, including protein, iron, and zinc. Cereals commonly are mixed with breast milk, formula, or water and later with fruits. To help identify possible allergies or food intolerances that may arise when new foods are added to the diet, single-grain cereals (rice, oatmeal, barley) are recommended as starting cereals. If juice is given, it should be started only after 6 months of age, be given in a cup (as opposed to a bottle), and limited to 4 oz daily of 100% natural unsweetened juice. An infant should never be put to sleep with a bottle or cup filled with milk, formula, or juice because this can result in Early Childhood Caries (ECC) (see Chapter 127).

Green vegetables bring nutrients, vitamin, minerals, and micronutrients. Children should get two to three servings of vegetables. For infants with a strong family history of food allergy, foods with high allergic potential, such as fish, peanuts, tree nuts, dairy products, and eggs, should probably be avoided. All foods with the potential to obstruct the young infant's main airway should be avoided in general until 4 years of age or older. Because of the risk of infant botulism, honey should not be given before 1 year of age.

Commercially prepared or homemade foods help meet the nutritional needs of the infant. If the introduction of solid foods is delayed, nutritional deficiencies can develop, and oral sensory issues (texture and oral aversion) may occur. General signs of readiness include the ability to hold the head up, maturity (around double the birth weight), opening their mouths wide, showing eager anticipation of eating food and interest in foods, sitting unassisted, bringing objects to the mouth, and the ability to track a spoon. The choice of foods to meet micronutrient needs is less critical for formula.

Caries are tooth infections that start as early as when the deciduous teeth (baby teeth) have erupted. A tooth cavity is caused by a combination of sugar and bacteria in the mouth. Eating a healthy diet and brushing regularly will control sugar and bacteria. Rubbing infant gums with a wet washcloth can be the first step in oral hygiene. There are also ergonomically designed tooth brushes, comfortable and safe for infants, used to rub their gums and create the habit of oral hygiene. A variety of feeding habits beyond nursing and bottle feeding are implicated as causes of dental caries in childhood. Other factors that can lead to these problems are adult age and height. This infection can be prevented by healthy food choices and habits starting in infancy. Exposure to different textures and the process of self-feeding are important neurodevelopmental experiences for infants. A healthy diet is recommended to take full advantage of the child's developmental milestones and for the child's well-being. For the first 2 months, it is important to set the stage by making distinctions between sleeping and feeding time. At 4 to 6 months of age, beginning to actively separate mealtime from bedtime is recommended.

DIET OF THE NORMAL CHILD AND ADOLESCENT

NUTRITION ISSUES FOR TODDLERS AND OLDER CHILDREN

Learning healthy eating behaviors at an early age is an important preventive measure because of the association of diet with several chronic and noncommunicable diseases (NCDs), such as obesity, diabetes, and cardiovascular disease, which may account for approximately 60% of all deaths worldwide. These diseases share risk factors that can be modified by lifestyle changes such as eating less processed food and increasing physical activity. Diets high in fruits and vegetables together with increased physical activity improve metabolic risk factors. The first 1000 days of life are an important time to engage in healthy nutrition behaviors that will promote well-being. Accelerated postnatal growth in infants and young children is an important risk factor for obesity; interventions should be aimed at identifying underlying causes for early prevention. For a discussion of nutrient needs for children and adolescents, see http://www.health.gov/dietaryguidelines.

MILK

The consumption of cow's milk is ideally not introduced until approximately 1 year of age when it is better tolerated. Low-fat (2%) or whole milk is recommended until 2 years of age, after which fat-free or 1% milk is recommended. Excessive milk intake (more than 24 oz/day) should be avoided in toddlers because larger intakes may reduce the intake of a good variety of nutritionally important solid foods and also result in iron deficiency anemia; large intakes also may contribute to excessive caloric intake.

JUICES

Juice intake for toddlers and young children should be limited to 4 oz, and juice intake for children 7 to 18 years of age should be limited to 8 oz/day. Water and milk are the recommended drinks during the day.

GENERAL RECOMMENDATIONS

"ChooseMyPlate" by the U.S. Department of Agriculture can provide parents with a general guideline for the types of foods to be offered on a regular basis. A child should eat three meals a day and two healthy snacks. A general rule for the quantity of food to offer to a child is one tablespoon per age of each food provided per meal, with more given if the child requests. As a rule of thumb, children should not be eating more than an adult palm per serving. By 1 year of age, infants should be eating meals with the family, have a regular schedule of meals and snacks, and be encouraged to self-feed with appropriate finger foods.
The “plate” image is divided into five sections: Fruits, Grains, Vegetables, Protein, and Dairy (Figure 28-1; Table 28-1). Half of the “plate” should be vegetables and fruits, and the other half grains and proteins, with dairy on the side. The “plate” is simple, organized, and serves as a guide for healthy eating. A weekly recommendation for vegetable intake is also provided (Table 28-1).

Other suggestions include the following: switch to fat free or low-fat (1%) milk; make at least half of the grains whole instead of refined grains; avoid oversize proportions; compare sodium (salt) in foods such as soup, bread, and frozen meals; choose foods with lower sodium content; and drink water instead of sugary drinks. After 2 years, it is recommended that the fat intake gradually be reduced to approximately 30% and not less than 20% of calories. Replace proteins from red meat with a mix of fish, chicken, nuts, and legumes.

Power struggles over eating are common between parents and toddlers. The parent’s role is to decide the what, when, and where of the meals. The child’s role is to decide if, what, and how much to eat.

**IRON INTAKE**

Iron intake may be inadequate in some children between 1 and 3 years of age in the United States. Significant iron deficiency anemia exists in some high-risk minority or low-income populations of young children. Toddlers with excessive milk intakes (>32 oz/day) and/or those who consume little meat, green leaves rich in iron, or grains are at risk for iron deficiency.

**NUTRITION ISSUES FOR ADOLESCENTS**

Teen nutrition can be a challenge. Ads for junk food and images of incredibly thin adolescents provide conflicting and unhealthy ideas about what they should eat. Girls ages 14 to 18 need anywhere from 1800 to 2400 calories per day, depending on their activity level and stage of development. Boys of the same age group need 2000 to 3200 calories daily. Poor eating habits may develop during adolescence. Skipped meals (especially breakfast), binge eating with friends or alone, dieting, and consumption of nutrient-poor, calorically dense foods are common problems. Excessive consumption of sugar from soda, fruit drinks, and specialty coffee and tea drinks may contribute to excess weight gain as well as tooth decay and may displace other needed nutrients. Poor calcium intake during adolescence may predispose the adult to future osteoporotic hip fracture. Osteoporosis (osteopenia) during adolescence caused by poor dietary calcium or vitamin D intake or poor absorption of ingested calcium in children and adolescents is a potential problem. Only 1 of 10 teenage girls and 1 of 4 teenage boys get enough calcium every day. Adolescents ages 9 to 18 need 1300 milligrams of calcium daily. Good sources include milk, yogurt, fortified orange juice, cheese, soybeans, and tofu.

Inadequate iron intake may result in symptoms of fatigue and iron deficiency anemia. Iron needs increase during growth spurts, which is why teens are more likely to suffer from iron deficiency anemia. Teenage girls are especially prone to anemia. Student athletes are also vulnerable to inadequate iron intakes, severely restrictive eating patterns, and use of inappropriate nutritional and vitamin supplements. Adolescents should be counseled on specific and healthy dietary choices (see Chapter 70).

**Table 28-1 Recommended Weekly Vegetable Intake** (in cups)

<table>
<thead>
<tr>
<th>AGE (YEARS)</th>
<th>GREEN</th>
<th>ORANGE</th>
<th>STARCH</th>
<th>DRY BEANS/PEAS</th>
<th>OTHER*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3</td>
<td>1</td>
<td>½</td>
<td>1½</td>
<td>½</td>
<td>4</td>
</tr>
<tr>
<td>4-8</td>
<td>1½</td>
<td>1</td>
<td>2½</td>
<td>5½</td>
<td>4½</td>
</tr>
<tr>
<td>&gt;9 Girls</td>
<td>2</td>
<td>1½</td>
<td>2½</td>
<td>5½</td>
<td>6½</td>
</tr>
<tr>
<td>&gt;9 Boys</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>6½</td>
</tr>
</tbody>
</table>

*Including cabbage, cauliflower, green beans, lettuce, zucchini.

**OBESITY**

**Epidemiology**

Childhood obesity is an epidemic in the United States. Data indicate that approximately 17% of children in the United States ages 2 to 20 are obese (body mass index of ≥95th percentile) and more than 30% of U.S. adults are obese. Many obese children become obese adults, and the risk of remaining obese increases with age and degree of obesity. Obesity runs in families and is rarely related to genetic influences. The largest increases in the prevalence of obesity are seen in the most severely overweight classifications and in certain ethnic groups, such as African-American and Mexican-American children. In 2008, obesity cost the nation $147 billion in medical costs. The associations between obesity and television
watching and excessive dietary intake as well as the different rates of obesity observed in urban versus rural areas support the important influence of environment. One important risk factor is maternal obesity during pregnancy. Children born to obese mothers are three to five times more likely to be obese in childhood. Women who gain much more weight than recommended during pregnancy have children who have a higher BMI than normal in adolescence. Also, some small for gestational age (SGA) newborns have higher risks for abnormal postnatal weight gain and diabetes.

**CLINICAL MANIFESTATIONS**

Complications of obesity in children and adolescents can affect virtually every major organ system. High BMI increases the risk of metabolic and cardiovascular diseases and some cancers; it is also the most important modifiable risk factor for glycemia and diabetes. The history and physical examination should screen for many potential complications noted among obese patients (Table 29-1), in addition to specific syndromes associated with obesity (Table 29-2). Medical complications are often related to the degree of obesity and usually decrease in severity or resolve with weight reduction. Obesity is associated with the presence of precursors of coronary heart disease that are already evident in 12- and 13-year-old children. Type 2 diabetes is also increasing in children.

**ASSESSMENT**

The diagnosis of obesity depends on the measurement of excess body fat. Actual measurement of body composition is not practical in most clinical situations.

<table>
<thead>
<tr>
<th>Table 29-1</th>
<th>Complications of Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMPLICATION</strong></td>
<td><strong>EFFECTS</strong></td>
</tr>
<tr>
<td>Psychosocial</td>
<td>Peer discrimination, teasing, reduced college acceptance, isolation, depression, eating disorders (binge-eating), reduced job promotion*</td>
</tr>
<tr>
<td>Growth</td>
<td>Advance bone age, increased height, early menarche</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Pseudotumor cerebri</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypertension, cardiac hypertrophy, arrhythmias, ischemic heart disease, sudden death*</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>Slipped capital femoral epiphysis, Blount disease</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Insulin resistance, type 2 diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, gout*, hepatic steatosis, polycystic ovary disease, cholelithiasis</td>
</tr>
</tbody>
</table>

*BMI (body mass index; BMI = wt (kg) / Ht² (m)) is a convenient screening tool that correlates fairly strongly with body fatness in children and adults. **BMI age-specific and gender-specific percentile curves** (for 2- to 20-year-olds) allow an assessment of BMI percentile (available online at [http://www.cdc.gov/growthcharts](http://www.cdc.gov/growthcharts)). Table 29-3 provides BMI interpretation guidelines. For children younger than 2 years of age, weight-for-length measurements greater than 95th percentile may indicate overweight and warrant further assessment. A BMI for age and gender above the 95th percentile is strongly associated with excessive body fat and is associated with multiple cardiovascular disease risk factors.

Early recognition of excessive rates of weight gain, overweight, or obesity in children is essential because the earlier the interventions, the more likely they are to be successful.

<table>
<thead>
<tr>
<th>Table 29-2</th>
<th>Diseases Associated with Childhood Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SYNDROME</strong></td>
<td><strong>MANIFESTATIONS</strong></td>
</tr>
<tr>
<td>Alström syndrome</td>
<td>Hypogonadism, retinal degeneration, deafness, diabetes mellitus</td>
</tr>
<tr>
<td>Carpenter syndrome</td>
<td>Polydactyly, syndactyly, cranial synostosis, mental retardation</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Adrenal hyperplasia or pituitary tumor</td>
</tr>
<tr>
<td>Fröhlich syndrome</td>
<td>Hypothalamic tumor</td>
</tr>
<tr>
<td>Hyperinsulinism</td>
<td>Nesidioblastosis, pancreatic adenoma, hypoglycemia, Mauriac syndrome</td>
</tr>
<tr>
<td>Laurence-Moon-Bardet-Biedl syndrome</td>
<td>Retinal degeneration, syndactyly, hypogonadism, mental retardation, autosomal recessive syndrome</td>
</tr>
<tr>
<td>Muscular dystrophy</td>
<td>Late onset of obesity</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>Spina bifida</td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td>Neonatal hypotonia, normal growth immediately after birth, small hands and feet, mental retardation, hypogonadism; some have partial deletion of chromosome 15</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>Variable hypocalcemia, cutaneous calcifications</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>Ovarian dysgenesis, lymphedema, web neck; XO chromosome</td>
</tr>
</tbody>
</table>

*These diseases represent <5% of cases of childhood obesity.

<table>
<thead>
<tr>
<th>Table 29-3</th>
<th>Body Mass Index (BMI)* Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI/AGE PERCENTILE</strong></td>
<td><strong>INTERPRETATION</strong></td>
</tr>
<tr>
<td>&lt;5th</td>
<td>Underweight</td>
</tr>
<tr>
<td>5th–85th</td>
<td>Normal</td>
</tr>
<tr>
<td>85th–95th</td>
<td>Overweight</td>
</tr>
<tr>
<td>&gt;95th</td>
<td>Obese</td>
</tr>
</tbody>
</table>

*From [www.cdc.gov/healthyweight](http://www.cdc.gov/healthyweight).
Routine evaluation at well-child visits should include the following:

1. **Anthropometric data**, including weight, height, and calculation of BMI. Data should be plotted on age-appropriate and gender-appropriate growth charts and assessed for BMI trends (see Table 29-3).

2. **Dietary and physical activity history** (Table 29-4). Assess patterns and potential targets for behavioral change.

3. **Physical examination.** Assess blood pressure, adiposity distribution (central versus generalized), markers of comorbidities (acanthosis nigricans, hirsutism, hepatomegaly, orthopedic abnormalities), and physical stigmata of a genetic syndrome (explains fewer than 5% of cases).

4. **Laboratory studies.** These are generally reserved for children who are obese (BMI > 95th percentile), who have evidence of comorbidities, or both. Other studies should be guided by findings in the history and physical examination. The American Academy of Pediatrics endorses the government guidelines from 2011, which recommend that all 9- to 11-year-olds be screened for cholesterol. Other useful laboratory tests may include hemoglobin A1c, fasting lipid profile, fasting glucose levels, liver function tests, and thyroid function tests (if there is a faster increase in weight than height).

### PREVENTION

The approach to therapy and aggressiveness of treatment should be based on risk factors, including age, severity of overweight and obesity, and comorbidities, as well as family history and support. The primary goal for all children with uncomplicated obesity and fast-rising weight-for-height is to achieve healthy eating and activity patterns. For children with a secondary complication, specific treatment of the complication is an important goal. Childhood and adolescent obesity treatment programs can lead to sustained weight loss and decreases in BMI when treatment focuses on behavioral changes and is family centered. Concurrent changes in dietary and physical activity patterns are most likely to provide success (Table 29-5).

Goal setting needs to be specific and attainable. Instead of recommending that the child walk or bike to school, suggest walking or biking to school two or more days a week. Rather than recommending that a child watch less television, suggest watching no television on school days. It is important to keep it simple and set one or two short-term goals at a time. In addition, behavioral risk factors need to be identified, such as avoiding fast food when family life gets hectic. Helping the family think of healthy alternatives is important.

Families need to be counseled on age-appropriate and healthy eating patterns, beginning with the promotion of breastfeeding. For infants, transition to complementary and table foods and the importance of regularly scheduled meals and snacks, versus grazing behavior, should be emphasized. Age-appropriate portion sizes for meals and snacks should be encouraged. Children should be taught to recognize hunger and satiety cues, guided by reasonable portions and healthy food choices by parents. Smaller bowls should be used, and children should never eat directly from a bag or box. No juices or soda should be the rule. Children should never be forced to eat when they are not willing, and overemphasis on food as a reward should be avoided. “Choose My Plate” by the U.S. Department of Agriculture can provide parents with a general guideline for the types of foods to be offered on a regular basis, including fruits, vegetables, grains, protein, and dairy.

The importance of physical activity should be emphasized. For some children, organized sports and school-based activities provide opportunities for vigorous activity and fun, whereas for others a focus on activities of daily living, such as increased walking, using stairs, and more active play may be better received. Time spent in sedentary behavior, such as television viewing and video/computer games, should be limited. Television in children’s rooms is associated with more television time and with higher rates of overweight, and the risks of this practice should be discussed with parents. Clinicians may need to help families identify alternatives to sedentary activities, especially for families with deterrents to activity, such as unsafe neighborhoods or lack of supervision after school.

### TREATMENT

More aggressive therapies are considered only for those who have not responded to other interventions. Treatment includes...
a systematic approach that promotes multidisciplinary brief, office-based interventions for obese children as well as reducing weight. Before enrolling any patient in a weight-loss program, the clinician must have a clear idea of that individual’s expectations. Patients with unrealistic expectations should not be enrolled until these are changed to realistic and attainable goals. Using the pneumonic described, the clinician should guide the patient who seeks weight reduction to create SMART goals: Specific, Measurable, Attainable, Realistic, and Timely.

Surgical treatment may be advocated as a preferred and cost-effective solution for certain children and adolescents. The role of bariatric surgery in the treatment of obese children or adolescents is controversial. The concerns about surgery to treat obesity in young populations include whether or not surgery is cost effective; how to ensure healthy growth through to adulthood; what support services are needed after surgery; compliance with the postoperative nutrition regimen; and attendance at appointments for long-term follow-up and care. There is very limited evidence available to adequately estimate long-term safety, effectiveness, cost effectiveness or durability of bariatric surgery in growing children. The existing evidence suggests that bariatric surgery in severely obese adolescent results in significant weight loss and improvements in comorbidities and quality of life. Postoperative complications (both physical and psychological), compliance, and follow-up may be more problematic in adolescents than adults, and long-term data on safety, effectiveness, and cost remain largely unavailable.

### Table 29-5 Setting Explicit Goals to Prevent or Treat Obesity

<table>
<thead>
<tr>
<th>FIGHT OBESITY EFFECTIVELY</th>
<th>AMBIGUOUS GOALS</th>
<th>SPECIFIC GOALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep it simple</td>
<td>Walk or bike more</td>
<td>Walk or bike to school 2 days a week</td>
</tr>
<tr>
<td>Countable goals/ambiguous</td>
<td>Watch less TV</td>
<td>Watch no TV on school days</td>
</tr>
<tr>
<td>2 short-term goals/time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Be able to count</td>
<td>Decrease size of serving</td>
<td>Small bowls (parent palm)</td>
</tr>
<tr>
<td>Aim to change behaviors</td>
<td></td>
<td>Avoid eating from the box</td>
</tr>
<tr>
<td>Don’t focus on consumption of carbohydrates, fat, protein</td>
<td>Decrease to 20 g of fat</td>
<td>Eat fish once a week</td>
</tr>
<tr>
<td>Focus on specific categories</td>
<td>Decrease sugars</td>
<td>Avoid sweetened foods</td>
</tr>
<tr>
<td>Focus on healthier preparation methods</td>
<td></td>
<td>Avoid frying</td>
</tr>
<tr>
<td>Focus on eating patterns</td>
<td></td>
<td>Avoid double dinner</td>
</tr>
<tr>
<td>Focus on portion size</td>
<td>Eat less junk food</td>
<td>Portion parent’s palm size</td>
</tr>
<tr>
<td>Eating fast food</td>
<td></td>
<td>Limit trips to McDonalds to once a week</td>
</tr>
<tr>
<td>Sweetened beverages</td>
<td>Avoid soda/juices</td>
<td>No soda or juices</td>
</tr>
<tr>
<td>Healthy beverages</td>
<td></td>
<td>Drink only milk or water</td>
</tr>
<tr>
<td>Fruits</td>
<td>Buy fewer juices</td>
<td>Have no juices in the refrigerator</td>
</tr>
<tr>
<td></td>
<td>Increase eating fruits</td>
<td>Keep a bowl of fruits in the kitchen</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Increase eating veggies</td>
<td>Have a bowl of veggies in the refrigerator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cooperation, competition, and social interaction such as building a house of veggies</td>
</tr>
<tr>
<td>Physical activities</td>
<td>Walk more</td>
<td>Family hikes every Sunday</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Specific activity time for activities and sedentary behavior</td>
</tr>
<tr>
<td></td>
<td>Increase walking from school</td>
<td>Parents picking up from school 2 days a week</td>
</tr>
</tbody>
</table>

### PEDIATRIC UNDERNUTRITION

Pediatric undernutrition is usually the result of inadequate food supply, access, or utilization; poor access to health and sanitation; and/or inappropriate feeding or child care practices. The greatest risk of undernutrition is in utero through age 2. Various guidelines can be used to classify pediatric malnutrition (Table 30-1). International references are established that allow normalization of anthropometric measures in terms of z scores. Other measurements include height and weight for age, weight for height, BMI, and mid-upper arm circumference. The greatest consequence of undernutrition is death, but significant intellectual and physical disability exists in many who survive.

Protein-energy malnutrition (PEM) is a spectrum of conditions caused by varying levels of protein and calorie deficiencies. Primary PEM is caused by social or economic factors that result in a lack of food. Secondary PEM occurs in children with various conditions associated with increased caloric requirements (infection, trauma, cancer) (Fig. 30-1), increased caloric loss (malabsorption), reduced caloric intake (anorexia, cancer, oral intake restriction, social factors), or a combination of these three variables. Protein and calorie malnutrition may
Table 30-1  Definitions of Malnutrition

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>DEFINITION</th>
<th>GRADING</th>
</tr>
</thead>
</table>
| Gomez          | Weight below % median WFA | Mild (grade 1)  
|                |            | Moderate (grade 2)  
|                |            | Severe (grade 3)  |
|                |            | 75%–90% WFA  
|                |            | 60%–74% WFA  
|                |            | <60% WFA |
| Waterlow       | z-scores (SD) below median WFH | Mild  
|                |            | Moderate  
|                |            | Severe  |
|                |            | 80%–90% WFH  
|                |            | 70%–80% WFH  
|                |            | <70% WFH |
| WHO (wasting)  | z-scores (SD) below median WFH | Moderate  
|                |            | Severe  |
|                |            | −3 ≤ z-score < −2  
|                |            | z-score < −3 |
| WHO (stunting) | z-scores (SD) below median HFA | Moderate  
|                |            | Severe  |
|                |            | −3 ≤ z-score < −2  
|                |            | z-score < −3 |
| Kanawati       | MUAC divided by occipitofrontal head circumference | Mild  
|                |            | Moderate  
|                |            | Severe  |
|                |            | <0.31  
|                |            | <0.28  
|                |            | <0.25 |
| Cole           | z-scores of BMI for age | Grade 1  
|                |            | Grade 2  
|                |            | Grade 3  |
|                |            | BMI for age z-score < −1  
|                |            | BMI for age z-score < −2  
|                |            | BMI for age z-score < −3 |


**BMI,** body mass index; **HFA,** height for age; **MUAC,** mid-upper arm circumference; **NCHS,** U.S. National Center for Health Statistics; **SD,** standard deviation; **WFA,** weight for age; **WFH,** weight for height; **WHO,** World Health Organization.

Pediatric undernutrition in the United States is often termed failure to thrive and describes circumstances in which a child fails to gain weight appropriately or, in more severe cases, experiences failure in linear growth or head circumference. The terms organic and nonorganic failure to thrive have lost favor in recognition of the frequent interplay between underlying medical conditions that may cause maladaptive behaviors. Similarly, social and behavioral factors that initially may have been associated with feeding problems (see Chapter 21), and poor growth also may be associated with medical problems, including frequent minor acute illnesses.

**MARASMUS**

Marasmus results from the body’s physiologic response to inadequate calories and nutrients. Loss of muscle mass and subcutaneous fat stores can be confirmed by inspection or palpation and quantified by anthropometric measurements. The head may appear large but generally is proportional to the body length. Edema usually is absent. The skin is dry and thin, and the hair may be thin, sparse, and easily pulled out. Marasmic children may be apathetic, weak, and may be irritable when touched. Bradycardia and hypothermia signify severe and life-threatening malnutrition. Inappropriate or inadequate weaning practices and chronic diarrhea are common findings in developing countries. Stunting (impaired linear growth) results from a combination of malnutrition, especially micronutrients, and recurrent infections.

**KWASHIORKOR**

Kwashiorkor results from inadequate protein intake in the presence of fair to good caloric intake. The hypoalbuneminic state results in pitting edema that starts in the lower extremities and ascends with increasing severity. Other factors, such as acute infection, toxins, and possibly specific micronutrient or amino acid imbalances, are likely to contribute to the etiology. The major clinical manifestation of kwashiorkor is that the body weight is near normal for age; weight alone does not accurately reflect the nutritional status because of edema. Physical


be associated with other nutrient deficiencies, which may be evident on physical examination (Table 30-2).

**FAILURE TO THRIVE**
**Table 30-2 Physical Signs of Nutritional Deficiency Disorders**

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>SIGN</th>
<th>DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>General appearance</td>
<td>Reduced weight for height</td>
<td>Calories</td>
</tr>
<tr>
<td>Skin and hair</td>
<td>Pallor</td>
<td>Anemias (iron, vitamin B₁₂, vitamin E, folate, and copper)</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td>Protein, thiamine</td>
</tr>
<tr>
<td></td>
<td>Nasolabial seborrhea</td>
<td>Calories, protein, vitamin B₆, niacin, riboflavin</td>
</tr>
<tr>
<td></td>
<td>Dermatitis</td>
<td>Riboflavin, essential fatty acids, biotin</td>
</tr>
<tr>
<td></td>
<td>Photosensitivity dermatitis</td>
<td>Niacin</td>
</tr>
<tr>
<td></td>
<td>Acrodermatitis</td>
<td>Zinc</td>
</tr>
<tr>
<td></td>
<td>Follicular hyperkeratosis (sandpaper-like)</td>
<td>Vitamin A</td>
</tr>
<tr>
<td></td>
<td>Depigmented skin</td>
<td>Calories, protein</td>
</tr>
<tr>
<td></td>
<td>Purpura</td>
<td>Vitamins C, K</td>
</tr>
<tr>
<td></td>
<td>Scrotal, vulval dermatitis</td>
<td>Riboflavin</td>
</tr>
<tr>
<td></td>
<td>Alopecia</td>
<td>Zinc, biotin, protein</td>
</tr>
<tr>
<td></td>
<td>Depigmented, dull hair, easily pluckable</td>
<td>Protein, calories, copper</td>
</tr>
<tr>
<td>Subcutaneous tissue</td>
<td>Decreased</td>
<td>Calories</td>
</tr>
<tr>
<td>Eye (vision)</td>
<td>Adaptation to dark</td>
<td>Vitamins A, E, zinc</td>
</tr>
<tr>
<td></td>
<td>Color discrimination</td>
<td>Vitamin A</td>
</tr>
<tr>
<td></td>
<td>Bitot spots, xerophthalmia, keratomalacia</td>
<td>Vitamin A</td>
</tr>
<tr>
<td></td>
<td>Conjunctival pallor</td>
<td>Nutritional anemias</td>
</tr>
<tr>
<td></td>
<td>Fundal capillary microaneurysms</td>
<td>Vitamin C</td>
</tr>
<tr>
<td>Face, mouth, and neck</td>
<td>Moon facies</td>
<td>Kwashiorkor</td>
</tr>
<tr>
<td></td>
<td>Simian facies</td>
<td>Marasmus</td>
</tr>
<tr>
<td></td>
<td>Angular stomatitis</td>
<td>Riboflavin, iron</td>
</tr>
<tr>
<td></td>
<td>Cheilosis</td>
<td>Vitamins B₆, niacin, riboflavin</td>
</tr>
<tr>
<td></td>
<td>Bleeding gums</td>
<td>Vitamins C, K</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Heart failure</td>
<td>Thiamine, selenium, nutritional anemias</td>
</tr>
<tr>
<td>Genital</td>
<td>Hypogonadism</td>
<td>Zinc</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Costochondral beading</td>
<td>Vitamins D, C</td>
</tr>
<tr>
<td></td>
<td>Subperiosteal hemorrhage</td>
<td>Vitamin C, copper</td>
</tr>
<tr>
<td></td>
<td>Cranial bossing</td>
<td>Vitamin D</td>
</tr>
<tr>
<td></td>
<td>Wide fontanel</td>
<td>Vitamin D</td>
</tr>
<tr>
<td></td>
<td>Epiphyseal enlargement</td>
<td>Vitamin D</td>
</tr>
<tr>
<td></td>
<td>Craniotabes</td>
<td>Vitamin D, calcium</td>
</tr>
<tr>
<td></td>
<td>Tender bones</td>
<td>Vitamin C</td>
</tr>
<tr>
<td></td>
<td>Tender calves</td>
<td>Thiamine, selenium, vitamin C</td>
</tr>
<tr>
<td></td>
<td>Spoon-shaped nails (koilonychia)</td>
<td>Iron</td>
</tr>
<tr>
<td></td>
<td>Transverse nail line</td>
<td>Protein</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Sensory, motor neuropathy</td>
<td>Thiamine, vitamins E, B₆, B₁₂</td>
</tr>
<tr>
<td></td>
<td>Ataxia, areflexia</td>
<td>Vitamin E</td>
</tr>
<tr>
<td></td>
<td>Ophthalmoplegia</td>
<td>Vitamin E, thiamine</td>
</tr>
<tr>
<td></td>
<td>Tetany</td>
<td>Vitamin D, Ca²⁺, Mg²⁺</td>
</tr>
<tr>
<td></td>
<td>Retardation</td>
<td>Iodine, niacin</td>
</tr>
<tr>
<td></td>
<td>Dementia, delirium</td>
<td>Vitamin E, niacin, thiamine</td>
</tr>
<tr>
<td></td>
<td>Poor position sense, ataxia</td>
<td>Thiamine, vitamin B₁₂</td>
</tr>
</tbody>
</table>

**examination** reveals a relative maintenance of subcutaneous adipose tissue and a marked atrophy of muscle mass. Edema varies from a minor pitting of the dorsum of the foot to generalized edema with involvement of the eyelids and scrotum. The hair is sparse; is easily plucked; and appears dull brown, red, or yellow-white. Nutritional repletion restores hair color, leaving a band of hair with altered pigmentation followed by a band with normal pigmentation (flag sign). Skin changes are common and range from hyperpigmented hyperkeratosis to an erythematous macular rash (pellagroid) on the trunk and extremities. In the most severe form of kwashiorkor, a superficial desquamation occurs over pressure surfaces (“flaky paint” rash). Angular cheilosis, atrophy of the filiform papillae of the tongue, and monilial stomatitis are common. Enlarged parotid glands and facial edema result in moon facies; apathy and disinterest in eating are typical of kwashiorkor. Examination of the abdomen may reveal an enlarged, soft liver with an indefinite edge. Lymph node and tonsils are commonly atrophic. Chest examination may reveal basilar rales. The abdomen is distended, and bowel sounds tend to be hypoactive.

**MIXED MARASMUS-KWASHIORKOR**

These children often have concurrent wasting and edema in addition to stunting. These children exhibit features of dermatitis, neurologic abnormalities, and fatty liver.

**TREATMENT OF MALNUTRITION**

The basal metabolic rate and immediate nutrient needs decrease in cases of malnutrition. When nutrients are provided, the metabolic rate increases, stimulating anabolism and increasing
nutrient requirements. The body of the malnourished child may have compensated for micronutrient deficiencies with lower metabolic and growth rates, and refeeding may unmask these deficiencies. Nutritional rehabilitation should be initiated and advanced slowly to minimize these complications. The initial approach involves correction of dehydration and anti-infective (bacteria, parasites) therapy if indicated. Oral rehydration is recommended over intravenous fluid to avoid excessive fluid and solute load and resultant heart or renal failure.

When nutritional rehabilitation is initiated, calories can be safely started at 20% above the child’s recent intake. If no estimate of the caloric intake is available, 50% to 75% of the normal energy requirement is safe. High-calorie oral solutions or ready-to-use therapeutic foods (a mixture of powdered milk, peanuts, sugar, vitamins, and minerals) are frequently used in developing countries. Nutritional rehabilitation can be complicated by refeeding syndrome, which is characterized by fluid retention, hypophosphatemia, hypomagnesemia, and hypokalemia. Careful monitoring of laboratory values and clinical status with severe malnutrition is essential.

When nutritional rehabilitation has begun, caloric intake can be increased 10% to 20% per day, monitoring for electrolyte imbalances, poor cardiac function, edema, or feeding intolerance. If any of these occurs, further caloric increases are not made until the child’s status stabilizes. Caloric intake is increased until appropriate regrowth or catch-up growth is initiated. Catch-up growth refers to gaining weight at greater than 50th percentile for age and may require 150% or more of the recommended calories for an age-matched, well-nourished child. A general rule of thumb for infants and children up to 3 years of age is to provide 100 to 120 kcal/kg based on ideal weight for height. Protein needs also are increased as anabolism begins and are provided in proportion to the caloric intake. Vitamin and mineral intake in excess of the daily recommended intake is provided to account for the increased requirements; this is frequently accomplished by giving an age-appropriate daily multiple vitamin, with other individual micronutrient supplements as warranted by history, physical examination, or laboratory studies. Iron supplements are not recommended during the acute rehabilitation phase, especially for children with kwashiorkor, for whom ferritin levels are often high. Additional iron may pose an oxidative stress; iron supplementation is associated with higher morbidity and mortality.

In most cases, cow’s milk–based formulas are tolerated and provide an appropriate mix of nutrients. Other easily digested foods, appropriate for the age, also may be introduced slowly. If feeding intolerance occurs, lactose-free or semielemental formulas should be considered.

**COMPLICATIONS OF MALNUTRITION**

Malnourished children are more susceptible to infection, especially sepsis, pneumonia, and gastroenteritis. Hypoglycemia is common after periods of severe fasting but may also be a sign of sepsis. Hypothermia may signify infection or, with bradycardia, may signify a decreased metabolic rate to conserve energy. Bradycardia and poor cardiac output predispose the malnourished child to heart failure, which is exacerbated by acute fluid or solute loads. Micronutrient deficiencies also can complicate malnutrition. Vitamin A and zinc deficiencies are common in the developing world and are an important cause of altered immune response and increased morbidity and mortality. Depending on the age at onset and the duration of the malnutrition, malnourished children may have permanent growth stunting (from malnutrition in utero, infancy, or adolescence) and delayed development (from malnutrition in infancy or adolescence). Environmental (social) deprivation may interact with the effects of the malnutrition to impair further development and cognitive function.

**VITAMIN AND MINERAL DEFICIENCIES**

Micronutrients include vitamins and trace elements. In industrialized societies, frank clinical deficiencies are unusual in healthy children, but they can and do occur in certain high-risk circumstances. Risk factors include diets that are consistently limited in variety, especially with the exclusion of entire food groups, malabsorption syndromes, and conditions causing high physiologic requirements. Various common etiologies of vitamin and nutrient deficiency states are highlighted in Table 31-1, and characteristics of vitamin deficiencies are outlined in Table 31-2. Treatment is noted in Table 31-3.

**WATER-SOLUBLE VITAMINS**

Water-soluble vitamins are not stored in the body except for vitamin B₁₂; intake therefore alters tissue levels. Absorption from the diet is usually high, and the compounds exchange readily between intracellular and extracellular fluids; excretion is via the urine. Water-soluble vitamins typically function as coenzymes in energy, protein, amino acid, and nucleic acid metabolism; as cosubstrates in enzymatic reactions; and as structural components.

**Ascorbic Acid**

The principal forms of vitamin C are ascorbic acid and the oxidized form, dehydroascorbic acid. Ascorbic acid accelerates hydroxylation reactions in many biosynthetic reactions, including hydroxylation of proline in the formation of collagen. The needs of full-term infants for ascorbic acid and dehydroascorbic acid are calculated by estimating the availability in human milk.

A deficiency of ascorbic acid results in the clinical manifestations of scurvy. Infantile scurvy is manifested by irritability, bone tenderness with swelling, and pseudoparalysis of the legs. The disease may occur if infants are fed unsupplemented cow’s milk in the first year of life or if the diet is devoid of fruits.
and vegetables. Subperiosteal hemorrhage, bleeding gums and petechiae, hyperkeratosis of hair follicles, and a succession of mental changes characterize the progression of the illness. Anemia secondary to bleeding, decreased iron absorption, or abnormal folate metabolism is also seen in chronic scurvy. Treatment is noted in Table 31-3.

**B Vitamins**

The B vitamins thiamine, riboflavin, and niacin are routinely added to enriched grain products; deficiencies in normal hosts are rare in the United States. Levels from human milk reflect maternal intake, and deficiency can develop in breastfed infants of deficient mothers.

### Thiamine

Vitamin B₁ functions as a coenzyme in biochemical reactions related to carbohydrate metabolism, decarboxylation of α-ketoacids and pyruvate, and transketolase reactions of the pentose pathway. Thiamine also is involved in the decarboxylation of branched-chain amino acids. Thiamine is lost during milk pasteurization and sterilization.

Thiamine deficiency occurs in alcoholics and has been reported in adolescents who have undergone bariatric surgery for severe obesity. **Infantile beriberi** occurs between 1 and 4 months of age in breastfed infants whose mothers have a thiamine deficiency (alcoholism), in infants with protein-calorie malnutrition, in infants receiving unsupplemented hyperalimentation fluid, and in infants receiving boiled milk. Acute **wet beriberi** with cardiac symptoms and signs predominates in infantile beriberi. Anorexia, apathy, vomiting, restlessness, and pallor progress to dyspnea, cyanosis, and death from heart failure. Infants with beriberi have a characteristic aphonic cry; they appear to be crying, but no sound is uttered. Other signs include peripheral neuropathy and paresthesias. For treatment see Table 31-3.

### Riboflavin

Vitamin B₂ is a constituent of two coenzymes, riboflavin 5′-phosphate and flavin-adenine dinucleotide, essential components of glutathione reductase and xanthine oxidase, which are involved in electron transport. A deficiency of riboflavin affects glucose, fatty acid, and amino acid metabolism. Riboflavin and its phosphate are decomposed by exposure to light and by strong alkaline solutions.

**Ariboflavinosis** is characterized by an angular stomatitis; glossitis; cheilosis; seborrheic dermatitis around the nose and mouth; and eye changes that include reduced tearing, photophobia, corneal vascularization, and the formation of cataracts. Subclinical riboflavin deficiencies have been found in diabetic subjects, children in families with low socioeconomic status, children with chronic cardiac disease, and infants undergoing prolonged phototherapy for hyperbilirubinemia.

### Niacin

Niacin consists of the compounds nicotinic acid and nicotinamide (niacinamide). Nicotinamide, the predominant form of the vitamin, functions as a component of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Niacin is involved in multiple metabolic processes, including fat synthesis, intracellular respiratory metabolism, and glycolysis.

In determining the needs for niacin, the content of tryptophan in the diet must be considered because tryptophan is converted to niacin. Niacin is stable in foods and withstands heating and prolonged storage. Approximately 70% of the total niacin equivalents in human milk are derived from tryptophan. **Pellagra**, or niacin deficiency disease, is characterized by weakness, lassitude, dermatitis, photosensitivity, inflammation of mucous membranes, diarrhea, vomiting, dysphagia, and, in severe cases, dementia.

### Table 31-1: Etiology of Vitamin and Nutrient Deficiency States

<table>
<thead>
<tr>
<th>ETIOLOGY</th>
<th>DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIET</strong></td>
<td></td>
</tr>
<tr>
<td>Vegans (strict)</td>
<td>Protein, vitamins B₁₂, D, riboflavin, iron</td>
</tr>
<tr>
<td>Breastfed infant</td>
<td>Vitamins K, D</td>
</tr>
<tr>
<td>Cow’s milk-fed infant</td>
<td>Iron</td>
</tr>
<tr>
<td>Bulimia, anorexia nervosa</td>
<td>Electrolytes, other deficiencies</td>
</tr>
<tr>
<td>Parenteral alimentation</td>
<td>Essential fatty acids, trace elements</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Calories, vitamin B₁, B₆, folate</td>
</tr>
<tr>
<td><strong>MEDICAL PROBLEMS</strong></td>
<td></td>
</tr>
<tr>
<td>Malabsorption syndromes</td>
<td>Vitamins A, D, E, K, zinc, essential fatty acids</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Vitamins E, D, K, A, zinc, essential fatty acids</td>
</tr>
<tr>
<td><strong>MEDICATIONS</strong></td>
<td></td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Folate</td>
</tr>
<tr>
<td>Phenytoin, phenobarbital</td>
<td>Vitamins D, K, folate</td>
</tr>
<tr>
<td>Mineral oil</td>
<td>Vitamins A, D, E, K</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Vitamin K</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Vitamin B₆</td>
</tr>
<tr>
<td>Antacids</td>
<td>Iron, phosphate, calcium</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Magnesium, calcium</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Vitamin B₆</td>
</tr>
<tr>
<td><strong>SPECIFIC MECHANISMS</strong></td>
<td></td>
</tr>
<tr>
<td>Transcobalamin II</td>
<td>Vitamin B₁₂</td>
</tr>
<tr>
<td>Other digestive enzyme</td>
<td>Carbohydrate, fat, protein deficiencies</td>
</tr>
<tr>
<td>Menkes kinky hair syndrome</td>
<td>Copper</td>
</tr>
<tr>
<td>Acrodermatitis enteropathica</td>
<td>Zinc</td>
</tr>
<tr>
<td>Reduced exposure to direct sunlight</td>
<td>Vitamin D</td>
</tr>
</tbody>
</table>
### Table 31-2: Characteristics of Vitamin Deficiencies

<table>
<thead>
<tr>
<th>VITAMIN</th>
<th>PURPOSE</th>
<th>DEFICIENCY</th>
<th>COMMENTS</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WATER SOLUBLE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine (B₁)</td>
<td>Coenzyme in ketoacid decarboxylation (e.g., pyruvate → acetyl-CoA transketolase reaction)</td>
<td>Beriberi: polyneuropathy, calf tenderness, heart failure, edema, ophthalmoplegia</td>
<td>Inborn errors of lactate metabolism; boiling milk destroys B₁</td>
<td>Liver, meat, milk, cereals, nuts, legumes</td>
</tr>
<tr>
<td>Riboflavin (B₂)</td>
<td>FAD coenzyme in oxidation-reduction reactions</td>
<td>Anorexia, mucositis, anemia, cheilosis, nasolabial seborrhea</td>
<td>Photosensitizer</td>
<td>Milk, cheese, liver, meat, eggs, whole grains, green leafy vegetables</td>
</tr>
<tr>
<td>Niacin (B₃)</td>
<td>NAD coenzyme in oxidation-reduction reactions</td>
<td>Pellagra: photosensitivity, dermatitis, dementia, diarrhea, death</td>
<td>Tryptophan is a precursor</td>
<td>Meat, fish, liver, whole grains, green leafy vegetables</td>
</tr>
<tr>
<td>Pyridoxine (B₆)</td>
<td>Cofactor in amino acid metabolism</td>
<td>Seizures, hyperacausis, microcytic anemia, nasolabial seborrhea, neuropathy</td>
<td>Dependency state: deficiency secondary to drugs</td>
<td>Meat, liver, whole grains, peanuts, soybeans</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>CoA in Krebs cycle</td>
<td>None reported</td>
<td>Meat, vegetables</td>
<td></td>
</tr>
<tr>
<td>Biotin</td>
<td>Cofactor in carboxylase reactions of amino acids</td>
<td>Alopecia, dermatitis, hypotonia, death</td>
<td>Bowel resection, inborn error of metabolism; ingestion of raw eggs</td>
<td>Yeast, meats, made by intestinal flora</td>
</tr>
<tr>
<td>B₁₂</td>
<td>Coenzyme for 5-methyltetrahydrofolate formation; DNA synthesis</td>
<td>Megaloblastic anemia, peripheral neuropathy, posterior lateral spinal column disease, vitiligo</td>
<td>Vegans; fish tapeworm; short gut syndrome; transcobalamin or intrinsic factor deficiencies</td>
<td>Meat, fish, cheese, eggs</td>
</tr>
<tr>
<td>Folate</td>
<td>DNA synthesis</td>
<td>Megaloblastic anemia; neural tube defects</td>
<td>Goat milk deficient; drug antagonists; heat inactivates</td>
<td>Liver, greens, vegetables, cereals, cheese</td>
</tr>
<tr>
<td>Ascorbic acid (C)</td>
<td>Reducing agent; collagen metabolism</td>
<td>Scurvy: irritability, purpura, bleeding gums, periosteal hemorrhage, aching bones</td>
<td>May improve tyrosine metabolism in preterm infants</td>
<td>Citrus fruits, green vegetables, cooking destroys it</td>
</tr>
<tr>
<td><strong>FAT SOLUBLE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Epithelial cell integrity; vision</td>
<td>Night blindness, xerophthalmia, Bitot spots, follicular hyperkeratosis; immune defects</td>
<td>Common with protein-calorie malnutrition; malabsorption</td>
<td>Liver, milk, eggs, green and yellow vegetables, fruits</td>
</tr>
<tr>
<td>D</td>
<td>Maintain serum calcium, phosphorus levels</td>
<td>Rickets: reduced bone mineralization</td>
<td>Prohormone of 25- and 1,25-vitamin D</td>
<td>Fortified milk, cheese, liver; sunlight</td>
</tr>
<tr>
<td>E</td>
<td>Antioxidant</td>
<td>Hemolysis in preterm infants; areflexia, ataxia, ophthalmoplegia</td>
<td>May benefit patients with G6PD deficiency</td>
<td>Seeds, vegetables, germ oils, grains</td>
</tr>
<tr>
<td>K</td>
<td>Post-translation carboxylation of clotting factors II, VII, IX, X and proteins C, S</td>
<td>Prolonged prothrombin time; hemorrhage; elevated protein induced in vitamin K absence (PIVKA)</td>
<td>Malabsorption; breastfed infants</td>
<td>Liver, green vegetables; made by intestinal flora</td>
</tr>
</tbody>
</table>

CoA, Coenzyme A; FAD, flavin adenine dinucleotide; G6PD, glucose-6-phosphate dehydrogenase; NAD, nicotinamide adenine dinucleotide.

*Biotinidase deficiency.

**Vitamin B₆**

Vitamin B₆ refers to three naturally occurring pyridines: pyridoxine (pyridoxol), pyridoxal, and pyridoxamine. The phosphates of the latter two pyridines are metabolically and functionally related and are converted in the liver to the coenzyme form, pyridoxal phosphate. The metabolic functions of vitamin B₆ include interconversion reactions of amino acids, conversion of tryptophan to niacin and serotonin, metabolic reactions in the brain, carbohydrate metabolism, immune development, and the biosynthesis of heme and prostaglandins. The pyridoxal and pyridoxamine forms of the vitamin are destroyed by heat; heat treatment was responsible for vitamin B₆ deficiency and seizures in infants fed improperly processed formulas. Goat’s milk is deficient in vitamin B₆.

Dietary deprivation or malabsorption of vitamin B₆ in children results in hypochromic microcytic anemia, vomiting, diarrhea, failure to thrive, listlessness, hyperirritability, and seizures. Children receiving isoniazid or penicillamine may require additional vitamin B₆ because the drug binds to the vitamin. Vitamin B₆ is unusual as a water-soluble vitamin in that very large doses (≥500 mg/day) have been associated with a sensory neuropathy.

**Folate**

[Decision-Making Algorithms](Available @ StudentConsult.com)
## Table 31-3: Treatment of Vitamin Deficiencies

<table>
<thead>
<tr>
<th>CLINICAL FEATURES</th>
<th>SUGGESTED DOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin A</strong></td>
<td></td>
</tr>
<tr>
<td>Severe deficiency with xerophthalmia</td>
<td>Infants: 7,500–15,000 U/day IM, followed by oral 5000–10,000 U/day for 10 days. Children 1–8 yr of age: oral 5,000–10,000 U/kg/day for 5 days or until recovery. Children &gt;8 yr of age and adults: oral 500,000 U/day for 3 days; then 50,000 U/day for 14 days; then 10,000–20,000 U/day for 2 mo.</td>
</tr>
<tr>
<td>Deficiency without corneal changes</td>
<td>Infants &lt;1 yr of age: 100,000 U/day orally, q4–6mo. Children 1–8 yr of age: 200,000 U/day orally, q4–6mo. Children &gt;8 yr and adults: 100,000 U/day for 3 days, followed by 50,000 U/day for 10 days.</td>
</tr>
<tr>
<td>Deficiency</td>
<td>IM given only to those patients with malabsorption in whom oral dosing is not possible. Infants: 7,500–15,000 U/day for 10 days. Children 1–8 yr of age: 17,500–35,000 U/day for 10 days. Children &gt;8 yr of age and adults: 100,000 U/day for 3 days, then 50,000 U/day for 14 days. Give follow-up oral multivitamin that contains vitamin A: LBW infants: no dose established, children ≤ 8 years of age: 5,000–10,000 U/day, children &gt;8 yr of age and adults: 10,000–20,000 U daily.</td>
</tr>
<tr>
<td>Malabsorption syndrome (prophylaxis)</td>
<td>Children &gt;8 yr of age and adults: oral 10,000–50,000 U/day of water-miscible product.</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1,500–10,000 U/day prophylaxis (CF Foundation).</td>
</tr>
<tr>
<td>Measles</td>
<td>WHO recommendations: single dose, repeating the dose next day and at 4 wk for children with eye findings: 6 mo to 1 yr of age: 100,000 U; &gt;1 yr of age: 200,000 U.</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>4,000–8,000 U/day ergocalciferol.</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>1000 U/day ergocalciferol</td>
</tr>
<tr>
<td>Nutritional rickets and osteomalacia</td>
<td>Ergocalciferol: children and adults with normal absorption: 1,000–5,000 U/day. Children with malabsorption: 10,000–25,000 U/day. Adults with malabsorption: 10,000–300,000 U/day.</td>
</tr>
<tr>
<td>Renal disease and failure</td>
<td>Ergocalciferol: child: 4,000–40,000 U/day; adults: 20,000 U/day.</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Ergocalciferol: 400–800 U/day PO (CF Foundation).</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Children: 50,000–200,000 U/day ergocalciferol and calcium supplements. Adults: 25,000–200,000 U/day ergocalciferol and calcium supplements.</td>
</tr>
<tr>
<td>Vitamin D-dependent rickets</td>
<td>Children: 3000–5000 U/day ergocalciferol; max: 60,000 U/day. Adults: 10,000–60,000 U/day ergocalciferol.</td>
</tr>
<tr>
<td>Vitamin D-resistant rickets</td>
<td>Children: initial 40,000–80,000 U/day with phosphate supplements, daily dosage is increased at 3– to 4–mo intervals in 10,000–20,000 U increments. Adults: 10,000–60,000 U/day with phosphate supplements.</td>
</tr>
<tr>
<td><strong>Vitamin E</strong></td>
<td></td>
</tr>
<tr>
<td>Premature infant, neonates, infants of low birth weight</td>
<td>δ–α–tocopherol: 25–50 U/day for 1 wk orally.</td>
</tr>
<tr>
<td>Fat malabsorption and liver disease</td>
<td>10–25 U/kg/day of water–miscible vitamin E preparation.</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>&lt;1 yr of age: 25–50 U/day; 1–2 years of age: 100 U/day; &gt;2 yr of age: 100 U/day bid or 200 U daily orally (CF Foundation).</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>450 U/day orally.</td>
</tr>
<tr>
<td>β-Thalassemia</td>
<td>750 U/day orally.</td>
</tr>
<tr>
<td><strong>Vitamin K</strong></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic disease of the newborn</td>
<td>Phytonadione: 0.5–1.0 mg SC or IM as prophylaxis within 1 hr of birth, may repeat 6–8 hours later; 1–2 mg/day as treatment. Infants and children: 2.5–5 mg/day orally, or 1–2 mg/dose SC, IM, IV as a single dose; adults: 5–25 mg/day or 10 mg IM, IV. 2.5 mg, twice a week (CF Foundation).</td>
</tr>
<tr>
<td>Deficiency</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td><strong>Folate, folic acid, and folacin</strong></td>
<td></td>
</tr>
<tr>
<td>Deficiency</td>
<td>Infants: 50 μg daily. Children 1–10 yr of age: 1 mg/day initially, then 0.1–0.4 mg/day as maintenance. Children &gt;11 yr of age and adults: 1 mg/day initially, then 0.5 mg/day as maintenance. May require higher doses than those listed previously.</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td></td>
</tr>
<tr>
<td>Pellagra</td>
<td>Children: 50–100 mg tid. Adults: 50–100 mg/day, max 100 mg/day.</td>
</tr>
</tbody>
</table>

Continued
A variety of chemical forms of folate are nutritionally active. Folate functions in transport of single-carbon fragments in synthesis of nucleic acids and for normal metabolism of certain amino acids and in conversion of homocysteine to methionine. Food sources include green leafy vegetables, oranges, and whole grains; folate fortification of grains is now routine in the United States. Folate is particularly heat labile. Heat-sterilizing treatments to body weight but have scant stores of folate in the newborn period. Folate is particularly heat labile. Heat-sterilizing home-prepared formula can decrease the folate content by half. Evaporated milk and goat’s milk are low in folate. Patients with chronic hemolysis (sickle cell anemia, thalassemia) may require extra folate to avoid deficiency because of the relatively high requirement of the vitamin to support erythropoiesis. Other conditions with risk of deficiency include pregnancy, alcoholism, and treatment with anticonvulsants (phenytoin) or antimetabolites (methotrexate). First occurrence and recurrence of neural tube defects are reduced significantly by maternal supplementation during embryogenesis. Because closure of the neural tube occurs before usual recognition of pregnancy, all women of reproductive age are recommended to have a folate intake of at least 400 μg/day as prophylaxis.

**Vitamin B₁₂**

<table>
<thead>
<tr>
<th>CLINICAL FEATURES</th>
<th>SUGGESTED DOES</th>
<th>CLINICAL FEATURES</th>
<th>SUGGESTED DOES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridoxine (B₆)</td>
<td>Seizures</td>
<td>Neonates and infants: initial 50–100 mg/day orally, IM, IV, SC. Adults: 100–200 mg/day as treatment, 25–100 mg/day as prophylaxis.</td>
<td>Adults: 100–200 mg/day as treatment, 25–100 mg/day as prophylaxis.</td>
</tr>
<tr>
<td></td>
<td>Drug-induced deficiencies</td>
<td>Children: 10–50 mg/day as treatment, 1–2 mg/kg/day as prophylaxis.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dietary deficiency</td>
<td>Children: 5–25 mg/day for 3 wk, then 1.5–2.5 mg/day in a multivitamin product. Adults: 10–20 mg/day for 3 wk.</td>
<td></td>
</tr>
<tr>
<td>Riboflavin (B₂)</td>
<td>Children: 2.5–10 mg/day in divided doses. Adults: 5–30 mg/day in divided doses.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine (B₁)</td>
<td>Beriberi: critically ill</td>
<td>Children: 10–25 mg/day IM or IV. Adults: 5–30 mg/dose IM, IV tid, then 5–30 mg/day orally in a single or three divided doses for 1 mo.</td>
<td>Beriberi: not critically ill Adults: 10–20 mg/day orally.</td>
</tr>
<tr>
<td></td>
<td>Metabolic disease</td>
<td>Children: 10–50 mg/day orally for 2 wk, then 5–10 mg/day for 1 mo. Wernicke encephalopathy Adults: initially 100 mg IV, then 50–100 mg/day IM/IV until eating a balanced diet.</td>
<td></td>
</tr>
<tr>
<td>Cyanocobalamin (B₁₂)</td>
<td>Nutritional deficiency</td>
<td>Intranasal gel: 500 μg once a wk. Oral: 25–250 μg/wk.</td>
<td>Hematologic remission Adults: 100 μg/day for 6–7 days; if improvement, administer same dose on alternate days for 7 doses, then every 3–4 days for 2–3 wk. Once hematologic values are normal, give maintenance doses of 100 μg/mo parenterally.</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>Give IM or deep SC; oral route not recommended because of poor absorption and IV route not recommended because of more rapid elimination.</td>
<td>Vitamin B₁₂ deficiency If evidence of neurologic involvement in neonates and infants (congenital), 1,000 μg/day IM, SC, for at least 2 wk, and then maintenance, 50–100 μg/mo or 100 μg/day for 6–7 days. If clinical improvement, give 100 μg every other day for 7 doses, then every 3–4 days for 2–3 wk, followed by 100 μg/mo for life. Administer with folic acid if needed (1 mg/day for 1 mo concomitantly). Children: 30–50 μg/day for 2 or more wk (total dose of 1000 μg) IM, SC, then 100 μg/mo as maintenance.</td>
</tr>
<tr>
<td></td>
<td>Pernicious anemia</td>
<td>If evidence of neurologic involvement in neonates and infants (congenital), 1,000 μg/day IM, SC, for at least 2 wk, and then maintenance, 50–100 μg/mo or 100 μg/day for 6–7 days. If clinical improvement, give 100 μg every other day for 7 doses, then every 3–4 days for 2–3 wk, followed by 100 μg/mo for life. Administer with folic acid if needed (1 mg/day for 1 mo concomitantly). Children: 30–50 μg/day for 2 or more wk (total dose of 1000 μg) IM, SC, then 100 μg/mo as maintenance.</td>
<td>Vitamin B₁₂ deficiency If evidence of neurologic involvement in neonates and infants (congenital), 1,000 μg/day IM, SC, for at least 2 wk, and then maintenance, 50–100 μg/mo or 100 μg/day for 6–7 days. If clinical improvement, give 100 μg every other day for 7 doses, then every 3–4 days for 2–3 wk, followed by 100 μg/mo for life. Administer with folic acid if needed (1 mg/day for 1 mo concomitantly). Children: 30–50 μg/day for 2 or more wk (total dose of 1000 μg) IM, SC, then 100 μg/mo as maintenance.</td>
</tr>
<tr>
<td></td>
<td>Children with hematologic signs: 10–50 μg/day for 5–10 days, followed by 100–250 μg/day every 2–4 wk.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Scurvy</td>
<td>Children: 100–300 mg/day in divided doses orally, IM, IV, or SC for several days. Adults: 100–250 mg/day one to two times/day.</td>
<td></td>
</tr>
</tbody>
</table>


*bid, Two times per day; CF, cystic fibrosis; IM, intramuscular; IV, intravenous; LBW, low birth weight; PO, by mouth; q, every; SC, subcutaneous; tid, three times per day; WHO, World Health Organization.*
Vitamin B₁₂ is one of the most complex of the vitamin molecules, containing an atom of cobalt held in a corrin ring (similar to that of iron in hemoglobin). The cobalt ion is at the active center of the ring and serves as the site for attachment of alkyl groups during their transfer. The vitamin functions in single-carbon transfers and is intimately related to folate function and interconversions. Vitamin B₁₂ is essential for normal lipid and carbohydrate metabolism in energy production and in protein biosynthesis and nucleic acid synthesis.

In contrast to other water-soluble vitamins, absorption of vitamin B₁₂ is complex, involving cleavage of the vitamin from dietary protein and binding to a glycoprotein called intrinsic factor, which is secreted by the gastric mucosa (parietal cells). The cobalamin–intrinsic factor complex is efficiently absorbed from the distal ileum.

As vitamin B₁₂ is absorbed into the portal circulation, it is transported bound to a specific protein, transcobalamin II. Its large stores in the liver also are unusual for a water-soluble vitamin. Efficient enterohpatic circulation normally protects from deficiency for months to years. Dietary sources of the vitamin are animal products only. Strict vegetarians should take a vitamin B₁₂ supplement.

Vitamin B₁₂ deficiency in children is rare. Early diagnosis and treatment of this disorder in childhood are important because of the danger of irreversible neurologic damage. Most cases in childhood result from a specific defect in absorption (see Table 31-2). Such defects include congenital pernicious anemia (absent intrinsic factor), juvenile pernicious anemia (autoimmune), and deficiency of transcobalamin II transport. Gastric or intestinal resection and small bowel bacterial overgrowth also cause vitamin B₁₂ deficiency. Exclusively breastfed infants ingest adequate vitamin B₁₂ unless the mother is a strict vegetarian without supplementation.

Depression of serum vitamin B₁₂ and the appearance of hypersegmented neutrophils and macrocytosis (indistinguishable from folate deficiency) are early clinical manifestations of deficiency. Vitamin B₁₂ deficiency also causes neurologic manifestations, including depression, peripheral neuropathy, posterior spinal column signs, dementia, and eventual coma. The neurologic signs do not occur in folate deficiency, but administration of folate may mask the hematologic signs of vitamin B₁₂ deficiency, while the neurologic manifestations progress. Patients with vitamin B₁₂ deficiency also have increased urine levels of methylmalonic acid. Most cases of vitamin B₁₂ deficiency in infants and children are not of dietary origin and require treatment throughout life. Maintenance therapy consists of repeated monthly intramuscular injections, although a form of vitamin B₁₂ is administered intranasally.

**FAT-SOLUBLE VITAMINS**

Fat-soluble vitamins generally have stores in the body, and dietary deficiencies generally develop more slowly than for water-soluble vitamins. Absorption of fat-soluble vitamins depends on normal fat intake, digestion, and absorption. The complexity of normal fat absorption and the potential for perturbation in many disease states explains the more common occurrence of deficiencies of these vitamins.

**Vitamin A**

The basic constituent of the vitamin A group is retinol. Ingested plant carotene or animal tissue retinol esters release retinol after hydrolysis by pancreatic and intestinal enzymes. Chylomicron-transported retinol esters are stored in the liver as retinol palmitate. Retinol is transported from the liver to target tissues by retinol-binding protein, releasing free retinol to the target tissues. The kidney then excretes the retinol-binding protein. Diseases of the kidney diminish excretion of retinol-binding protein, whereas liver parenchymal disease or malnutrition lowers the synthesis of retinol-binding protein. Specific cellular binding proteins facilitate the uptake of retinol by target tissues. In the eye, retinol is metabolized to form rhodopsin; the action of light on rhodopsin is the first step of the visual process. Retinol also influences the growth and differentiation of epithelia. The clinical manifestations of vitamin A deficiency in humans appear as a group of ocular signs termed xerophthalmia. The earliest symptom is night blindness, which is followed by xerosis of the conjunctiva and cornea. Untreated, xerophthalmia can result in ulceration, necrosis, keratomalacia, and a permanent corneal scar. Clinical and subclinical vitamin A deficiencies are associated with immunodeficiency; increased risk of infection, especially measles; and increased risk of mortality, especially in developing nations. Xerophthalmia and vitamin A deficiency should be urgently treated. Hypervitaminosis A also has serious sequelae, including headaches, pseudotumor cerebri, hepatotoxicity, and teratogenicity.

**Vitamin E**

Eight naturally occurring compounds have vitamin E activity. The most active of these, α-tocopherol, accounts for 90% of the vitamin E present in human tissues and is commercially available as an acetate or succinate. Vitamin E acts as a biologic antioxidant by inhibiting the peroxidation of polyunsaturated fatty acids present in cell membranes. It scavenges free radicals generated by the reduction of molecular oxygen and by the action of oxidative enzymes.

Vitamin E deficiency occurs in children with fat malabsorption secondary to liver disease, untreated celiac disease, cystic fibrosis, and abetalipoproteinemia. In these children, without vitamin E supplementation, a syndrome of progressive sensory and motor neuropathy develops; the first sign of deficiency is loss of deep tendon reflexes. Deficient preterm infants at 1 to 2 months of age have hemolytic anemia characterized by an elevated reticulocyte count, an increased sensitivity of the erythrocytes to hemolysis in hydrogen peroxide, peripheral edema, and thrombocytosis. All the abnormalities are corrected after oral, lipid, or water-soluble vitamin E therapy.
Cholecalciferol (vitamin D₃) is the mammalian form of vitamin D and is produced by ultraviolet irradiation of inactive precursors in the skin. Ergocalciferol (vitamin D₂) is derived from plants. Vitamin D₂ and vitamin D₃ require further metabolism to become active. They are of equivalent potency. Clothing, lack of sunlight exposure, and skin pigmentation decrease generation of vitamin D in the epidermis and dermis.

Vitamin D (D₂ and D₃) is metabolized in the liver to calcidiol, or 25-hydroxyvitamin D (25-[OH]-D); this metabolite, which has little intrinsic activity, is transported by a plasma-binding globulin to the kidney, where it is converted to the most active metabolite calcitriol, or 1,25-dihydroxyvitamin D (1,25-[OH]₂-D). The action of 1,25-(OH)₂-D results in a decrease in the concentration of messenger RNA (mRNA) for collagen in bone and an increase in the concentration of mRNA for vitamin D–dependent calcium-binding protein in the intestine (directly mediating increased intestinal calcium transport). The antirachitic action of vitamin D probably is mediated by provision of appropriate concentrations of calcium and phosphate in the extracellular space of bone and by enhanced intestinal absorption of these minerals. Vitamin D also may have a direct anabolic effect on bone. 1,25-(OH)₂-D has direct feedback to the parathyroid gland and inhibits secretion of parathyroid hormone.

Vitamin D deficiency appears as rickets in children and as osteomalacia in postpubertal adolescents. Inadequate direct sun exposure and vitamin D intake are sufficient causes, but other factors, such as various drugs (phenobarbital, phenytoin) and malabsorption, may increase the risk of development of vitamin-D–deficiency rickets. Breastfed infants, especially those with dark-pigmented skin, are at risk for vitamin D deficiency.

The pathophysiology of rickets results from defective bone growth, especially at the epiphyseal cartilage matrix, which fails to mineralize. The uncalcified osteoid results in a wide, irregular zone of poorly supported tissue, the rachitic metaphysis. This soft, rather than hardened, zone produces many of the skeletal deformities through compression and lateral bulging or flaring of the ends of bones.

The clinical manifestations of rickets are most common during the first 2 years of life and may become evident only after several months of a vitamin D–deficient diet. Cranio-orbitosphenoid bone growth may be delayed. In advanced rickets, scoliosis and exaggerated lordosis may be present. Bowlegs or knock-knees may be evident in older infants, and greenstick fractures may be observed in long bones.

The diagnosis of rickets is based on a history of poor vitamin D intake and little exposure to direct ultraviolet sunlight. The serum calcium usually is normal but may be low; the serum phosphorus level usually is reduced, and serum alkaline phosphatase activity is elevated. When serum calcium levels decline to less than 7.5 mg/dL, tetany may occur. Levels of 24,25-(OH)₂-D are undetectable, and serum 1,25-(OH)₂-D levels are commonly less than 7 ng/mL, although 1,25-(OH)₂-D levels also may be normal. The best measure of vitamin D status is the level of 25-(OH)-D. Characteristic radiographic changes of the distal ulna and radius include widening; concave cupping; and frayed, poorly demarcated ends. The increased space seen between the distal ends of the radius and ulna and the metacarpal bones is the enlarged, nonossified metaphysis.

Breastfed infants born of mothers with adequate vitamin D stores usually maintain adequate serum vitamin D levels for at least 2 months, but rickets may develop subsequently if these infants are not exposed to the sun or do not receive supplemental vitamin D. The American Academy of Pediatrics recommends vitamin D supplementation of all breastfed infants in the amount of 400 IU/day, started soon after birth and given until the infant is taking more than 1000 mL/day of formula or vitamin D–fortified milk (for age >1 year). Toxic effects of excessive chronic vitamin D may include hypercalcemia, muscle weakness, polyuria, and nephrocalcinosis.

The plant form of vitamin K is phylloquinone, or vitamin K₁. Another form is menaquinone, or vitamin K₂, one of a series of compounds with unsaturated side chains synthesized by intestinal bacteria. Plasma factors II (prothrombin), VII, IX, and X in the cascade of blood coagulation factors depend on vitamin K for synthesis and for post-translational conversion of their precursor proteins. The post-translational conversion of glutamyl residues to carboxylglutamic acid residues of a prothrombin molecule creates effective calcium-binding sites, making the protein active.

Other vitamin K–dependent proteins include proteins C, S, and Z in plasma and γ-carboxyglutamic acid–containing proteins in several tissues. Bone contains a major vitamin K–dependent protein, osteocalcin, and lesser amounts of other glutamic acid–containing proteins.

Phylloquinone is absorbed from the intestine and transported by chylomicrons. The rarity of dietary vitamin K deficiency in humans with normal intestinal function suggests that the absorption of menaquinones is possible. Vitamin K deficiency has been observed in subjects with impaired fat absorption caused by obstructive jaundice, pancreatic insufficiency, and celiac disease; often these problems are combined with the use of antibiotics that change intestinal flora.

Hemorrhagic disease of the newborn, a disease more common among breastfed infants, occurs in the first few weeks of life. It is rare in infants who receive prophylactic intramuscular vitamin K on the first day of life. Hemorrhagic disease of the newborn usually is marked by generalized ecchymoses, gastrointestinal hemorrhage, or bleeding from a circumcision or umbilical stump; intracranial hemorrhage can occur, but...
is uncommon. The American Academy of Pediatrics recommends that parenteral vitamin K (0.5 to 1 mg) be given to all newborns shortly after birth.

**MINERALS**

The major minerals are those that require intakes of more than 100 mg/day and contribute at least 0.1% of total body weight. There are seven essential major minerals: calcium, phosphorus, magnesium, sodium, potassium, chloride, and sulfur. Ten trace minerals, which constitute less than 0.1% of body weight, have essential physiologic roles. Characteristics of trace mineral deficiencies are listed in Table 31-4.

**Calcium**

Calcium is the most abundant major mineral. Ninety-nine percent of calcium is in the skeleton; the remaining 1% is in extracellular fluids, intracellular compartments, and cell membranes. The nonskeletal calcium has a role in nerve conduction, muscle contraction, blood clotting, and membrane permeability. There are two distinct bone calcium phosphate pools—a large, crystalline form and a smaller, amorphous phase. Bone calcium constantly turns over, with concurrent bone reabsorption and formation. Approximately half of bone mineral accretion occurs during adolescence. Bone mineral density peaks in early adulthood and is influenced by prior and concurrent dietary calcium intake, exercise, and hormone status (testosterone, estrogen).

Calcium intake can come from a variety of sources, with dairy products providing the most common and concentrated source. The calcium equivalent of 1 cup of milk (about 300 mg of calcium) is ¾ cup of plain yogurt, 1.5 oz of cheddar cheese, 2 cups of ice cream, ¼ cup of almonds, or 2.5 oz of sardines. Other sources of calcium include some leafy green vegetables (broccoli, kale, collards); lime-processed tortillas; calcium-precipitated tofu; and calcium-fortified juices, cereals, and breads.

There is no classic calcium deficiency syndrome because blood and cell levels are closely regulated. The body can mobilize skeletal calcium and increase the absorptive efficiency of dietary calcium. **Osteoporosis** that occurs in childhood is related to protein-calorie malnutrition, vitamin C deficiency, steroid therapy, endocrine disorders, immobilization and disuse, osteogenesis imperfecta, or calcium deficiency (in premature infants). It is believed that the primary method of prevention of **postmenopausal osteoporosis** is to ensure maximum peak bone mass by providing optimal calcium intake during childhood and adolescence. Bone mineral status can be monitored by dual-energy x-ray absorptiometry.

No adverse effects are observed in adults with dietary calcium intakes of 2.5 g/day. There is concern that higher intakes may increase the risk of urinary stone formation, constipation, and decreased renal function and may inhibit intestinal absorption of other minerals (iron, zinc).

<table>
<thead>
<tr>
<th>MINERAL</th>
<th>FUNCTION</th>
<th>MANIFESTATIONS OF DEFICIENCY</th>
<th>COMMENTS</th>
<th>SOURCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Heme-containing macromolecules (e.g., hemoglobin, cytochrome, and myoglobin)</td>
<td>Anemia, spoon nails, reduced muscle and mental performance</td>
<td>History of pica, cow’s milk, gastrointestinal bleeding</td>
<td>Meat, liver, grains, legumes</td>
</tr>
<tr>
<td>Copper</td>
<td>Redox reactions (e.g., cytochrome oxidase)</td>
<td>Hypochromic anemia, neutropenia, osteoporosis, hypotonia, hypoproteinemia</td>
<td>Inborn error, Menkes kinky hair syndrome</td>
<td>Liver, nuts, grains, legumes, chocolate</td>
</tr>
<tr>
<td>Zinc</td>
<td>Metalloenzymes (e.g., alkaline phosphatase, carbonic anhydrase, DNA polymerase); wound healing</td>
<td>Acrodystrophic enteropathica: poor growth, acro-orificial rash, alopecia, delayed sexual development, hypogeousica, infection</td>
<td>Protein-calorie malnutrition; weaning; malabsorption syndromes</td>
<td>Meat, grains, legumes</td>
</tr>
<tr>
<td>Selenium</td>
<td>Antioxidant; glutathione peroxidase</td>
<td>Keshan cardiomyopathy in China</td>
<td>Endemic areas; long-term TPN without Se</td>
<td>Meat, vegetables</td>
</tr>
<tr>
<td>Chromium</td>
<td>Insulin cofactor</td>
<td>Poor weight gain, glucose intolerance, neuropathy</td>
<td>Protein-calorie malnutrition, long-term TPN without Cr</td>
<td>Yeast, breads</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Strengthening of dental enamel</td>
<td>Caries</td>
<td>Supplementation during tooth growth, narrow therapeutic range, fluorosis may cause staining of the teeth</td>
<td>Seafood, fortified water</td>
</tr>
<tr>
<td>Iodine</td>
<td>Thyroxine, triiodothyronine production</td>
<td>Simple endemic goiter</td>
<td>Myxedematous cretinism: congenital hypothyroidism</td>
<td>Neurologic cretinism: mental retardation, deafness, spasticity, normal thyroxine level at birth</td>
</tr>
</tbody>
</table>

TPN, Total parenteral nutrition.
Iron, the most abundant trace mineral, is used in the synthesis of hemoglobin, myoglobin, and enzyme iron. Body iron content is regulated primarily through modulation of iron absorption, which depends on the state of body iron stores, the form and amount of iron in foods, and the mixture of foods in the diet. There are two categories of iron in food. The first is heme iron, present in hemoglobin and myoglobin, which is supplied by meat and rarely accounts for more than one fourth of the iron ingested by infants. The absorption of heme iron is relatively efficient and is not influenced by other constituents of the diet. The second category is nonheme iron, which represents the preponderance of iron intake consumed by infants and exists in the form of iron salts. The absorption of nonheme iron is influenced by the composition of consumed foods. Enhancers of nonheme iron absorption are ascorbic acid, meat, fish, and poultry. Inhibitors are bran, polyphenols (including the tannates in tea), and phytic acid, a compound found in legumes and whole grains. The percent intestinal absorption of the small amount of iron in human milk is 10%; 4% is absorbed from iron-fortified cow’s milk formula and from iron-fortified infant dry cereals.

In a normal term infant, there is little change in total body iron and little need for exogenous iron before 4 months of age. Iron deficiency is rare in term infants during the first 4 months, unless there has been substantial blood loss (see Chapter 62). After about 4 months of age, iron reserves become marginal, and, unless exogenous sources of iron are provided, the infant becomes progressively at risk for anemia as the iron requirement to support erythropoiesis and growth increases (see Chapter 150). Premature or low birth weight infants have a lower amount of stored iron because significant amounts of iron are transferred from the mother in the third trimester. In addition, their postnatal iron needs are greater because of rapid rates of growth and when frequent phlebotomy occurs. Iron needs can be met by supplementation (ferrous sulfate) or by iron-containing complementary foods. Under normal circumstances, iron-fortified formula should be the only alternative to breast milk in infants younger than 1 year of age. Premature infants fed human milk may develop iron deficiency anemia earlier unless they receive iron supplements. Formula-fed preterm infants should receive iron-supplemented formula.

In older children, iron deficiency may result from inadequate iron intake with excessive cow’s milk intake or from intake of foods with poor iron bioavailability. Iron deficiency also can result from blood loss from such sources as menses or gastric ulceration. Iron deficiency affects many tissues (muscle and central nervous system) in addition to producing anemia. Iron deficiency and anemia have been associated with lethargy and decreased work capacity and impaired neurocognitive development, the deficits of which may be irreversible when onset is in the first 2 years of life.

The diagnosis of iron deficiency anemia is established by the presence of a microcytic hypochromic anemia, low serum ferritin levels, low serum iron levels, reduced transferrin saturation, normal to elevated red blood cell width distribution, and enhanced iron-binding capacity. The mean corpuscular volume and red blood cell indices are reduced, and the reticulocyte count is low. Iron deficiency may be present without anemia. Clinical manifestations are noted in Table 31-4.

Treatment of iron deficiency anemia includes changes in the diet to provide adequate iron and the administration of 2 to 6 mg iron/kg/24 hr (as ferrous sulfate) divided bid or tid. Reticulocytosis is noted within 3 to 7 days of starting treatment. Oral treatment should be continued for 5 months. Rarely, intramuscular or intravenous iron therapy is needed if oral iron cannot be given. Parenteral therapy carries the risk of anaphylaxis and should be administered according to a strict protocol, including a test dose.

Zinc is the second most abundant trace mineral and is important in protein metabolism and synthesis, in nucleic acid metabolism, and in stabilization of cell membranes. Zinc functions as a cofactor for more than 200 enzymes and is essential to numerous cellular metabolic functions. Adequate zinc status is especially crucial during periods of growth and for tissue proliferation (immune system, wound healing, skin and gastrointestinal tract integrity); physiologic functions for which zinc is essential include normal growth, sexual maturation, and immune function.

Dietary zinc is absorbed (20% to 40%) in the duodenum and proximal small intestine. The best dietary sources of zinc are animal products, including human milk, from which it is readily absorbed. Whole grains and legumes also contain moderate amounts of zinc, but phytic acid inhibits absorption from these sources. On a global basis, poor bioavailability secondary to phytic acid is thought to be a more important factor than low intake in the widespread occurrence of zinc deficiency. Excretion of zinc occurs from the gastrointestinal tract. In the presence of ongoing losses, such as in chronic diarrhea, requirements can drastically increase.

Zinc deficiency dwarfism syndrome was first described in a group of children in the Middle East with low levels of zinc in their hair, poor appetite, diminished taste acuity, hypogonadism, and short stature. Zinc supplementation reduces morbidity and mortality from diarrhea and pneumonia and enhances growth in developing countries. Mild to moderate zinc deficiency is considered to be highly prevalent in developing countries, particularly in populations with high rates of stunting. Mild zinc deficiency occurs in older breastfed infants without adequate zinc intake from complementary foods or in young children with poor total or bioavailable zinc intake in the general diet. A high infectious burden also may increase the risk of zinc deficiency in developing countries. Acute, acquired severe zinc deficiency occurs in patients receiving...
total parenteral nutrition without zinc supplementation and in premature infants fed human milk without fortification. Clinical manifestations of mild zinc deficiency include anorexia, growth faltering, and immune impairment. Moderately severe manifestations include delayed sexual maturation, rough skin, and hepatosplenomegaly. The signs of severe deficiency include acral and periorificial erythematous, scaling dermatitis; growth and immune impairment; diarrhea; mood changes; alopecia; night blindness; and photophobia.

Diagnosis of zinc deficiency is challenging. Plasma zinc concentration is most commonly used, but levels are frequently normal in conditions of mild deficiency; levels in moderate to severe deficiency are typically less than 60 μg/dL. Acute infection also can result in depression of circulating zinc levels. The standard for the diagnosis of deficiency is response to a trial of supplementation, with outcomes such as improved linear growth or weight gain, improved appetite, and improved immune function. Because there is no pharmacologic effect of zinc on these functions, a positive response to supplementation is considered evidence of a preexisting deficiency. Clinically an empirical trial of zinc supplementation (1 μg/kg/day) is a safe and reasonable approach in situations in which deficiency is considered possible.

Acrodermatitis enteropathica is an autosomal recessive disorder that begins within 2 to 4 weeks after infants have been weaned from breast milk. It is characterized by an acute perioral and perianal dermatitis, alopecia, and failure to thrive. The disease is caused by severe zinc deficiency from a specific defect of intestinal zinc absorption. Plasma zinc levels are markedly reduced, and serum alkaline phosphatase activity is low. Treatment is with high-dose oral zinc supplements. A relatively uncommon condition associated with presentation of severe zinc deficiency is due to a defect in the secretion of zinc from the mammary gland, resulting in abnormally low milk zinc concentrations. Breastfed infants, especially those born prematurely, present with classic signs of zinc deficiency: growth failure, diarrhea, and dermatitis. Because there is no defect in the infant's ability to absorb zinc, treatment consists of supplementing the infant with zinc for the duration of breastfeeding, which can be successfully continued. Subsequent infants born to the mother will also need zinc supplementation if breastfed. Zinc is relatively nontoxic. Excess intake produces nausea, emesis, abdominal pain, headache, vertigo, and seizures.

Fluoride

Dental enamel is strengthened when fluoride is substituted for hydroxyl ions in the hydroxyapatite crystalline mineral matrix of the enamel. The resulting fluoroapatite is more resistant to chemical and physical damage. Fluoride is incorporated into the enamel during the mineralization stages of tooth formation and by surface interaction after the tooth has erupted. Fluoride is similarly incorporated into bone mineral and may protect against osteoporosis later in life.

Because of concern about the risk of fluorosis, infants should not receive fluoride supplements before 6 months of age. Commercial formulas are made with defluoridated water and contain small amounts of fluoride. The fluoride content of human milk is low and is not influenced significantly by maternal intake. Practitioners should evaluate all potential fluoride sources and conduct a caries risk assessment before prescribing fluoride supplementation.

Suggested Readings

http://www.nal.usda.gov
http://www.choosemyplate.gov
www.pediatrics.org/cgi/content/full/102/3/e38
MAINTENANCE FLUID THERAPY

BODY COMPOSITION

Water is the most plentiful constituent of the human body. Total body water (TBW) as a percentage of body weight varies with age. The fetus has a high TBW, which gradually decreases to about 75% of birth weight for a term infant. Premature infants have a higher TBW content than term infants. During the first year of life, TBW decreases to about 60% of body weight and basically remains at this level until puberty. At puberty, the fat content of females increases more than that of males, who acquire more muscle mass than females. Because fat has low water content, and muscle has high water content, by the end of puberty TBW in males remains at 60%, but it decreases to 50% of body weight in females. During dehydration, TBW decreases and is a smaller percentage of body weight.

TBW has two main compartments: intracellular fluid (ICF) and extracellular fluid (ECF). In the fetus and newborn, the ECF volume is larger than the ICF volume. The normal postnatal diuresis causes an immediate decrease in the ECF volume. This decrease in ECF volume is followed by continued expansion of the ICF volume because of cellular growth. By 1 year of age, the ratio of the ICF volume to the ECF volume approaches adult levels. The ECF volume is 20% to 25% of body weight, and the ICF volume is 30% to 40% of body weight (Fig. 32-1). With puberty, the increased muscle mass of males results in a higher ICF volume than in females.

The ECF is divided further into plasma water and interstitial fluid (see Fig. 32-1). Plasma water is about 5% of body weight. The blood volume, given a hematocrit of 40%, is usually 8% of body weight, although it is higher in newborns and young infants. The interstitial fluid, normally 15% of body weight, can increase dramatically in diseases associated with edema, such as heart failure, protein-losing enteropathy, liver failure, and nephrotic syndrome.

The composition of solutes in the ICF and ECF is different. Sodium and chloride are the dominant cation and anion in the ECF. Potassium is the most abundant cation in the ICF, and proteins, organic anions, and phosphate are the most plentiful anions in the ICF. The dissimilarity between the anions in the ICF and the ECF is determined largely by the presence of intracellular molecules that do not cross the cell membrane, the barrier separating the ECF and the ICF. In contrast, the difference in the distribution of cations—sodium and potassium—is due to the activity of the Na⁺,K⁺-ATPase pump, which extrudes sodium from cells in exchange for potassium.

REGULATION OF INTRAVASCULAR VOLUME AND OSMOLALITY

Proper cell functioning requires close regulation of plasma osmolality and intravascular volume; these are controlled by independent systems for water balance, which determines osmolality, and sodium balance, which determines volume status. Maintenance of a normal osmolality depends on control of water balance. Control of volume status depends on regulation of sodium balance.

The plasma osmolality is tightly controlled between 285 and 295 mOsm/kg through regulation of water intake and urinary water losses. A small increase in the plasma osmolality stimulates thirst. Urinary water losses are regulated by the secretion of antidiuretic hormone (ADH), which increases in response to an increasing plasma osmolality. ADH, by stimulating renal tubular reabsorption of water, decreases urinary water losses. Control of osmolality is subordinate to maintenance of an adequate intravascular volume. When significant volume depletion is present, ADH secretion and thirst are stimulated, regardless of the plasma osmolality.

Volume depletion and volume overload may cause significant morbidity and mortality. Because sodium is the principal extracellular cation and is restricted to the ECF, adequate body sodium is necessary for maintenance of intravascular volume. The kidney determines sodium balance because there is little homeostatic control of sodium intake, although salt craving occasionally occurs, typically in children with chronic renal salt loss. The kidney regulates sodium balance by altering the percentage of filtered sodium that is reabsorbed along the nephron. The renin-angiotensin system is an important regulator of renal sodium reabsorption and excretion. The juxtaglomerular apparatus produces renin in response to decreased effective intravascular volume. Renin cleaves angiotensinogen, producing angiotensin I, which angiotensin-converting enzyme converts into angiotensin II. The actions of angiotensin
Dehydration and Replacement Therapy

II include direct stimulation of the proximal tubule to increase sodium reabsorption and stimulation of the adrenal gland to increase aldosterone secretion, which increases sodium reabsorption in the distal nephron. In contrast, volume expansion stimulates the synthesis of atrial natriuretic peptide, which increases urinary sodium excretion.

MAINTENANCE FLUIDS

Maintenance intravenous (IV) fluids are used in children who cannot be fed enterally. Along with maintenance fluids, children may require concurrent replacement fluids if they have excessive ongoing losses, such as may occur with drainage from a nasogastric tube. In addition, if dehydration is present, the patient also needs to receive deficit replacement (see Chapter 33).

Maintenance fluids are composed of a solution of water, glucose, sodium, potassium, and chloride. This solution replaces electrolyte losses from the urine and stool, as well as water losses from the urine, stool, skin, and lungs. The glucose in maintenance fluids provides approximately 20% of the normal caloric needs of the patient. This percentage is enough to prevent the development of starvation ketoacidosis and diminishes the protein degradation that would occur if the patient received no calories.

Maintenance fluids do not provide adequate calories, protein, fat, minerals, or vitamins. Patients should not remain on maintenance therapy indefinitely; parenteral nutrition (see Chapter 34) should be used for children who cannot be fed enterally for more than a few days.

Daily water losses are measurable (urine and stool) and not measurable (insensible losses from the skin and lungs). Failure to replace these losses leads to a thirsty child and, ultimately, a dehydrated child. Table 32-1 provides a system for calculating 24-hour maintenance water needs based on the patient’s weight. Sodium and potassium are given in maintenance fluids to replace losses from urine and stool.

After calculation of water needs and electrolyte needs, children typically receive either 5% dextrose (D5) in ¼ normal saline (NS) plus 20 mEq/L of potassium chloride (KCl) or D5 in ½ NS plus 20 mEq/L of KCl. Children weighing less than 10 kg do best with the solution containing ¼ NS (38.5 mEq/L) because of their high water needs per kilogram. In contrast, larger children and adults may receive the solution with ½ NS (77 mEq/L). These guidelines assume that there is no disease process present that would require an adjustment in either the volume or the electrolyte composition of maintenance fluids. Children with renal insufficiency may be hyperkalemic or unable to excrete potassium and may not tolerate 20 mEq/L of KCl. In children with complicated pathophysiologic derangements, it may be necessary to adjust the electrolyte composition and rate of maintenance fluids empirically based on electrolyte measurements and assessment of fluid balance.

DEHYDRATION AND REPLACEMENT THERAPY

REPLACEMENT THERAPY

There are three sources of normal water loss—the components of maintenance water (see Chapter 32): urine (60%), insensible losses from the skin and lungs (35%), and stool (5%) (Table 33-1). Sweating is not insensible and, in contrast to evaporative losses, sweat contains water and electrolytes.
A variety of clinical situations modify normal maintenance water balance (Table 33-2). Evaporative skin water losses can be higher in neonates, especially premature infants who are under radiant warmers or undergoing phototherapy. Burns can result in massive losses of water and electrolytes (see Chapter 44). Fever increases insensible losses. Tachypnea or a trachoeostomy increases evaporative losses from the lungs.

The gastrointestinal tract is potentially a source of considerable water and electrolyte losses. A child who has large amounts of gastrointestinal losses should have these losses measured and replaced with an appropriate replacement solution (Table 33-3).

Urine output is normally the largest cause of water loss. Diseases such as renal failure and the syndrome of inappropriate antidiuretic hormone (SIADH) can lead to a decrease in urine volume. Maintenance fluids in a patient with oliguria or anuria produce fluid overload. In contrast, other conditions produce an increase in urine volume; these include the polyuric phase of acute tubular necrosis, diabetes mellitus, and diabetics insipidus. When the urine output is excessive, the patient must receive more than standard maintenance fluids to prevent dehydration.

The approach to decreased or increased urine output is similar (Table 33-4). Insensible losses are replaced by a solution that is administered at a rate one third of the normal maintenance rate. Placing the anuric child on “insensibles” theoretically maintains an even fluid balance, with the caveat that one third of maintenance fluid is only an estimate of insensible losses. This rate may need to be adjusted based on monitoring of the patient’s weight and hydration status. An oliguric child needs to receive a urine replacement solution. Most children with polyuria (except for children with diabetes mellitus [see Chapter 171]) should be placed on insensible fluids plus urine replacement.

Output from surgical drains and chest tubes, when significant, should be measured and replaced. Third space losses manifest with edema and ascites and are due to a shift of fluid from the intravascular space into the interstitial space. Third space losses cannot be quantitated. Nonetheless, these losses can be large and lead to intravascular volume depletion, despite weight gain from edema or ascites. Replacement of third space fluid is empirical but should be anticipated in patients who are at risk, such as children who have burns or abdominal surgery. Third space losses and chest tube output are isotonic and usually require replacement with an isotonic fluid, such as normal saline or Ringer’s lactate. Adjustments in the amount of replacement fluid for third space losses are based on continuing assessment of the patient’s intravascular volume status.

**DEHYDRATION**

Dehydration, most often due to gastroenteritis, is common in children. The first step in caring for a dehydrated child is to assess the degree of dehydration. The degree of dehydration dictates the urgency of the situation and the volume of fluid needed for rehydration. Table 33-5 summarizes the clinical features that are present with varying degrees of dehydration.

A patient with mild dehydration has few clinical signs or symptoms. The history may describe decreased intake but...
Dehydration and Replacement Therapy

An infant with moderate dehydration has demonstrable physical signs and symptoms. The patient needs fairly prompt intervention. A patient with severe dehydration is gravely ill. The decrease in blood pressure indicates that vital organs may be receiving inadequate perfusion (shock) (see Chapter 40). Such a patient should receive immediate and aggressive intravenous (IV) therapy. Clinical assessment of dehydration is only an estimate; the patient must be continually re-evaluated during therapy. The degree of dehydration is underestimated in hypernatremic dehydration because the osmotically driven shift of water from the intracellular space to the extracellular space helps to preserve the intravascular volume.

Laboratory Evaluation

Serum blood urea nitrogen (BUN) and creatinine concentrations are useful in assessing a child with dehydration. Volume depletion without renal insufficiency may cause a disproportionate increase in the BUN, with little or no change in the creatinine concentration. This is secondary to increased passive reabsorption of urea in the proximal tubule caused by appropriate renal conservation of sodium and water. This increase in the BUN may be absent or blunted in a child with poor protein intake because urea production depends on protein degradation. Conversely, the BUN may be disproportionately increased in a child with increased urea production, as occurs in a child with a gastrointestinal bleed or a child who is receiving glucocorticoids. A significant elevation of the creatinine concentration suggests renal injury.

The urine specific gravity is usually elevated (≥1.025) in cases of significant dehydration but decreases after rehydration. With dehydration, a urinalysis may show hyaline and granular casts, a few white blood cells and red blood cells, and 30 to 100 mg/dL of proteinuria. These findings usually are not associated with significant renal pathology, and they remit with therapy. Hemoconcentration from dehydration causes an increase in the hematocrit and hemoglobin.

Calculation of Fluid Deficit

A child with dehydration has lost water; there is usually a concurrent loss of sodium and potassium. The fluid deficit is the percentage of dehydration multiplied by the patient’s weight (for a 10-kg child, 10% of 10 kg = 1 L deficit).

Approach to Dehydration

The child with dehydration requires acute intervention to ensure that there is adequate tissue perfusion (see Chapter 40). This resuscitation phase requires rapid restoration of the circulating intravascular volume, which should be done with an isotonic solution, such as normal saline (NS) or Ringer’s lactate. Blood is an appropriate fluid choice for a child with acute blood loss. The child is given a fluid bolus, usually 20 mL/kg of the isotonic solution, over about 20 minutes. A child with severe dehydration may require multiple fluid boluses and may need to receive fluid at a faster rate. The initial resuscitation and rehydration is complete when signs of intravascular volume depletion resolve. The child typically becomes more alert and has a lower heart rate, normal blood pressure, and improved perfusion.

With adequate intravascular volume, it is now appropriate to plan the fluid therapy for the next 24 hours (Table 33-6). To
ensure that the intravascular volume is restored, the patient receives an additional 20 mL/kg bolus of isotonic fluid over 2 hours. The child’s total fluid needs are added together (maintenance + deficit). The volume of isotonic fluids the patient has received as acute resuscitation is subtracted from this total. The remaining fluid volume is then administered over 24 hours. Potassium usually is not included in the IV fluids until the patient voids, unless significant hypokalemia is present. Children with significant ongoing losses need to receive an appropriate replacement solution.

**Monitoring and Adjusting Therapy**

**Table 33-6** Fluid Management of Dehydration

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Restore intravascular volume</td>
</tr>
<tr>
<td>2.</td>
<td>Normal saline: 20 mL/kg over 20 minutes</td>
</tr>
<tr>
<td>3.</td>
<td>Repeat as needed</td>
</tr>
<tr>
<td>4.</td>
<td>Rapid volume repletion: 20 mL/kg normal saline (maximum = 1 L) over 2 hours</td>
</tr>
<tr>
<td>5.</td>
<td>Calculate 24-hour fluid needs: maintenance + deficit volume</td>
</tr>
<tr>
<td>6.</td>
<td>Subtract isotonic fluid already administered from 24-hour fluid needs</td>
</tr>
<tr>
<td>7.</td>
<td>Administer remaining volume over 24 hours using D5 ½ normal saline + 20 mEq/L KCl</td>
</tr>
<tr>
<td>8.</td>
<td>Replace ongoing losses as they occur</td>
</tr>
</tbody>
</table>

**Table 33-7** Monitoring Therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs</td>
<td>Pulse</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Intake and output</td>
</tr>
<tr>
<td>Fluid balance</td>
<td>Urine output and specific gravity</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Weight</td>
</tr>
<tr>
<td>Clinical signs of depletion or overload</td>
<td>Electrolytes</td>
</tr>
</tbody>
</table>

All calculations in fluid therapy are only approximations. Thus, the patient needs to be monitored during treatment with therapy modifications based on the clinical situation (Table 33-7).

**Hyponatremic dehydration** occurs in children who have diarrhea and consume a hypotonic fluid (water or diluted formula). Volume depletion stimulates secretion of antidiuretic hormone, preventing the water excretion that should correct the hyponatremia. Some patients develop symptoms, predominantly neurologic, from the hyponatremia (see Chapter 35). Most patients with hyponatremic dehydration do well with the same general approach outlined in Table 33-6. Overly rapid correction of hyponatremia (>12 mEq/L/24 hr) should be avoided because of the remote risk of *central pontine myelinolysis*.

**Hypernatremic dehydration** is usually a consequence of an inability to take in fluid, because of a lack of access, a poor thirst mechanism (neurologic impairment), intractable emesis, or anorexia. The movement of water from the intracellular space to the extracellular space during hypernatremic dehydration partially protects the intravascular volume. Urine output may be preserved longer, and there may be less tachycardia. Children with hypernatremic dehydration are often lethargic and irritable. Hypernatremia may cause fever, hypertonicity, hyperreflexia, and seizures. More severe neurologic symptoms may develop if cerebral bleeding or thrombosis occurs.

Overly rapid treatment of hypernatremic dehydration may cause significant morbidity and mortality. *Idiogenic osmoles* are generated within the brain during the development of hypernatremia. Idiogenic osmoles increase the osmolality within the cells of the brain, providing protection against brain cell shrinkage secondary to movement of water out of cells into the hypertonic extracellular fluid. These idiogenic osmoles dissipate slowly during correction of hypernatremia. With rapid lowering of the extracellular osmolality during correction of hypernatremia, a new gradient may be created that causes water movement from the extracellular space into the cells of the brain, producing *cerebral edema*. Possible manifestations of the resultant cerebral edema include altered mental status, seizures, and potentially lethal brain herniation.

To minimize the risk of cerebral edema during correction of hypernatremic dehydration, the serum sodium concentration should not decrease more than 12 mEq/L every 24 hours (Figure 33-1). The deficits in severe hypernatremic dehydration may need to be corrected over 2 to 4 days. The choice and rate of fluid are not nearly as important as vigilant monitoring of the serum sodium concentration and adjustment of the therapy based on the result (see Figure 33-1). Nonetheless, the initial resuscitation-rehydration phase of therapy remains the same as for other types of dehydration.

**Oral Rehydration**

Mild to moderate dehydration from diarrhea of any cause can be treated effectively using a simple, oral rehydration solution (ORS) containing glucose and electrolytes (see Chapter 112). The ORS relies on the coupled transport of sodium and glucose in the intestine. Oral rehydration therapy has significantly reduced the morbidity and mortality from acute diarrhea but is underused in developed countries. It should be attempted for most patients with mild to moderate diarrheal dehydration. Oral rehydration therapy is less expensive than IV therapy and has a lower complication rate. IV therapy may still be required for patients with severe dehydration; patients with uncontrollable vomiting; patients unable to drink because of extreme fatigue, stupor, or coma; or patients...
with gastric or intestinal distention. Rapidly absorbed ondansetron may be used to treat vomiting, thus facilitating oral rehydration.

As a guideline for oral rehydration, 50 mL/kg of the ORS should be given within 4 hours to patients with mild dehydration, and 100 mL/kg should be given over 4 hours to patients with moderate dehydration. Supplementary ORS is given to replace ongoing losses from diarrhea or emesis. An additional 10 mL/kg of ORS is given for each stool. Fluid intake should be decreased if the patient appears fully hydrated earlier than expected or develops periorbital edema. After rehydration, patients should resume their usual diet (breast milk, formula).

When rehydration is complete, maintenance therapy should be started, using 100 mL of ORS/kg in 24 hours until the diarrhea stops. Breastfeeding or formula feeding should be maintained and not delayed for more than 24 hours. Patients with more severe diarrhea require continued supervision. The volume of ORS ingested should equal the volume of stool losses. If stool volume cannot be measured, an intake of 10 to 15 mL of ORS/kg/hr is appropriate.

Parenteral nutrition (PN) is necessary when enteral feeding is inadequate to meet the nutritional needs of a patient. Enteral nutrition is always preferred because it is more physiologic, less expensive, and associated with fewer complications. Fewer complications are expected if at least some nutrition can be provided enterally.

**INDICATIONS**

A variety of clinical situations necessitate PN (Table 34-1). Acute PN is frequently given in an intensive care unit when there is poor tolerance of enteral feeds, potentially secondary to a transient ileus; concerns regarding bowel ischemia; or the
risk of aspiration pneumonia. **Short bowel syndrome** is the most common indication for long-term PN; it may be caused by a congenital gastrointestinal anomaly or acquired after necrotizing enterocolitis (see Chapter 63). Some patients with a chronic indication for PN eventually may be transitioned to partial or full enteral feedings.

### ACCESS FOR PARENTERAL NUTRITION

PN can be given via either a peripheral intravenous (IV) line or a central venous line. Long-term PN should be given via a central venous line (CVL). Acute PN may be given peripherally, although a temporary CVL often is used. Most children with cancer or receiving a bone marrow transplant have a CVL. A **peripherally inserted central catheter** is an excellent source of central access for acute PN because of the lower risk for complications than with a standard CVL.

A peripheral IV line has two major limitations. First, it frequently fails, necessitating interruption of PN and potentially painful placement of a new line. Second, high-osmolality solutions cause **phlebitis** of peripheral veins; this limits the dextrose and amino acid content of peripheral PN. The dextrose content of peripheral PN cannot be greater than 12%, with a lower limit if the amino acid concentration is high. Lipid emulsion has a low osmolality; therefore, it can be administered peripherally via the same IV line as the dextrose and amino acid solution. Patients can receive adequate nutrition via a peripheral IV line, but the volume of PN needs to be higher than is necessary when central access is available because of the limitations on dextrose and amino acid concentration. This situation may be problematic in patients who cannot tolerate larger fluid volumes.

### COMPOSITION OF PARENTERAL NUTRITION

PN can provide calories, amino acids, electrolytes, minerals, essential fatty acids, vitamins, iron, and trace elements. The **calories** in PN are from dextrose and fat. The amino acids in PN are a potential source of calories, but they should be used predominantly for protein synthesis. PN is given as two separate solutions: a dextrose plus amino acid solution and a 20% lipid emulsion. The dextrose solution has all of the other components of PN except for fat.

The dextrose concentration of peripheral PN is typically 10% to 12%, whereas central PN has a concentration of about 20%, although it may be increased to 25% to 30% in patients who are fluid restricted. To avoid hyperglycemia, the dextrose delivery is increased gradually when starting PN. Protein delivery in PN is via amino acids in the dextrose solution. The goal is 0.8 to 2 g protein/kg/24 hr for older children, 1.5 to 3 g/kg/24 hr for full-term and older infants, and 2.5 to 3.5 g/kg/24 hr for preterm infants.

The electrolyte and mineral composition of PN depends on the age and the underlying illness. The 20% lipid emulsion provides essential fatty acids and calories. The lipid emulsion is started at a rate of 0.5 to 1 g/kg/24 hr, gradually increasing the rate so that the patient receives adequate calories; this typically requires 2.5 to 3.5 g/kg/24 hr. The lipid emulsion usually provides 30% to 40% of the required calories; it should not exceed 60%. The serum triglyceride concentration is monitored as the rate of lipid emulsion is increased, with reduction of the lipid emulsion rate if significant hypertriglyceridemia develops.

### COMPLICATIONS

There are many potential complications of PN. CVLs are associated with complications during insertion (pneumothorax or bleeding) and long-term issues (thrombosis). **Catheter-related sepsis**, most commonly due to coagulase-negative staphylococci, is common and, on occasion, necessitates catheter removal. Other potential pathogens are **Staphylococcus aureus**, gram-negative bacilli, and fungi. Electrolyte abnormalities, nutritional deficiencies, hyperglycemia, and complications from excessive protein intake (azotemia or hyperammonemia) can be detected with careful monitoring.

The most concerning complication of long-term PN is **cholestatic liver disease**, which can lead to cirrhosis and liver failure. Current PN decreases the risk of liver disease by including reduced amounts of hepatotoxic amino acids. The best preventive strategy is early use of the gastrointestinal tract, even if only trophic feeds are tolerated.

### SODIUM DISORDERS

The kidney regulates sodium balance and is the principal site of sodium excretion. Sodium is unique among electrolytes because water balance, not sodium balance, usually determines its concentration. When the sodium concentration increases, the resultant higher plasma osmolality causes increased thirst and increased secretion of antidiuretic hormone (ADH), which leads to renal conservation of water. Both of these mechanisms increase the water content of the body, and the sodium concentration returns to normal. During hyponatremia, the fall in plasma osmolality decreases ADH secretion, and consequent renal water excretion leads to an
increase in the sodium concentration. Although water balance usually is regulated by osmolality, volume depletion stimulates thirst, ADH secretion, and renal conservation of water. In fact, volume depletion takes precedence over osmolality; volume depletion stimulates ADH secretion, even if a patient has hyponatremia.

The excretion of sodium by the kidney is not determined by the plasma osmolality. The patient’s effective plasma volume regulates the amount of sodium in the urine through a variety of regulatory systems, including the renin-angiotensin-aldosterone system. In hyponatremia or hypernatremia, the underlying pathophysiology determines the urinary sodium concentration, not the serum sodium concentration.

**HYPONATREMIA**

**Etiology**

Different mechanisms can cause hyponatremia (Fig. 35-1). **Pseudohyponatremia** is a laboratory artifact that is present when the plasma contains high concentrations of protein or lipid. It does not occur when a direct ion-selective electrode determines the sodium concentration, a technique that is increasingly used in clinical laboratories. In true hyponatremia, the measured osmolality is low, whereas it is normal in pseudohyponatremia. **Hyperosmolality**, resulting from mannitol infusion or hyperglycemia, causes a low serum sodium concentration because water moves down its osmotic gradient from the intracellular space into the extracellular space, diluting the sodium concentration. For every 100 mg/dL increment of the serum glucose, the serum sodium decreases by 1.6 mEq/L. Because the manifestations of hyponatremia are due to the low plasma osmolality, patients with hyponatremia caused by hyperosmolality do not have symptoms of hyponatremia and do not require correction of hyponatremia.

Classification of true hyponatremia is based on the patient’s volume status (see Fig. 35-1). In **hypovolemic hyponatremia**, the child has lost sodium from the body. Water balance may be positive or negative, but there has been a higher net sodium loss than water loss; this is often due to oral or intravenous (IV) water intake, with water retention by the kidneys to compensate for the intravascular volume depletion. If the sodium loss is due to a nonrenal disease (e.g., diarrhea), the urine sodium concentration is very low, as the kidneys attempt to preserve the intravascular volume by conserving sodium. In renal diseases, the urine sodium is inappropriately elevated.

Patients with hyponatremia and no evidence of volume overload or volume depletion have **euvolemic hyponatremia**. These patients typically have an excess of total body water and a slight decrease in total body sodium. Some of these patients have an increase in weight, implying that they are volume overloaded. Nevertheless, they usually appear normal or have only subtle signs of fluid overload. In **syndrome of inappropriate ADH (SIADH)**, there is secretion of ADH that is not inhibited by either low serum osmolality or expanded intravascular volume. Retention of water causes hyponatremia, and the expansion of the intravascular volume results in an increase in renal sodium excretion. Hyponatremia in hospitalized patients is often due to SIADH secondary to stress in the presence of hypotonic fluids.

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**Figure 35-1** Differential diagnosis of hyponatremia. Assessment of hyponatremia is a three-step process: (1) Determine if the osmolality is low; if yes, the patient has true hyponatremia. (2) Evaluate the patient’s volume status. (3) Determine the urine sodium concentration to help narrow the differential diagnosis. **ATN**, Acute tubular necrosis; **SIADH**, syndrome of inappropriate secretion of antidiuretic hormone.
SIADH is also associated with pneumonia, mechanical ventilation, meningitis, and other central nervous system disorders (trauma). Ectopic (tumor) production of ADH is rare in children. Infants can develop euvoletic hyponatremia as a result of excessive water consumption or inappropriately diluted formula.

In **hypervolemic hyponatremia**, there is an excess of total body water and sodium, although the increase in water is greater than the increase in sodium. In renal failure, there is an inability to excrete sodium or water; the urine sodium may be low or high, depending on the cause of the renal insufficiency. In other causes of hypervolemic hyponatremia, there is a decrease in the effective blood volume because of either third space fluid loss or poor cardiac output (see Chapter 145). In response to the low effective blood volume, ADH causes renal water retention, and the kidneys also retain sodium, leading to a low urine sodium concentration. The patient's serum sodium concentration decreases when water intake exceeds sodium intake, and ADH prevents the normal loss of excess water.

### Clinical Manifestations

Hyponatremia causes a fall in the osmolality of the extracellular space. Because the intracellular space then has a higher osmolality, water moves from the extracellular space to the intracellular space to maintain osmotic equilibrium. The increase in intracellular water may cause cells to swell. **Brain cell swelling** is responsible for most of the symptoms of hyponatremia. Neurologic symptoms of hyponatremia include anorexia, nausea, emesis, malaise, lethargy, confusion, agitation, headache, seizures, coma, and decreased reflexes. Patients may develop hypothermia and Cheyne-Stokes respirations. Hyponatremia can cause muscle cramps and weakness. Symptoms are more severe when hyponatremia develops rapidly; chronic hyponatremia can be asymptomatic because of a compensatory decrease in brain cell osmolality, which limits cerebral swelling.

### Treatment

Rapid correction of hyponatremia can produce **central pontine myelinolysis**. Avoiding more than a 12-mEq/L increase in the serum sodium every 24 hours is prudent, especially in chronic hyponatremia. Treatment of hypovolemic hyponatremia requires administration of IV fluids with sodium to provide maintenance requirements and deficit correction, as well as to replace ongoing losses (see Chapter 33). For children with SIADH, water restriction is the cornerstone of therapy. Children with hyponatremia secondary to hypothyroidism or nephrogenic diabetes insipidus may be secondary to interstitial nephritis, sickle cell disease, hypercalcemia, hypokalemia, or medications (lithium or amphotericin). If the defect is due to **central diabetes insipidus**, urine output decreases and urine osmolality increases in response to administration of an ADH analog. Central causes of ADH deficiency include tumor, infarction, or trauma. There is no response to an ADH analog in a child with nephrogenic diabetes insipidus.

Diabetes insipidus in children with gastroenteritis do not develop hyponatremia because they drink enough hypotonic fluid to compensate at least partially for stool water losses. Hyponatremia is most likely in a child with diarrhea who has inadequate intake because of emesis, lack of access to water, or anorexia. Some renal diseases, including obstructive uropathy, renal dysplasia, and juvenile nephronophthisis, can cause losses of sodium and water, potentially producing hyponatremia if the patient consumes insufficient water.

In situations with combined sodium and water deficits, analysis of the urine differentiates renal and nonrenal etiologies. When the losses are extrarenal, the kidney responds to volume depletion with low urine volume, a concentrated urine, and sodium retention (urine sodium <10 mEq/L). With renal causes, the urine volume is usually high, the urine is not maximally concentrated, and the urine sodium may be inappropriately elevated.
Chapter 35  Sodium Disorders

Clinical Manifestations
Most children with hypernatremia are dehydrated and have the typical signs and symptoms of dehydration (see Chapter 33). Children with hypernatremic dehydration tend to have better preservation of intravascular volume owing to the shift of water from the intracellular space to the extracellular space. Hypernatremic infants potentially become more dehydrated before seeking medical attention. Probably because of intracellular water loss, the pinched abdominal skin of a dehydrated, hypernatremic infant has a doughy feel.

Hypernatremia, even without dehydration, causes central nervous system symptoms that tend to parallel the degree of sodium elevation and the acuity of the increase. Patients are irritable, restless, weak, and lethargic. Some infants have a high-pitched cry and hyperpnea. Alert patients are very thirsty, although nausea may be present. Hypernatremia causes fever, although many patients have an underlying process that contributes to the fever.

Brain hemorrhage is the most devastating consequence of hypernatremia. As the extracellular osmolality increases, water moves out of brain cells, resulting in a decrease in brain volume. This decrease in volume can result in tearing of intracerebral veins and bridging blood vessels as the brain moves away from the skull and the meninges. Patients may have subarachnoid, subdural, and parenchymal hemorrhage. Seizures and coma are possible sequelae of the hemorrhage.

Treatment
As hypernatremia develops, the brain generates idiogenic osmoles to increase the intracellular osmolality and prevent the loss of brain water. This mechanism is not instantaneous and is most prominent when hypernatremia has developed gradually. If the serum sodium concentration is lowered rapidly, there is movement of water from the serum into the brain cells to equalize the osmolality in the two compartments. The resultant brain swelling manifests as seizures or coma. Because of these dangers, corrected hypernatremia should be treated gradually. The goal is to decrease the serum sodium by less than 12 mEq/L every 24 hours (see Fig. 33-1). The most important component of correcting moderate or severe hypernatremia is frequent monitoring of the serum sodium to allow adjustment of fluid therapy and provide adequate correction that is neither too slow nor too fast.

In a child with hypernatremic dehydration, as in any child with dehydration, the first priority is restoration of intravascular volume with isotonic fluid. Figure 33-1 outlines a general approach for correcting hypernatremic dehydration secondary to gastroenteritis. If the hypernatremia and dehydration are secondary to water loss, as occurs with diabetes insipidus, a more hypotonic IV fluid is appropriate. A child with central diabetes insipidus should receive an ADH analog to prevent further excessive water loss. A child with nephrogenic diabetes insipidus requires a urine replacement solution to offset ongoing water losses. Chronically, reduced sodium intake, thiazide diuretics, and nonsteroidal anti-inflammatory drugs can decrease water losses in nephrogenic diabetes insipidus.

Acute, severe hypernatremia, usually secondary to sodium administration, can be corrected more rapidly because idiogenic osmoles have not had time to accumulate; this balances the high morbidity and mortality from severe, acute hypernatremia with the dangers of overly rapid correction. When hypernatremia is due to sodium intoxication, and the hypernatremia is severe, it may be impossible to administer enough water to correct the hypernatremia rapidly without worsening volume overload. Some patients require use of a loop diuretic or dialysis.

Figure 35-2 Differential diagnosis of hypernatremia by mechanism. GI, Gastrointestinal; NG, nasogastric.
Chapter 36

POTASSIUM DISORDERS

The kidneys are the principal regulator of potassium balance, adjusting excretion based on intake. Factors affecting renal potassium excretion include aldosterone, acid-base status, serum potassium concentration, and renal function. The intracellular potassium concentration is approximately 30 times the extracellular potassium concentration. A variety of conditions alter the distribution of potassium between the intracellular and extracellular compartments, potentially causing either hypokalemia or hyperkalemia. The plasma concentration does not always reflect the total body potassium content.

HYPOKALEMIA

Etiology

Hypokalemia is common in children, with most cases related to gastroenteritis. Spurious hypokalemia occurs in patients with leukemia and elevated white blood cell counts if plasma for analysis is left at room temperature, permitting the white blood cells to take up potassium from the plasma. There are four basic mechanisms of hypokalemia (Table 36-1). Low intake, nonrenal losses, and renal losses all are associated with total body potassium depletion. With a transcellular shift, total body potassium is normal unless there is concomitant potassium depletion secondary to other factors.

The transcellular shift of potassium after initiation of insulin therapy in children with diabetic ketoacidosis (see Chapter 171) can be dramatic. These patients have reduced total body potassium because of urinary losses, but they often have a normal serum potassium level before insulin therapy from a transcellular shift into the extracellular space secondary to insulin deficiency and metabolic acidosis. Children receiving aggressive doses of β-adrenergic agonists (albuterol) for asthma can have hypokalemia resulting from the intracellular movement of potassium. Poor intake is an unusual cause of hypokalemia, unless also associated with significant weight loss (anorexia nervosa).

Diarrhea has a high concentration of potassium, and the resulting hypokalemia usually is associated with a metabolic acidosis secondary to stool losses of bicarbonate. With emesis or nasogastric suction, there is gastric loss of potassium, but this is fairly minimal given the low potassium content of gastric fluid (approximately 10 mEq/L). More important is the gastric loss of hydrochloride, leading to a metabolic alkalosis and a state of volume depletion. Metabolic alkalosis and volume depletion increase urinary losses of potassium.

Urinary potassium wasting may be accompanied by a metabolic acidosis (proximal or distal renal tubular acidosis) (see Chapter 37). Loop and thiazide diuretics lead to hypokalemia and a metabolic alkalosis. Bartter syndrome and Gitelman syndrome are autosomal recessive disorders resulting from defects in tubular transporters. Both disorders are associated with hypokalemia and a metabolic alkalosis. Bartter syndrome is usually associated with hypercalcuria, often with nephrocalcinosis; children with Gitelman syndrome have low urinary calcium losses, but hypomagnesemia secondary to urinary losses.

In the presence of a high aldosterone level, there is urinary loss of potassium, hypokalemia, and a metabolic alkalosis. There also is renal retention of sodium, leading to hypertension. A variety of genetic and acquired disorders can cause high aldosterone levels. Liddle syndrome, an autosomal dominant disorder caused by constitutively active sodium channels, has the same clinical features as hyperaldosteronism, but the serum aldosterone level is low.

Clinical Manifestations

The heart and skeletal muscle are especially vulnerable to hypokalemia. Electrocardiographic (ECG) changes include a flattened T wave, a depressed ST segment, and the appearance of a U wave, which is located between the T wave (if still visible) and P wave. Ventricular fibrillation and torsades de pointes may occur, although usually only in the context of underlying heart disease. Hypokalemia makes the heart especially susceptible to digitalis-induced arrhythmias.

The clinical consequences in skeletal muscle include muscle weakness and cramps. Paralysis is a possible complication (generally only at potassium levels <2.5 mEq/L). Paralysis usually starts with the legs, followed by the arms. Respiratory paralysis may require mechanical ventilation.

Some hypokalemic patients develop rhabdomyolysis, especially following exercise. Hypokalemia slows gastrointestinal motility; potassium levels less than 2.5 mEq/L may cause an ileus. Hypokalemia impairs bladder function, potentially leading to urinary retention. Hypokalemia causes polyuria by producing secondary nephrogenic diabetes insipidus. Chronic hypokalemia may cause kidney damage, including interstitial nephritis and renal cysts. In children, chronic hypokalemia, as in Bartter syndrome, leads to poor growth.

Diagnosis

It is important to review the child’s diet, history of gastrointestinal losses, and medications. Emesis and diuretic use can be surreptitious. The presence of hypertension suggests excess mineralocorticoids. Concomitant electrolyte abnormalities are useful clues. The combination of hypokalemia and metabolic acidosis is characteristic of diarrhea, distal renal tubular acidosis, and proximal renal tubular acidosis. A concurrent metabolic alkalosis is characteristic of gastric losses, aldosterone excess, diuretics, Bartter syndrome, or Gitelman syndrome.

Treatment

Factors that influence the therapy of hypokalemia include the potassium level, clinical symptoms, renal function, presence of transcellular shifts of potassium, ongoing losses, and the patient’s ability to tolerate oral potassium. Severe, symptomatic hypokalemia requires aggressive treatment. Supplementation
is more cautious if renal function is decreased because of the kidney's limited ability to excrete excessive potassium. The plasma potassium level does not always provide an accurate estimation of the total body potassium deficit because there may be shifts of potassium from the intracellular space to the plasma. Clinically, this shift occurs most commonly with metabolic acidosis and as a result of the insulin deficiency of diabetic ketoacidosis; the plasma potassium underestimates the degree of total body potassium depletion. When these problems are corrected, potassium moves into the intracellular space, and these patients require more potassium supplementation to correct the hypokalemia. Patients who have ongoing losses of potassium need correction of the deficit and replacement of the ongoing losses.

Because of the risk of hyperkalemia, intravenous (IV) potassium should be used cautiously. Oral potassium is safer in nonurgent situations. The dose of IV potassium is 0.5 to 1 mEq/kg, usually given over 1 hour. The adult maximum dose is 40 mEq. Conservative dosing is generally preferred. For patients with excessive urinary losses, potassium-sparing diuretics are effective. When hypokalemia, metabolic alkalosis, and volume depletion are present, restoration of intravascular volume decreases urinary potassium losses.

**HYPERKALEMIA**

### Etiology

Three basic mechanisms cause hyperkalemia (Table 36-2). In the individual patient, the etiology is sometimes multifactorial. **Factitious hyperkalemia** is usually due to hemolysis during phlebotomy, but it can be the result of prolonged tourniquet application or fist clenching, which causes local potassium release from muscle. Falsely elevated serum potassium levels can occur when serum levels are measured in patients with markedly elevated white blood cell or platelet counts; a promptly analyzed plasma sample usually provides an accurate result. Because of the kidney's ability to excrete potassium, it is unusual for excessive intake, by itself, to cause hyperkalemia. This mechanism can occur in a patient who is receiving large quantities of IV or oral potassium for excessive losses that are no longer present. Frequent or rapid blood transfusions can increase the potassium level acutely secondary to the high
potassium content of stored blood. Increased intake may precipitate hyperkalemia if there is an underlying defect in potassium excretion.

The intracellular space has a high potassium concentration, so a shift of potassium from the intracellular space to the extracellular space can have a significant impact on the plasma potassium. This shift occurs with acidosis, cell destruction (rhabdomyolysis or tumor lysis syndrome), insulin deficiency, medications (succinylcholine, β-blockers), malignant hyperthermia, and hyperkalemic periodic paralysis.

Hyperkalemia secondary to decreased excretion occurs with renal insufficiency. Aldosterone deficiency or unresponsiveness to aldosterone causes hyperkalemia, often with associated metabolic acidosis (see Chapter 37) and hyponatremia. A form of congenital adrenal hyperplasia, 21-hydroxylase deficiency, is the most frequent cause of aldosterone deficiency in children. Male infants typically present with hyperkalemia, metabolic acidosis, hyponatremia, and volume depletion. Female infants with this disorder usually are diagnosed as newborns because of ambiguous genitalia.

Renin, via angiotensin II, stimulates aldosterone production. A deficiency in renin, resulting from kidney damage, can lead to decreased aldosterone production. These patients typically have hyperkalemia and a metabolic acidosis, without hyponatremia. Some patients have impaired renal function, partially accounting for the hyperkalemia, but the impairment in potassium excretion is more extreme than expected for the degree of renal insufficiency.

Children with pseudohypoaldosteronism type 1 have hyperkalemia, metabolic acidosis, and salt wasting, leading to hyponatremia and volume depletion; aldosterone levels are elevated. In the autosomal recessive variant, there is a defect in the renal sodium channel that is normally activated by aldosterone. In the autosomal dominant form, patients have a defect in the aldosterone receptor, and the disease is milder, often remitting in adulthood. Pseudohypoaldosteronism type 2, also called Gordon syndrome, is an autosomal dominant disorder characterized by hypertension secondary to salt retention and impaired excretion of potassium and acid leading to hyperkalemia and metabolic acidosis. The risk of hyperkalemia secondary to medications that decrease renal potassium excretion is greatest in patients with underlying renal insufficiency.

### Clinical Manifestations

The most important effects of hyperkalemia are due to the role of potassium in membrane polarization. The cardiac conduction...
system is usually the dominant concern. ECG changes begin with peaking of the T waves. As the potassium level increases, an increased P-R interval, flattening of the P wave, and widening of the QRS complex occur; this eventually can progress to ventricular fibrillation. Asystole also may occur. Some patients have paresthesias, weakness, and tingling, but cardiac toxicity usually precedes these clinical symptoms.

**Diagnosis**

The etiology of hyperkalemia is often readily apparent. Spurious hyperkalemia is common in children, so a repeat potassium level is often appropriate. If there is a significant elevation of the white blood cells or platelets, the repeat sample should be from plasma that is evaluated promptly. The history initially should focus on potassium intake, risk factors for transcellular shifts of potassium, medications that cause hyperkalemia, and the presence of signs of renal insufficiency, such as oliguria or an abnormal urinalysis. Initial laboratory evaluation should include serum creatinine and assessment of acid-base status. Many causes of hyperkalemia, such as renal insufficiency and aldosterone insufficiency or resistance, cause a metabolic acidosis. Cell destruction, as seen in rhabdomyolysis or tumor lysis syndrome, can cause concomitant hyperphosphatemia, hyperuricemia, and an elevated serum lactate dehydrogenase.

**Treatment**

The plasma potassium level, the ECG, and the risk of the problem worsening determine the aggressiveness of the therapeutic approach. A high serum potassium level with ECG changes requires more vigorous treatment. An additional source of concern is a patient with increasing plasma potassium despite minimal intake. This situation can occur if there is cellular release of potassium (tumor lysis syndrome), especially in the setting of diminished excretion (renal failure).

The first action in a child with a concerning elevation of plasma potassium is to stop all sources of additional potassium (oral and IV). If the potassium level is greater than 6.5 mEq/L, an ECG should be obtained to help assess the urgency of the situation. Therapy of hyperkalemia has two basic goals: 1. Prevent life-threatening arrhythmias. 2. Remove potassium from the body (Table 36-3).

**Table 36-3** Treatment of Hyperkalemia

<table>
<thead>
<tr>
<th>Rapidly decrease the risk of life-threatening arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shift potassium intracellularly</td>
</tr>
<tr>
<td>Sodium bicarbonate administration (IV)</td>
</tr>
<tr>
<td>Insulin and glucose (IV)</td>
</tr>
<tr>
<td>β-Agonist (albuterol via nebulizer)</td>
</tr>
<tr>
<td>Cardiac membrane stabilization</td>
</tr>
<tr>
<td>IV calcium</td>
</tr>
<tr>
<td>Remove potassium from the body</td>
</tr>
<tr>
<td>Loop diuretic (IV or PO)</td>
</tr>
<tr>
<td>Sodium polystyrene (PO or rectal)</td>
</tr>
<tr>
<td>Dialysis</td>
</tr>
</tbody>
</table>

Treatments that acutely prevent arrhythmias all work quickly (within minutes), but do not remove potassium from the body.

Long-term management of hyperkalemia includes reducing intake via dietary changes and eliminating or reducing medications that cause hyperkalemia. Some patients require medications, such as sodium polystyrene sulfonate and loop or thiazide diuretics, to increase potassium losses. The disorders due to a deficiency in aldosterone respond to replacement therapy with fludrocortisone, a mineralocorticoid.

**ACID-BASE DISORDERS**

Close regulation of pH is necessary for cellular enzymes and other metabolic processes, which function optimally at a normal pH (7.35 to 7.45). Chronic, mild derangements in acid-base status may interfere with normal growth and development, whereas acute, severe changes in pH can be fatal. Control of acid-base balance depends on the kidneys, the lungs, and intracellular and extracellular buffers.

The lungs and the kidneys maintain a normal acid-base balance. Carbon dioxide (CO₂) generated during normal metabolism is a weak acid. The lungs prevent an increase in the partial pressure of CO₂ (Pco₂) in the blood by excreting the CO₂. Production of CO₂ varies depending on the body’s metabolic needs. The rapid pulmonary response to changes in CO₂ concentration occurs via central sensing of the Pco₂ and a subsequent increase or decrease in ventilation to maintain a normal Pco₂ (35 to 45 mm Hg).

The kidneys excrete endogenous acids. An adult normally produces about 1 to 2 mEq/kg/day of hydrogen ions, whereas a child produces 2 to 3 mEq/kg/day. The hydrogen ions from endogenous acid production are neutralized by bicarbonate, potentially causing the bicarbonate concentration to fall. The kidneys regenerate this bicarbonate by secreting hydrogen ions, maintaining the serum bicarbonate concentration in the normal range (20 to 28 mEq/L).

**CLINICAL ASSESSMENT OF ACID-BASE DISORDERS**

**Acidemia** is a pH below normal (<7.35), and **alkalemia** is a pH above normal (>7.45). **Acidosis** is a pathologic process that causes an increase in the hydrogen ion concentration, and **alkalosis** is a pathologic process that causes a decrease in the hydrogen ion concentration. A **simple acid-base disorder** is a single primary disturbance. During a simple metabolic disorder, there
is respiratory compensation; the Pco₂ decreases during a metabolic acidosis and increases during a metabolic alkalosis. With metabolic acidosis, the decrease in the pH increases the ventilatory drive, causing a decrease in the Pco₂. The fall in the CO₂ concentration leads to an increase in the pH. This appropriate respiratory compensation for a metabolic process happens quickly and is complete within 12 to 24 hours.

During a primary respiratory process, there is metabolic compensation mediated by the kidneys. The kidneys respond to a respiratory acidosis by increasing hydrogen ion excretion, increasing bicarbonate generation, and raising the serum bicarbonate concentration. The kidneys increase bicarbonate excretion to compensate for a respiratory alkalosis; the serum bicarbonate concentration decreases. In contrast to a rapid respiratory compensation, it takes 3 to 4 days for the kidneys to complete appropriate metabolic compensation. However, there is a small and rapid compensatory change in the bicarbonate concentration during a primary respiratory process. The expected appropriate metabolic compensation for a respiratory disorder depends on whether the process is acute or chronic.

A mixed acid-base disorder is present when there is more than one primary acid-base disturbance. An infant with bronchopulmonary dysplasia may have a respiratory acidosis from chronic lung disease and a metabolic acidosis from a diuretic used to treat the chronic lung disease. Formulas are available for calculating the appropriate metabolic or respiratory compensation for the six primary simple acid-base disorders (Table 37-1). Appropriate compensation is expected in a simple disorder; it is not optional. If a patient does not have appropriate compensation, a mixed acid-base disorder is present.

**METABOLIC ACIDOSIS**

Metabolic acidosis occurs frequently in hospitalized children; diarrhea is the most common cause. For a patient with an unknown medical problem, the presence of a metabolic acidosis is often helpful diagnostically because it suggests a relatively narrow differential diagnosis (Table 37-2).

### Etiology

Diarrhea causes a loss of bicarbonate from the body. The amount of bicarbonate lost in the stool depends on the volume of diarrhea and the bicarbonate concentration of the stool, which tends to increase with more severe diarrhea. Diarrhea often causes volume depletion because of losses of sodium and water, potentially exacerbating the acidosis by causing hypoperfusion (shock) and a lactic acidosis. There are three forms of renal tubular acidosis (RTA):

- Distal (type I)
- Proximal (type II)
- Hyperkalemic (type IV)

In distal RTA, children may have accompanying hypokalemia, hypercalciuria, nephrolithiasis, and nephrocalcinosis; rickets is a less common finding. Failure to thrive, resulting from chronic metabolic acidosis, is the most common presenting complaint. Autosomal dominant and autosomal recessive forms of distal RTA exist. The autosomal dominant form is relatively mild. Autosomal recessive distal RTA is more severe and often associated with deafness secondary to a defect in the gene for a H⁺-ATPase that is present in the kidney and the inner ear. Distal RTA also may be secondary to medications or congenital or acquired renal disease. Patients with distal RTA cannot acidify their urine and have a urine pH greater than 5.5, despite a metabolic acidosis.

**Proximal RTA** is rarely present in isolation. In most patients, proximal RTA is part of Fanconi syndrome, a generalized dysfunction of the proximal tubule. Along with renal wasting of bicarbonate, Fanconi syndrome causes glycosuria, aminoaciduria, and excessive urinary losses of phosphate and uric acid. The chronic hypophosphatemia is more clinically significant because it ultimately leads to rickets in children. Rickets or failure to thrive may be the presenting complaint. Fanconi syndrome is rarely an isolated genetic disorder, with pediatric cases usually secondary to an underlying genetic disorder, most commonly cystinosis. Medications, such as ifosfamide or valproate, may cause Fanconi syndrome. The ability to acidify the urine is intact in proximal RTA, and untreated patients have a urine pH less than 5.5. However, bicarbonate therapy increases bicarbonate losses in the urine, and the urine pH increases.

In hyperkalemic RTA, renal excretion of acid and potassium is impaired because of either an absence of aldosterone

### Table 37-1: Appropriate Compensation During Simple Acid-Base Disorders

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>EXPECTED COMPENSATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Pco₂ = 1.5 × [HCO₃⁻] + 8 ± 2</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>Pco₂ increases by 7 mm Hg for each 10-mEq/L increase in the serum [HCO₃⁻]</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>[HCO₃⁻] increases by 1 for each 10-mm Hg increase in the Pco₂</td>
</tr>
<tr>
<td>Chronic</td>
<td>[HCO₃⁻] increases by 3.5 for each 10-mm Hg increase in the Pco₂</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>[HCO₃⁻] falls by 2 for each 10-mm Hg decrease in the Pco₂</td>
</tr>
<tr>
<td>Chronic</td>
<td>[HCO₃⁻] falls by 4 for each 10-mm Hg decrease in the Pco₂</td>
</tr>
</tbody>
</table>

*HCO₃⁻* is expressed in mEq/L.

### Table 37-2: Causes of Metabolic Acidosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORMAL ANION GAP</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td></td>
</tr>
<tr>
<td>Urinary tract diversions</td>
<td></td>
</tr>
<tr>
<td>Posthypocapnia</td>
<td></td>
</tr>
<tr>
<td>Ammonium chloride intake</td>
<td></td>
</tr>
<tr>
<td><strong>INCREASED ANION GAP</strong></td>
<td></td>
</tr>
<tr>
<td>Lactic acidosis (shock)</td>
<td></td>
</tr>
<tr>
<td>Ketoacidosis (diabetic, starvation, or alcoholic)</td>
<td></td>
</tr>
<tr>
<td>Kidney failure</td>
<td></td>
</tr>
<tr>
<td>Poisoning (e.g., ethylene glycol, methanol, or salicylates)</td>
<td></td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td></td>
</tr>
</tbody>
</table>
or an inability of the kidney to respond to aldosterone. In severe aldosterone deficiency, as occurs with congenital adrenal hyperplasia secondary to 21α-hydroxylase deficiency, the hyperkalemia and metabolic acidosis are accompanied by hyponatremia and volume depletion from renal salt wasting. Incomplete aldosterone deficiency causes less severe electrolyte disturbances; children may have isolated hyperkalemic RTA, hyperkalemia without acidosis, or isolated hyponatremia.

**Lactic acidosis** most commonly occurs when inadequate oxygen delivery to the tissues leads to anaerobic metabolism and excess production of lactic acid. Lactic acidosis may be secondary to shock, severe anemia, or hypoxemia. Inborn errors of carbohydrate metabolism produce a severe lactic acidosis (see Chapter 52). In diabetes mellitus, inadequate insulin leads to hyperglycemia and diabetic ketoacidosis (see Chapter 51). Renal failure (see Chapter 165) causes a metabolic acidosis because the kidneys are unable to excrete the acid produced by normal metabolism.

A variety of **toxic ingestions** cause a metabolic acidosis. Acute salicylate intoxication occurs after a large overdose. Chronic salicylate intoxication is possible because of the gradual build-up of the drug. In addition to a metabolic acidosis, some patients may have a respiratory alkalosis. Other symptoms of salicylate intoxication include fever, seizures, lethargy, and coma. Hyperventilation may be particularly marked. Tinnitus, vertigo, and hearing impairment are more likely with chronic salicylate intoxication. Ethylene glycol, a component of antifreeze, is converted in the liver to glyoxylic and oxalic acids, causing a severe metabolic acidosis. Excessive oxalate excretion causes calcium oxalate crystals to appear in the urine, and calcium oxalate precipitation in the kidney tubules can cause renal failure. The toxicity of methanol ingestion also depends on liver metabolism; formic acid is the toxic end product that causes the metabolic acidosis and other sequelae, which include damage to the optic nerve and central nervous system.

There are many **inborn errors of metabolism** that may cause a metabolic acidosis (see Section 10). The metabolic acidosis may be due to excessive production of ketoads, lactic acid, or other organic anions. Some patients have accompanying hyperammonemia. In most patients, acidosis occurs only episodically during acute decompensations, which may be precipitated by ingestion of specific dietary substrates (proteins), the stress of a mild illness (fasting, catabolism), or poor compliance with dietary or medical therapy.

### Clinical Manifestations

The underlying disorder usually produces most of the signs and symptoms in children with a mild or moderate metabolic acidosis. The clinical manifestations of the acidosis are related to the degree of acidemia; patients with appropriate respiratory compensation and less severe acidemia have fewer manifestations than patients with a concomitant respiratory acidosis. At a serum pH less than 7.20, there is impaired cardiac contractility and an increased risk of arrhythmias, especially if underlying heart disease or other predisposing electrolyte disorders are present. With acidemia, there is a decrease in the cardiovascular response to catecholamines, potentially exacerbating hypotension in children with volume depletion or shock. Acidemia causes vasoconstriction of the pulmonary vasculature, which is especially problematic in neonates with primary pulmonary hypertension of the newborn (see Chapter 61). The normal respiratory response to metabolic acidosis—compensatory hyperventilation—may be subtle with mild metabolic acidosis, but it causes discernible increased respiratory effort with worsening acidemia. Chronic metabolic acidosis causes failure to thrive.

### Diagnosis

The plasma **anion gap** is useful for evaluating patients with a metabolic acidosis. It divides patients into two diagnostic groups: normal anion gap and increased anion gap. The following formula determines the anion gap:

\[
\text{Anion gap} = [\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-] 
\]

A normal anion gap is 3 to 11. A decrease in the albumin concentration of 1 g/dL decreases the anion gap by roughly 4 mEq/L. Similarly, albeit less commonly, an increase in unmeasured cations, such as calcium, potassium, or magnesium, decreases the anion gap. Conversely, a decrease in unmeasured cations is a rare cause of an increased anion gap. Because of these variables, the broad range of a normal anion gap, and other factors, the presence of a normal or increased anion gap is not always reliable in differentiating the causes of a metabolic acidosis, especially when the metabolic acidosis is mild. Some patients have more than one explanation for their metabolic acidosis, such as a child with diarrhea and lactic acidosis secondary to hypoperfusion. The anion gap should not be interpreted in dogmatic isolation; consideration of other laboratory abnormalities and the clinical history improves its diagnostic utility.

### Treatment

The most effective therapeutic approach for patients with a metabolic acidosis is correction of the underlying disorder, if possible. The administration of insulin in diabetic ketoacidosis or restoration of adequate perfusion in lactic acidosis from shock eventually results in normalization of acid-base balance. The use of bicarbonate therapy is indicated when the underlying disorder is irreparable; examples include RTA and chronic renal failure. In salicylate poisoning, alkali administration increases renal clearance of salicylate and decreases the amount of salicylate in brain cells. Short-term base therapy is often necessary in other poisonings and inborn errors of metabolism.

### METABOLIC ALKALOSIS

#### Etiology

The causes of a metabolic alkalosis are divided into two categories based on the urinary chloride (Table 37-3). The alkalosis in patients with a low urinary chloride is maintained by volume depletion. They are called **chloride responsive** because volume repletion with fluid containing sodium chloride and potassium chloride is necessary to correct the metabolic alkalosis. Emesis, which causes loss of hydrochloride and volume depletion, is the most common cause of a metabolic alkalosis. Diuretic use increases chloride excretion in the urine. Consequently, while a patient is receiving diuretics, the urinary chloride is typically high (>20 mEq/L). After the diuretic effect resolves, the urinary chloride is low (<15 mEq/L), because of appropriate renal chloride retention in response to volume depletion. Categorization of diuretics based on urinary
chloride depends on the timing of the measurement. The metabolic alkalosis from diuretics is clearly chloride responsive; it corrects only after adequate volume repletion. This is the rationale for including it among the chloride-responsive causes of a metabolic alkalosis.

The chloride-resistant causes of metabolic alkalosis can be subdivided based on blood pressure. Patients with the rare disorders that cause a metabolic alkalosis and hypertension either have increased aldosterone or act as if they have increased aldosterone. Patients with Bartter syndrome or Gitelman syndrome (Chapter 36) have metabolic alkalosis, hypokalemia, and normal blood pressure secondary to renal tubular defects that cause continuous urinary losses of chloride.

Clinical Manifestations
The symptoms in patients with a metabolic alkalosis often are related to the underlying disease and associated electrolyte disturbances. Hypokalemia is often present, and occasionally severe, in the diseases that cause a metabolic alkalosis (see Chapter 36). Children with chloride-responsive causes of metabolic alkalosis often have symptoms related to volume depletion (see Chapter 33). In contrast, children with chloride-unresponsive causes may have symptoms related to hypertension. Severe alkalemia may cause arrhythmias, hypoxia secondary to hypoventilation, or decreased cardiac output.

Diagnosis
Measurement of the urinary chloride concentration is the most helpful test in differentiating among the causes of a metabolic alkalosis. The history usually suggests a diagnosis, although no obvious explanation may be present in the patient with bulimia, surreptitious diuretic use, or an undiagnosed genetic disorder, such as Bartter syndrome or Gitelman syndrome.

Treatment
The approach to therapy of metabolic alkalosis depends on the severity of the alkalosis and the underlying etiology. In children with a mild metabolic alkalosis ([HCO₃⁻] < 32 mEq/L), intervention is often unnecessary. Patients with chloride-responsive metabolic alkalosis respond to correction of hypokalemia and volume repletion with sodium and potassium chloride, but aggressive volume repletion may be contraindicated if mild volume depletion is medically necessary in the child receiving diuretic therapy. In children with chloride-resistant causes of a metabolic alkalosis that are associated with hypertension, volume repletion is contraindicated because it exacerbates the hypertension and does not repair the metabolic alkalosis. Treatment focuses on eliminating or blocking the action of the excess mineralocorticoid. In children with Bartter syndrome or Gitelman syndrome, therapy includes oral potassium supplementation and potassium-sparing diuretics.

RESPIRATORY ACID-BASE DISTURBANCES
During a respiratory acidosis, there is a decrease in the effectiveness of CO₂ removal by the lungs. The causes of a respiratory acidosis are either pulmonary or nonpulmonary (Table 37-4). A respiratory alkalosis is an inappropriate reduction in the blood CO₂ concentration. A variety of stimuli can increase the ventilatory drive and cause a respiratory alkalosis (Table 37-5). Treatment of respiratory acid-base disorders focuses on correction of the underlying disorder. Mechanical ventilation may be necessary in a child with a refractory respiratory acidosis.

<table>
<thead>
<tr>
<th>Table 37-3</th>
<th>Causes of Metabolic Alkalosis</th>
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</thead>
<tbody>
<tr>
<td><strong>CHLORIDE RESPONSIVE (URINARY CHLORIDE &lt;15 Meq/L)</strong></td>
<td></td>
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<tr>
<td>Gastric losses (emesis or nasogastric suction)</td>
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<tr>
<td>Pyloric stenosis</td>
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<tr>
<td>Diuretics (loop or thiazide)</td>
<td></td>
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<tr>
<td>Chloride-losing diarrhea</td>
<td></td>
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<tr>
<td>Chloride-deficient formula</td>
<td></td>
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<tr>
<td>Cystic fibrosis (sweat losses of chloride)</td>
<td></td>
</tr>
<tr>
<td>Posthypercapnia (chloride loss during respiratory acidosis)</td>
<td></td>
</tr>
<tr>
<td><strong>CHLORIDE RESISTANT (URINARY CHLORIDE &gt;20 Meq/L)</strong></td>
<td></td>
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<tr>
<td>High Blood Pressure</td>
<td></td>
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<tr>
<td>Adrenal adenoma or hyperplasia</td>
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<tr>
<td>Glucocorticoid-remediable aldosteronism</td>
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<tr>
<td>Renovascular disease</td>
<td></td>
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<tr>
<td>Renin-secreting tumor</td>
<td></td>
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<tr>
<td>17α-Hydroxylase deficiency</td>
<td></td>
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<tr>
<td>11β-Hydroxylase deficiency</td>
<td></td>
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<tr>
<td>Cushing syndrome</td>
<td></td>
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<tr>
<td>11 β-Hydroxysteroid dehydrogenase deficiency</td>
<td></td>
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<tr>
<td>Licorice ingestion</td>
<td></td>
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<tr>
<td>Liddle syndrome</td>
<td></td>
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<tr>
<td><strong>Normal Blood Pressure</strong></td>
<td></td>
</tr>
<tr>
<td>Gitelman syndrome</td>
<td></td>
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<tr>
<td>Bartter syndrome</td>
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<tr>
<td>Base administration</td>
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</table>

<table>
<thead>
<tr>
<th>Table 37-4</th>
<th>Causes of Respiratory Acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system depression (encephalitis or narcotic overdose)</td>
<td></td>
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<tr>
<td>Disorders of the spinal cord, peripheral nerves, or neuromuscular junction (botulism or Guillain-Barré syndrome)</td>
<td></td>
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<tr>
<td>Respiratory muscle weakness (muscular dystrophy)</td>
<td></td>
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<tr>
<td>Pulmonary disease (pneumonia or asthma)</td>
<td></td>
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<tr>
<td>Upper airway disease (laryngospasm)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 37-5</th>
<th>Causes of Respiratory Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia or tissue hypoxia (carbon monoxide poisoning or cyanotic heart disease)</td>
<td></td>
</tr>
<tr>
<td>Lung receptor stimulation (pneumonia or pulmonary embolism)</td>
<td></td>
</tr>
<tr>
<td>Central stimulation (anxiety or brain tumor)</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td></td>
</tr>
<tr>
<td>Hyperammonemias</td>
<td></td>
</tr>
</tbody>
</table>
Suggested Reading


ASSESSMENT AND RESUSCITATION

INITIAL ASSESSMENT
Initial assessment (the ABCs—airway, breathing, and circulation) of an acutely ill or injured child includes rapid identification of physiologic derangements in tissue perfusion and oxygenation. Once identified, immediate resuscitation must be implemented before pursuing the usual information needed to develop a differential diagnosis. Initial resuscitation measures are directed at achieving and maintaining adequate tissue perfusion and oxygenation. Oxygen delivery depends on cardiac output, hemoglobin concentration, and hemoglobin-oxygen saturation. The last mentioned depends on air movement, alveolar gas exchange, pulmonary blood flow, and oxygen-hemoglobin binding characteristics.

HISTORY
In the resuscitation phase, access to historical information may be limited. Characterization of the onset of symptoms, details of events, and a brief identification of underlying medical problems should be sought by members of the team not actively involved in the resuscitation. Attempts at identifying historical issues that affect the ABCs are useful but should not delay intervention if tissue oxygenation and perfusion are markedly impaired.

PHYSICAL EXAMINATION
Initial examination must focus rapidly on the ABCs (Table 38-1) to address the issues of oxygen delivery to tissues systematically. Airway patency is the first to be addressed, including assessment of the neurologically injured child’s ability to protect the airway. Protection of the cervical spine also should be initiated at this step in any child with traumatic injury or who presents with altered mental status of uncertain etiology. Assessment of breathing includes auscultation of air movement and application of a pulse oximeter (when available) to identify current oxygenation status. Circulatory status is assessed by palpation for distal and central pulses, focusing on the presence and quality of the pulses. Bounding pulses and a wide pulse pressure are often the first sign of the vasodilatory phase of shock and require immediate resuscitation measures. Weak, threadlike, or absent pulses are indicators for fluid resuscitation, initiation of chest compressions, or both. When assessment of the ABCs is complete and measures have been taken to achieve an acceptable level of tissue oxygenation, a more complete physical examination is performed. The sequence of this examination depends on whether the situation involves an acute medical illness or trauma. In trauma patients, the examination follows the ABCDE pathway. D stands for disability and prompts assessment of the neurologic system and evaluation for major traumatic injuries. E stands for exposure; the child is disrobed and examined for evidence of any life-threatening or limb-threatening problems. For the acutely ill and the injured child, the subsequent physical examination should identify evidence of organ dysfunction, starting with areas suggested in the chief complaint and progressing to a thorough and systematic investigation of the entire patient.

COMMON MANIFESTATIONS
The physiologic responses to acute illness and injury are mechanisms that attempt to correct inadequacies of tissue oxygenation and perfusion. When initial changes, such as increasing heart and respiratory rates, fail to meet the body’s needs, other manifestations of impending cardiopulmonary failure occur (Table 38-2). Respiratory failure, the most common cause of acute deterioration in children, may result in inadequate tissue oxygenation and in respiratory acidosis. Signs and symptoms of respiratory failure (tachypnea, tachycardia, increased work of breathing, abnormal mentation) progress as tissue oxygenation becomes more inadequate. Inadequate perfusion (shock) leads to inadequate oxygen delivery and a resulting metabolic acidosis. Shock is characterized by signs of inadequate tissue perfusion (pallor, cool skin, poor pulses, delayed capillary refill, oliguria, and abnormal mentation). The presence of any of these symptoms demands careful assessment and intervention to correct the abnormality and to prevent further deterioration.

INITIAL DIAGNOSTIC EVALUATION

Screening Tests
During the initial phase of resuscitation, monitoring vital signs and physiologic status is the key screening activity. Continuous monitoring with attention to changes may indicate response to
therapy or further deterioration requiring additional intervention. During the initial rapid assessment, diagnostic evaluation often is limited to pulse oximetry and bedside measurement of glucose levels. The latter is important in any child with altered mental status or at risk for inadequate glycogen stores (infants, malnourished patients). After resuscitation measures, further diagnostic tests and imaging are often necessary.

**Diagnostic Tests and Imaging**

The choice of appropriate diagnostic tests and imaging is determined by the mechanism of disease and results of evaluation after initial resuscitation. The initial evaluation of major trauma patients is focused on identifying evidence of hemorrhage and organ and tissue injury. For an acutely ill child with respiratory distress, a chest x-ray is important. Appropriate cultures should be obtained when sepsis is suspected. Children with historical or physical evidence of inadequate intravascular volume should have serum electrolyte levels obtained, including bicarbonate, blood urea nitrogen, and creatinine.

**RESUSCITATION**

Resuscitation is focused on correcting identified abnormalities of oxygenation and perfusion and preventing further deterioration. Oxygen supplementation may improve oxygen saturation but may not completely correct tissue oxygenation. When oxygen supplementation is insufficient or air exchange is inadequate, assisted ventilation must be initiated. Inadequate perfusion is usually best managed initially by providing a fluid bolus. Isotonic crystalloids (normal saline, lactated Ringer solution) are the initial fluid of choice. A bolus of 10 to 20 mL/kg should be delivered in monitored conditions. Improvement, but not correction, after an initial bolus should prompt repeated boluses until circulation has been re-established. Because most children with shock have noncardiac causes, fluid administration of this magnitude is well tolerated. If hemorrhage is known or highly suspected, administration of packed red blood cells is appropriate. Monitoring for deteriorating physiologic status during fluid resuscitation (increase in heart rate, decrease in blood pressure) identifies children who may have decreased cardiac function. Fluid resuscitation increases preload, which may worsen pulmonary edema and cardiac function. If deterioration occurs, fluid administration should be interrupted, and resuscitation should be aimed at improving cardiac function.

When respiratory support and fluid resuscitation are insufficient, introduction of vasoactive substances is the next step. The choice of which agent to use depends on the type of shock present. Hypovolemic shock (when further volume is contraindicated) and distributive shock benefit from drugs that increase systemic vascular resistance (drugs with α-agonist activity, such as epinephrine or norepinephrine). The treatment of cardiogenic shock is more complex. To improve cardiac output by increasing the heart rate, drugs with positive chronotropy are used (epinephrine, norepinephrine, and dopamine). Afterload reduction, using drugs such as

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**Table 38-1** Rapid Cardiopulmonary Assessment

<table>
<thead>
<tr>
<th>AIRWAY PATENCY</th>
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</thead>
<tbody>
<tr>
<td>Able to be maintained independently</td>
</tr>
<tr>
<td>Maintainable with positioning, suctioning</td>
</tr>
<tr>
<td>Unmaintainable, requires assistance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BREATHING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
</tr>
<tr>
<td>Mechanics</td>
</tr>
<tr>
<td>• Retractions</td>
</tr>
<tr>
<td>• Grunting</td>
</tr>
<tr>
<td>• Use of accessory muscles</td>
</tr>
<tr>
<td>• Nasal flaring</td>
</tr>
<tr>
<td>Air movement</td>
</tr>
<tr>
<td>• Chest expansion</td>
</tr>
<tr>
<td>• Breath sounds</td>
</tr>
<tr>
<td>• Stridor</td>
</tr>
<tr>
<td>• Wheezing</td>
</tr>
<tr>
<td>• Paradoxical chest motion</td>
</tr>
<tr>
<td>Color</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CIRCULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
</tr>
<tr>
<td>Peripheral and central pulses</td>
</tr>
<tr>
<td>• Present/absent</td>
</tr>
<tr>
<td>• Volume/strength</td>
</tr>
<tr>
<td>Skin perfusion</td>
</tr>
<tr>
<td>• Capillary refill time</td>
</tr>
<tr>
<td>• Skin temperature</td>
</tr>
<tr>
<td>• Color</td>
</tr>
<tr>
<td>• Mottling</td>
</tr>
<tr>
<td>Blood pressure</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CENTRAL NERVOUS SYSTEM PERFUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsiveness (AVPU)</td>
</tr>
<tr>
<td>Recognition of parents or caregivers</td>
</tr>
<tr>
<td>Pupil size</td>
</tr>
<tr>
<td>Posturing</td>
</tr>
</tbody>
</table>

AVPU, Alert, responds to voice, responds to pain, unresponsive.

**Table 38-2** Warning Signs and Symptoms Suggesting the Need for Resuscitation

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>SIGNS AND SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Lethargy, agitation, delirium, obtundation, confusion</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Apnea, grunting, nasal flaring, dyspnea, retracting, tachypnea, poor air movement, striidor, wheezing</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Arrhythmia, bradycardia, tachycardia, weak pulses, poor capillary refill, hypotension</td>
</tr>
<tr>
<td>Skin and mucous membranes</td>
<td>Mottling, pallor, cyanosis, diaphoresis, poor membrane turgor, dry mucous membranes</td>
</tr>
</tbody>
</table>

*Action would seldom be taken if only one or two of these signs and symptoms were present, but the occurrence of several in concert foreshadows grave consequences. Intervention should be directed at the primary disorder.
dobutamine, nitroprusside, or milrinone, also may be needed. Measuring mixed venous oxygen saturation, central venous pressure, and regional oxygen saturations helps guide therapy.

CARDIOPULMONARY ARREST
The outcome of cardiopulmonary arrest in children is poor; survival to hospital discharge is about 6% for out-of-hospital arrest and about 27% for in-hospital arrest, with most survivors having permanent neurologic disability. The ability to anticipate or recognize pre–cardiopulmonary arrest conditions and initiate prompt and appropriate therapy not only is lifesaving, but also preserves the quality of life (see Table 38-2).

Children who need cardiopulmonary resuscitation (CPR) usually have a primary respiratory arrest. Hypoxia usually initiates the cascade leading to arrest and also produces organ dysfunction or damage (Table 38-3). The approach to cardiopulmonary arrest extends beyond CPR and includes efforts to preserve vital organ function. The goal in resuscitating a pediatric patient following a cardiopulmonary arrest should be to optimize cardiac output and tissue oxygen delivery, which may be accomplished by using artificial ventilation and chest compression and by the judicious administration of pharmacologic agents.

Pediatric Advanced Life Support and CPR
In 2010 the American Heart Association revised the recommendations for resuscitation for adults, children, and infants. The biggest change is the recommendation to start chest compressions immediately, rather than beginning with airway and breathing.

Circulation
Chest compressions should be initiated if a pulse cannot be palpated or if the heart rate is less than 60 beats/min with signs of poor systemic perfusion. Chest compressions should be performed immediately by one person while a second person prepares to begin ventilation. Ventilation is extremely important in pediatric arrests because of the high likelihood of a primary respiratory cause; however, ventilation requires equipment and is, therefore, sometimes delayed. For this reason the recommendation is to start chest compressions first while preparing for ventilation.

For optimal chest compressions, the child should be supine on a flat, hard surface. Effective CPR requires a compression depth of one third to one half of the anterior-posterior diameter of the chest with complete recoil after each compression. The compression rate should be at least 100/min with breaths delivered 8 to 10 times per minute. If an advanced airway is in place, compressions should not pause for ventilation; both should continue simultaneously.

Airway
Ventilation requires a patent airway. In children, airway patency often is compromised by a loss of muscle tone, allowing the mandibular block of tissue, including the tongue, bony mandible, and the soft surrounding tissues, to rest against the posterior pharyngeal wall. The head–chin lift maneuver should be used to open the airway in children with no sign of head or neck trauma. In children with signs of head or neck trauma, the jaw thrust maneuver should be used.

Bag-mask ventilation can be as effective as, and possibly safer than, endotracheal intubation for short periods of time in an out-of-hospital setting. If skilled personnel and proper equipment are available, pediatric patients requiring resuscitation should be endotracheally intubated. Before intubation, the patient should be ventilated with 100% oxygen using a bag and mask. Cricoid pressure should be used to minimize inflation of the stomach. Many conscious patients may benefit from the use of induction medications (sedatives, analgesics, and paralytics) to assist intubation, but caution is necessary to prevent further cardiovascular compromise from vasodilating effects of many sedatives. The correct size of the tube may be estimated according to the size of the child’s mid-fifth phalanx or the following formula: 4 + (patient age in years/4).

When the endotracheal tube is in place, the adequacy of ventilation and the position of the tube must be assessed. Use of both clinical assessment and confirmatory devices is recommended. Clinical assessment may include looking for adequate chest wall movement and auscultation of the chest to detect bilateral and symmetric breath sounds. Confirmatory devices such as end-tidal carbon dioxide (CO₂) monitoring devices are useful for validation of endotracheal placement, but low levels of detected CO₂ may be seen secondary to lack of pulmonary circulation. If the patient’s condition fails to improve or deteriorates, consider the possibilities of tube Displacement or Obstruction, Pneumothorax, or Equipment failure (mnemonic DOPE).

Breathing
The major role of endotracheal intubation is to protect or maintain the airway and ensure the delivery of adequate oxygen to the patient. Because hypoxemia is the final common pathway in pediatric cardiopulmonary arrests, providing oxygen is more important than correcting the respiratory acidois. The clinician should deliver 100% oxygen at a rate of 8 to 10 breaths/min during CPR, or 12 to 20 breaths/min for a patient who has a perfusing rhythm. Use only the tidal volume necessary to produce visible chest rise. Care should be taken not to hyperventilate the patient.
Drugs
When mechanical means fail to re-establish adequate circulation, pharmacologic intervention is essential (Table 38-4). If intravascular access is not present or rapidly established, administration through an intraosseous route is recommended. Some drugs can also be administered effectively through the endotracheal tube.

Epinephrine, a catecholamine with mixed α-agonist and β-agonist properties, constitutes the mainstay of drug therapy for CPR. The α-adrenergic effects are most important during acute phases of resuscitation, causing an increase in systemic vascular resistance that improves coronary blood flow. Standard dose therapy is recommended for the first and subsequent boluses. There is no benefit offered by high-dose epinephrine. Vasopressin, an endogenous hormone, causes constriction of capillaries and small arterioles and may be useful. Insufficient data support its routine use, but vasopressin may be considered in children failing standard medication administration.

The routine use of sodium bicarbonate is currently not recommended. Sodium bicarbonate may be judiciously used to treat toxiidromes or hyperkalemic arrest; however, oxygen delivery and elimination of CO₂ must be established first. Side effects include hypernatremia, hyperosmolality, hypokalemia, metabolic alkalosis (shifting the oxyhemoglobin curve to the left and impairing tissue oxygen delivery), reduced ionized calcium level, and impaired cardiac function.

Routine administration of calcium is not recommended. It may be useful in cases of documented hypocalcemia, calcium channel blocker overdose, hypermagnesemia, or hypokalemia, but is otherwise not beneficial and potentially harmful.

Hypoglycemia is not uncommon in infants and children who sustain cardiac arrest. Blood glucose should be checked and hypoglycemia should be promptly treated with glucose.

Prompt electrical defibrillation is indicated when ventricular fibrillation or pulseless ventricular tachycardia is noted (Table 38-5). CPR should continue until immediately before defibrillation and resume immediately afterward, minimizing interruptions in compressions. If a second attempt at defibrillation is necessary, it should be followed by a dose of epinephrine. Children failing two episodes of defibrillation may benefit from administration of amiodarone. Defibrillation should be distinguished from cardioversion of supraventricular tachycardias, which also may compromise cardiac output. Cardioversion requires a lower starting dose and synchronization of the discharge to the electrocardiogram to prevent discharging during a susceptible period, which may convert supraventricular tachycardia to ventricular tachycardia or fibrillation.

<table>
<thead>
<tr>
<th>Table 38-4</th>
<th>Drug Doses for Cardiopulmonary Resuscitation</th>
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<tbody>
<tr>
<td><strong>DRUG</strong></td>
<td><strong>INDICATION</strong></td>
</tr>
<tr>
<td>Adenosine</td>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Pulseless VF/VT</td>
</tr>
<tr>
<td>Atropine</td>
<td>Supraventricular or junctional bradycardia</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>Hyperkalemia, some toxidromes</td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>Hypocalcemia, calcium channel blocker overdose, hypermagnesemia, hypokalemia</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Hypotension, chronotropy, inotropy</td>
</tr>
<tr>
<td>Fluid</td>
<td>Hypovolemia, sepsis</td>
</tr>
<tr>
<td>Glucose</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>VT</td>
</tr>
</tbody>
</table>


ABG, Arterial blood gas; ET, endotracheal; IO, intraosseous; IV, intravenous; VF, ventricular fibrillation; VT, ventricular tachycardia.

<table>
<thead>
<tr>
<th>Table 38-5</th>
<th>Recommendations for Defibrillation and Cardioversion in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DEFIBRILLATION</strong></td>
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</tr>
<tr>
<td>Place self-adhesive defibrillation pads or paddles with electrode gel at the apex of the heart and the upper right side of the chest • Use infant paddles or self-adhesive pads for children &lt;10 kg; adult size for children &gt;10 kg</td>
<td></td>
</tr>
<tr>
<td>Notify all participating personnel before discharging paddles so that no one is in contact with patient or bed Begin with 2 J/kg; resume chest compressions immediately If unsuccessful, increase to 4 J/kg and repeat Higher energy levels may be considered, not to exceed 10 J/kg or the adult maximum dose</td>
<td></td>
</tr>
<tr>
<td><strong>CARDIOVERSION</strong></td>
<td>Consider sedation if possible For symptomatic supraventricular tachycardia or ventricular tachycardia with a pulse, synchronize signal with ECG</td>
</tr>
<tr>
<td>Choose paddles, position pads, and notify personnel as above Begin with 0.5–1 J/kg If unsuccessful, use 2 J/kg</td>
<td></td>
</tr>
</tbody>
</table>

ECG, Electrocardiogram.
*Consider adenosine first (see Table 38-4)
Chapter 39

RESPIRATORY FAILURE

ETIOLOGY
Acute respiratory failure occurs when the pulmonary system is unable to maintain adequate gas exchange to meet metabolic demands. The resulting failure can be classified as hypercarbic (Paco2 >50 mm Hg in previously healthy children), hypoxemic (Pao2 <60 mm Hg in previously healthy children without an intracardiac shunt), or both. Hypoxemic respiratory failure is frequently caused by ventilation-perfusion mismatch (perfusion of lung that is not adequately ventilated) and shunting (deoxygenated blood bypasses ventilated alveoli). Hypercarbic respiratory failure results from inadequate alveolar ventilation secondary to decreased minute ventilation (tidal volume × respiratory rate) or an increase in dead space ventilation (ventilation of areas receiving no perfusion).

Respiratory failure may occur with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). The definitions of these are in the process of revision; however, currently ALI is defined as having the following four clinical features: acute onset, bilateral pulmonary edema, no clinical evidence of elevated left atrial pressure, and a ratio of Pao2 to Fio2 ≤300 mm Hg regardless of the level of positive end-expiratory pressure (PEEP). ARDS is a subset of ALI with more severe hypoxemia (Pao2/Fio2 of ≤200 mm Hg). These syndromes can be triggered by a variety of insults, including sepsis, pneumonia, shock, burns, or traumatic injury, all resulting in inflammation and increased vascular permeability leading to pulmonary edema. Numerous mediators of inflammation (tumor necrosis factor, interferon-γ, nuclear factor κB, and adhesion molecules) may be involved in the development of ARDS. Surfactant action also may be affected.

EPIDEMIOLOGY
Respiratory failure is frequently caused by bronchiolitis (often caused by respiratory syncytial virus), asthma, pneumonia, upper airway obstruction, and sepsis/ARDS. Respiratory failure requiring mechanical ventilation develops in 7% to 21% of patients hospitalized for respiratory syncytial virus.

Asthma is increasing in prevalence and is the most common reason for unplanned hospital admissions in children 3 to 12 years of age in the United States. Environmental factors (exposure to cigarette smoke) and prior disease characteristics (severity of asthma, exercise intolerance, delayed start of therapy, and previous intensive care unit admissions) affect hospitalization and near-fatal episodes. The mortality rate of asthma for children younger than 19 years of age has increased by nearly 80% since 1980. Deaths are more common in African-American children.

Chronic respiratory failure (with acute exacerbations) is often due to chronic lung disease (bronchopulmonary dysplasia, cystic fibrosis), neurologic or neuromuscular abnormalities, and congenital anomalies.

CLINICAL MANIFESTATIONS
Early signs of hypoxic respiratory failure include tachypnea and tachycardia in attempt to improve minute ventilation and cardiac output and to maintain delivery of oxygenated blood to the tissues. Further progression of disease may result in dyspnea, nasal flaring, grunting, use of accessory muscles of respiration, and diaphoresis. Late signs of inadequate oxygen delivery include cyanosis and altered mental status (initially confusion and agitation). Signs and symptoms of hypercarbic respiratory failure include attempts to increase minute ventilation (tachypnea and increased depth of breathing) and altered mental status (somnolence).

LABORATORY AND IMAGING STUDIES
A chest radiograph may show evidence of the etiology of respiratory failure. The detection of atelectasis, hyperinflation, infiltrates, or pneumothoraces assists with ongoing management. Diffuse infiltrates or pulmonary edema may suggest ARDS. The chest radiograph may be normal when upper airway obstruction or impaired respiratory controls are the etiology. In patients presenting with stridor or other evidence of upper airway obstruction, a lateral neck film or computed tomography (CT) may delineate anatomic defects. Direct visualization through flexible bronchoscopy allows identification of dynamic abnormalities of the anatomic airway. Helical CT helps diagnose a pulmonary embolus.

Pulse oximetry allows noninvasive, continuous assessment of oxygenation but is unable to provide information about ventilation abnormalities. Determination of CO2 levels requires a blood gas measurement (arterial, venous, or capillary). An arterial blood gas allows measurement of CO2 levels and analysis of the severity of oxygenation defect through calculation of an alveolar-arterial oxygen difference. A normal PaCO2 in a patient who is hyperventilating should heighten concern about the risk of further deterioration.

DIFFERENTIAL DIAGNOSIS
Hypoxic respiratory failure resulting from impairment of alveolar-capillary function is seen in ARDS; cardiogenic pulmonary edema; interstitial lung disease; aspiration pneumonia; bronchiolitis; bacterial, fungal, or viral pneumonia; and sepsis. It also can be due to intracardiac or intrapulmonary shunting seen with atelectasis and embolism.

Hypercarbic respiratory failure can occur when the respiratory center fails as a result of drug use (opioids, barbiturates, anesthetic agents), neurologic or neuromuscular junction abnormalities (cervical spine trauma, demyelinat ing diseases, anterior horn cell disease, botulism), chest wall injuries, or diseases that cause increased resistance to airflow (croup, vocal cord paralysis, post-extubation edema). Maintenance of ventilation requires adequate function of the chest wall and diaphragm. Disorders of the neuromuscular pathways, such as muscular dystrophy, myasthenia gravis, and botulism, result in inadequate chest wall movement, development of atelectasis, and respiratory failure. Scoliosis rarely results in significant chest deformity that leads to restrictive pulmonary function. Similar impairments of air exchange may result from distention of the abdomen (postoperatively or due to ascites, obstruction, or a mass) and thoracic trauma (flail chest).

Mixed forms of respiratory failure are common and occur when disease processes result in more than one
pathophysiologic change. Increased secretions seen in asthma often lead to atelectasis and hypoxia, whereas restrictions of expiratory airflow may lead to hypercarbia. Progression to respiratory failure results from peripheral airway obstruction, extensive atelectasis, and resultant hypoxemia and retention of CO₂.

**COMPLICATIONS**
The major complication of hypoxic respiratory failure is the development of organ dysfunction. **Multiple organ dysfunction** includes the development of two or more of the following: respiratory failure, cardiac failure, renal insufficiency/failure, gastrointestinal or hepatic insufficiency, disseminated intravascular coagulation, and hypoxic-ischemic brain injury. Mortality rates increase with increasing numbers of involved organs (see Table 38-3).

Complications associated with mechanical ventilation include pressure-related and volume-related lung injury. Both overdistention and insufficient lung distention (loss of functional residual capacity) are associated with lung injury. Pneumomediastinum and pneumothorax are potential complications of the disease process and overdistention. Inflammatory mediators may play a role in the development of chronic fibrotic lung diseases in ventilated patients.

**PREVENTION**
Prevention strategies are explicit to the etiology of respiratory failure. Some infectious causes can be prevented through active immunization against organisms causing primary respiratory disease (pertussis, pneumococcus, Haemophilus influenzae type b) and sepsis (pneumococcus, H. influenzae type b). Passive immunization with respiratory syncytial virus immunoglobulins prevents severe illness in highly susceptible patients (prematurity, bronchopulmonary dysplasia). Primary prevention of traumatic injuries may decrease the incidence of ARDS. Compliance with appropriate therapies for asthma may decrease the number of episodes of respiratory failure (see Chapter 78).

**PROGNOSIS**
Prognosis varies with the etiology of respiratory failure. Fewer than 1% of previously healthy children with bronchiolitis die. Asthma mortality rates, although still low, have increased. Despite advances in support and understanding of the pathophysiology of ARDS, the mortality rate remains approximately 30%.

**TREATMENT**
Initial treatment of patients in respiratory distress includes addressing the ABCs (see Chapter 38). **Bag/mask ventilation** must be initiated for patients with apnea. In other patients, oxygen therapy is administered using appropriate methods (e.g., simple mask). Administration of oxygen by nasal cannula allows the patient to entrain room air and oxygen, making it an insufficient delivery method for most children in respiratory failure. Delivery methods, including intubation and mechanical ventilation, should be escalated if there is inability to increase oxygen saturation appropriately.

Patients presenting with hypercarbic respiratory failure are often hypoxic as well. When oxygenation is established, measures should be taken to address the underlying cause of hypercarbia (reversal of drug action, control of fever, or seizures). Patients who are hypercarbic without signs of respiratory fatigue or somnolence may not require intubation based on the $P_{CO_2}$ alone; however, patients with marked increase in the work of breathing or inadequate respiratory effort may require assistance with ventilation.

After identification of the etiology of respiratory failure, specific interventions and treatments are tailored to the needs of the patient. External support of oxygenation and ventilation may be provided by **noninvasive ventilation** methods (heated humidified high-flow nasal cannula, continuous positive airway pressure, biphasic positive airway pressure, or negative pressure ventilation) or through invasive methods (traditional **mechanical ventilation**, high-frequency oscillatory ventilation, or extracorporeal membrane oxygenation). Elimination of CO₂ is achieved through manipulation of minute ventilation (tidal volume and respiratory rate). Oxygenation is improved by altering variables that affect oxygen delivery (fraction of inspired oxygen) or mean airway pressure (PEEP, peak inspiratory pressure, inspiratory time, gas flow).

**HYPOVOLEMIC SHOCK**
Acute hypovolemia is the most common cause of shock in children. It results from loss of fluid from the intravascular space secondary to inadequate intake or excessive losses (vomiting and diarrhea, blood loss, capillary leak syndromes, or pathologic renal fluid losses) (Table 40-1). Reduced blood volume decreases preload, stroke volume, and cardiac output. Hypovolemic shock results in increased sympathoadrenal activity, producing an increased heart rate and enhanced myocardial
presence of a normal or high cardiac output. This maldistribution of flow usually results from abnormalities in vascular tone. Septic shock is the most common type of distributive shock in children. Other causes include anaphylaxis, neurologic injury, and drug-related causes (see Table 40-1).

Distributive shock may present with the systemic inflammatory response syndrome (SIRS), defined as two or more of the following: temperature greater than 38°C or less than 36°C; heart rate greater than 90 beats/min or more than two standard deviations above normal for age; tachypnea; or white blood count greater than 12,000 cells/mm³, less than 4000 cells/mm³, or greater than 10% immature forms.

**CARDIOGENIC SHOCK**

Cardiogenic shock is caused by an abnormality in myocardial function and is expressed as depressed myocardial contractility and cardiac output with poor tissue perfusion. Compensatory mechanisms may contribute to the progression of shock by depressing cardiac function further. Neurohormonal vasoconstrictor responses increase afterload and add to the work of the failing ventricle. Tachycardia may impair coronary blood flow, which decreases myocardial oxygen delivery. Increased central blood volume caused by sodium and water retention and by incomplete emptying of the ventricles during systole results in elevated left ventricular volume and pressure, which impair subendocardial blood flow. As compensatory mechanisms are overcome, the failing left ventricle produces increased ventricular end-diastolic volume and pressure, which leads to increased left atrial pressure, resulting in pulmonary edema. This sequence also contributes to right ventricular failure because of increased pulmonary artery pressure and increased right ventricular afterload.

Primary cardiogenic shock may occur in children who have congenital heart disease. Cardiogenic shock also may occur in previously healthy children secondary to viral myocarditis, dysrhythmias, or toxic or metabolic abnormalities or after hypoxic-ischemic injury (see Chapters 142, 145, and 147, as well as Table 40-1).

**OBSTRUCTIVE SHOCK**

Obstructive shock results from mechanical obstruction of ventricular outflow. Causes include congenital lesions such as coarctation of the aorta, interrupted aortic arch, and severe aortic valvular stenosis, along with acquired diseases (e.g., hypertrophic cardiomyopathy) (see Table 40-1). For neonates presenting in shock, obstructive lesions must be considered.

**DISSOCIATIVE SHOCK**

Dissociative shock refers to conditions in which tissue perfusion is normal, but cells are unable to use oxygen because the hemoglobin has an abnormal affinity for oxygen, preventing its release to the tissues (see Table 40-1).

**CLINICAL MANIFESTATIONS**

All forms of shock produce evidence that tissue perfusion and oxygenation are insufficient (increased heart rate, abnormal blood pressure, alterations of peripheral pulses). The etiology of shock may alter the initial presentation of these signs and symptoms.
**Hypovolemic Shock**
Hypovolemic shock is distinguished from other causes of shock by history and the absence of signs of heart failure or sepsis. In addition to the signs of sympathoadrenal activity (tachycardia, vasoconstriction), clinical manifestations include signs of dehydration (dry mucous membranes, decreased urine output) or blood loss (pallor). Recovery depends on the degree of hypovolemia, the patient’s preexisting status, and rapid diagnosis and treatment. The prognosis is good, with a low mortality in uncomplicated cases.

**Distributive Shock**
Patients with distributive shock usually have tachycardia and alterations of peripheral perfusion. In early stages, when cytokine release results in vasodilation, pulses may be bounding, and vital organ function may be maintained (an alert patient, with rapid capillary refill and some urine output in warm shock). As the disease progresses untreated, extremities become cool and mottled with a delayed capillary refill time. At this stage, the patient has hypotension and vasoconstriction. If the etiology of distributive shock is sepsis, the patient often has fever, lethargy, petechiae, or purpura, and he or she may have an identifiable source of infection.

**Cardiogenic Shock**
Cardiogenic shock results when the myocardium is unable to supply the cardiac output required to support tissue perfusion and organ function. Because of this self-perpetuating cycle, heart failure progressing to death may be rapid. Patients with cardiogenic shock have tachycardia and tachypnea. The liver is usually enlarged, a gallop is often present, and jugular venous distention may be noted. Because renal blood flow is poor, sodium and water are retained, resulting in oliguria and peripheral edema.

**Obstructive Shock**
Restriction of cardiac output results in an increase in heart rate and an alteration of stroke volume. The pulse pressure is narrow (making pulses harder to feel), and capillary refill is delayed. The liver is often enlarged, and jugular venous distention may be evident.

**Dissociative Shock**
The principal abnormality in dissociative shock is the inability to deliver oxygen to tissues. Symptoms include tachycardia, tachypnea, alterations in mental status, and ultimately cardiovascular collapse.

**Laboratory and Imaging Studies**
Shock requires immediate resuscitation before obtaining laboratory or diagnostic studies. Following initial stabilization (including glucose administration if hypoglycemia is present), the type of shock dictates the necessary laboratory studies. All patients with shock may benefit from determination of a baseline arterial blood gas and blood lactate level to assess the impairment of tissue oxygenation. Measurement of mixed venous oxygen saturation aids in the assessment of the adequacy of oxygen delivery. In contrast to other forms of shock, patients with sepsis often have high mixed venous saturation values because of impairment of mitochondrial function and inability of tissues to extract oxygen. A complete blood count can potentially assess intravascular blood volume after equilibration following a hemorrhage. Electrolyte measurements in patients with hypovolemic shock may identify abnormalities from losses. Patients presenting in distributive shock require appropriate bacterial and viral cultures to identify a cause of infection. If cardiogenic or obstructive shock is suspected, an echocardiogram assists with the diagnosis and, in the case of tamponade, assists with placement of a pericardial drain to relieve the fluid. Patients with dissociative shock require detection of the causative agent (carbon monoxide, methemoglobin). The management of shock also requires monitoring of arterial blood gases for oxygenation, ventilation (CO2), and acidosis, and frequently assessing the levels of serum electrolytes, calcium, magnesium, phosphorus, and blood urea nitrogen (BUN).

**Differential Diagnosis**
SEE TABLE 40-1.

**Treatment**

**General Principles**
The key to therapy is the recognition of shock in its early, partially compensated state, when many of the hemodynamic and metabolic alterations may be reversible. Initial therapy for shock follows the ABCs of resuscitation. Later therapy can then be directed at the underlying cause. Therapy should minimize cardiopulmonary work, while ensuring cardiac output, blood pressure, and gas exchange. Intubation, combined with mechanical ventilation with oxygen supplementation, improves oxygenation and decreases or eliminates the work of breathing but may impede venous return if distending airway pressures (positive end-expiratory pressure [PEEP] or peak inspiratory pressure) are excessive. Blood pressure support is crucial because the vasodilation in sepsis may reduce perfusion despite supranormal cardiac output.

Monitoring a child in shock requires maintaining access to the arterial and central venous circulation to record pressure measurements, perform blood sampling, and measure systemic blood pressure continuously. These measurements facilitate the estimation of preload and afterload. Regional monitoring with near infrared spectroscopy may allow early, noninvasive detection of alterations in perfusion.

**Organ-Directed Therapeutics**

**Fluid Resuscitation**
Alterations in preload have a dramatic effect on cardiac output. In hypovolemic and distributive shock, decreased preload significantly impairs cardiac output. In these cases, early and aggressive fluid resuscitation is important and greatly affects outcome. In cardiogenic shock, an elevated preload contributes to pulmonary edema.

Selection of fluids for resuscitation and ongoing use is dictated by clinical circumstances. Crystalloid volume expanders generally are recommended as initial choices because they are effective and inexpensive. Most acutely ill children with
signs of shock may safely receive, and usually benefit greatly from, a 20-mL/kg bolus of an isotonic crystalloid over 5 to 15 minutes. This dose may be repeated until a response is noted. Colloids contain larger molecules that may stay in the intravascular space longer than crystalloid solutions and exert oncotic pressure, drawing fluid out of the tissues into the vascular compartment. However, long-term risks of colloids may exceed benefits. Care must be exercised in treating cardiogenic shock with volume expansion because the ventricular filling pressures may rise without improvement of the cardiac performance. Carefully monitoring cardiac output or central venous pressure guides safe volume replacement.

**Cardiovascular Support**

In an effort to improve cardiac output after volume resuscitation or when further volume replacement may be dangerous, a variety of inotropic and vasodilator drugs may be useful (Table 40-2). Therapy is directed first at increasing myocardial contractility, then at decreasing left ventricular afterload. The hemodynamic status of the patient dictates the choice of the agent.

Therapy may be initiated with dopamine at 3 to 15 mcg/kg/min; however, epinephrine or norepinephrine may be preferable in patients with decompensated shock. In addition to improving contractility, certain catecholamines cause an increase in systemic vascular resistance. The addition of a vasodilator drug may improve cardiac performance by decreasing the resistance against which the heart must pump (afterload). Afterload reduction may be achieved with dobutamine, milrinone, amrinone, nitropresside, nitroglycerin, and angiotensin-converting enzyme inhibitors. The use of these drugs may be particularly important in late shock, when vasoconstriction is prominent.

**Respiratory Support**

The lung is a target organ for inflammatory mediators in shock and SIRS. Respiratory failure may develop rapidly and become progressive. Intervention requires endotracheal intubation and mechanical ventilation accompanied by the use of supplemental oxygen and PEEP. Care must be taken with the process of intubation, because a child with compensated shock may suddenly decompensate on administration of sedative medications that reduce systemic vascular resistance. Severe cardiopulmonary failure may be managed with inhaled nitric oxide and, if necessary, extracorporeal membrane oxygenation.

**Renal Salvage**

Poor cardiac output accompanied by decreased renal blood flow may cause prerenal azotemia and oliguria/anuria. Severe hypotension may produce acute tubular necrosis and acute renal failure. Prerenal azotemia is corrected when blood volume deficits are replaced or myocardial contractility is improved, but acute tubular necrosis does not improve immediately when shock is corrected. Prerenal azotemia is associated with a serum BUN-to-creatinine ratio of greater than 10:1 and a urine sodium level less than 20 mEq/L; acute tubular necrosis has a BUN-to-creatinine ratio of 10:1 or less and a urine sodium level between 40 and 60 mEq/L (see Chapter 165). Aggressive fluid replacement is often necessary to improve oliguria associated with prerenal azotemia. Because the management of shock requires administering large volumes of fluid, maintaining urine output greatly facilitates patient management.

Prevention of acute tubular necrosis and the subsequent complications associated with acute renal failure (hyperkalemia, acidosis, hypocalcemia, fluid overload) is important. The use of pharmacologic agents to augment urine output is indicated when the intravascular volume has been replaced. The use of loop diuretics, such as furosemide, or combinations of a loop diuretic and a thiazide agent may enhance urine output. Infusion of low-dose dopamine, which produces renal artery vasodilation, also may improve urine output. Nevertheless, if hyperkalemia, refractory acidosis, hypervolemia, or altered mental status associated with uremia occurs, dialysis or hemofiltration should be initiated.

**COMPLICATIONS**

Shock results in impairment of tissue perfusion and oxygenation and activation of inflammation and cytokine pathways. The major complication of shock is multiple organ system failure, defined as the dysfunction of more than one organ, including respiratory failure, renal failure, liver dysfunction, coagulation abnormalities, or cerebral dysfunction. Patients with shock and multiple organ failure have a higher mortality rate and, for survivors, a longer hospital stay.

**PROGNOSIS**

Early recognition and goal-directed intervention in patients with shock improve survival. However, delays in treatment of hypotension increase the incidence of multiple organ failure and mortality. Goal-directed therapy focused on maintaining mixed venous oxygen saturation may improve survival.

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**Table 40-2** Medications Used to Improve Cardiac Output

<table>
<thead>
<tr>
<th></th>
<th><strong>POSITIVE INOTROPE</strong></th>
<th><strong>POSITIVE CHRONOTROPE</strong></th>
<th><strong>DIRECT PRESSOR</strong></th>
<th><strong>VASOCONSTRICTOR</strong></th>
<th><strong>VASODILATOR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>++</td>
<td></td>
<td>±</td>
<td>++ (high dose)</td>
<td>+ (low dose)*</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>++</td>
<td>±</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++ (high dose)</td>
<td>+ (low dose)†</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Milrinone</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

*Primarily splanchnic and renal in low doses (3-5 mcg/kg/min).
†Low dose (<0.3 mcg/kg/min).
PREVENTION

Prevention strategies for shock are focused, for the most part, on shock associated with sepsis and hypovolemia. Some forms of septic shock can be prevented through use of immunizations (Haemophilus influenzae type b, meningococcal, pneumococcal vaccines). Decreasing the risk of sepsis in a critically ill patient requires adherence to strict hand washing, isolation practices, and minimizing the duration of indwelling catheters. Measures to decrease pediatric trauma do much to minimize hemorrhage-induced shock.

INJURY PREVENTION

EPIDEMIOLOGY AND ETOLOGY

Unintentional injury is the leading cause of death in children 1 to 18 years of age. In 2010, approximately 52% of these deaths were caused by motor vehicle crashes. Most remaining unintentional injury-related deaths were the result of drowning (15%), poisoning (9%), burns (5%), and suffocation (4%). Geography, climate, population density (access to care), and population traits vary by region and affect the frequency, etiology, and severity of injuries.

Injury occurs through interaction of the host (child) with the agent (e.g., car and driver) through a vector and an environment (e.g., roadways, weather) that is conducive to exposure. The age of the child may determine the exposure to various agents and environments. For example, most injuries in infants and toddlers occur in the home as the result of exposure to agents found there (water heaters, bathtubs, soft bedding). Gender affects exposure to injury, with boys having a fatal injury rate greater than that of girls.

EDUCATION FOR PREVENTING INJURIES

The recognition that much of the morbidity and mortality are determined at the scene of an injury has stimulated the development of prevention measures. The Haddon matrix combines the epidemiologic components (host, agent, physical and social environments) with time factors (before, during, and after the event) to identify effective interventions focused on different aspects of the injury event. Primary strategies (preventing the event), secondary strategies (minimizing the severity of injury), and tertiary strategies (minimizing long-term impact) can be targeted for each epidemiologic component. Such strategies typically fall into one of three areas: education, enforcement, and environment (including engineering).

Education is often the first strategy considered but requires behavioral change and actions on the part of people. Most educational strategies are not well evaluated.

Despite the reliance on an action by the individuals involved, some active strategies benefit from enforcement. Children wearing bicycle helmets experience a significantly lower incidence of traumatic brain injury and death. Enforcement of seatbelt laws increases seatbelt use and may decrease injuries.

Automatic strategies require no action on the part of the population and often change the environment (speed bumps) or involve engineering (child-resistant pill bottles, air bags). Automatic strategies have more consistently resulted in a significant reduction in injuries. The most successful approaches to preventing injury have combined strategies (education, environmental changes, and engineering changes focused on the host, agent, and environment in all three time phases).

MAJOR TRAUMA

ASSESSMENT AND RESUSCITATION

The general goal of prehospital trauma care is rapid assessment, support of the ABCs, immobilization, and transportation. Outcomes of patients with major or life-threatening trauma are significantly improved in a pediatric trauma center or in an adult center with pediatric trauma certification compared with level I or II adult trauma centers.

Once the injured child arrives at the emergency department, the trauma team must initiate an organized and synchronized response. The initial assessment of a seriously injured child should involve a systematic approach, including a primary survey, resuscitation, secondary survey, postresuscitation monitoring, and definitive care. The primary survey focuses on the ABCDEs of emergency care, as modified for trauma from the ABCs of cardiopulmonary resuscitation (see Chapter 38). The assessment of the airway and breathing components should include meticulous control of the cervical spine (especially if the patient has an altered mental status), evaluation for anatomic injuries that could impair air entry or gas exchange, and consideration of the likelihood of a full stomach (risk of aspiration pneumonia). Circulation can be assessed via observation (heart rate, skin color, mental status) and palpation (pulse quality, capillary refill, skin temperature) and restored (via two large peripheral intravenous lines, when possible) while control of bleeding is accomplished through the use of direct pressure. Assessment for disabilities (D), including neurologic status, includes examination of pupil size and reactivity, a brief mental status assessment (AVPU—alert; responds to voice; responds to pain; unresponsive), and examination of extremity movement to assess for spinal cord injury. The Glasgow Coma Scale can direct decisions regarding the initiation of cerebral resuscitation in patients with suspected closed head injuries (Table 42-1). E, which stands for exposure, requires a full assessment of the patient by completely disrobing the child for a detailed examination of the entire body. The examiner should ensure a neutral thermal environment to prevent hypothermia.
On completion of the primary survey, a more detailed head-to-toe examination (the secondary survey) should ensue along with efforts to obtain a more complete history. The purpose of this careful re-examination is to identify life-threatening and limb-threatening injuries as well as less serious injuries. Coincident with the secondary survey and depending, in part, on the assessed physiologic status of the patient, certain procedures and resuscitative measures are initiated. The prioritization of definitive care needs is determined by the injury findings collected from the primary and secondary surveys, the child’s physiologic response to resuscitation, and data from continuous monitoring. A tertiary survey, including repeat primary and secondary surveys along with review of laboratory tests and radiologic studies, should be performed within 24 hours.

**ETIOLOGY AND EPIDEMIOLOGY**
SEE CHAPTER 41.

**LABORATORY AND IMAGING STUDIES**
Screening laboratory studies during initial resuscitation often include the tests listed in Table 42-2. Radiographic studies are determined by the pattern of injuries. A head computed tomography (CT) scan should be obtained in patients with evidence of head trauma or a history of loss of consciousness. Patients with obvious injury to the thorax or abdomen or who have pulmonary or abdominal symptoms may benefit from a CT scan. The focused abdominal sonography for trauma is gaining popularity because of concerns about radiation exposure. Diagnostic peritoneal lavage has limited utility. A spiral enhanced CT scan should be performed if there is concern about aortic injuries.

**CLINICAL MANIFESTATIONS AND TREATMENT**
Head injuries and injuries to the limbs are the most common. Multiple organ involvement is also common, and penetrating trauma is becoming more frequent. After the initial evaluation and stabilization, the team focuses on the involved organ systems.

**Head Trauma**
SEE CHAPTER 184.

**Spinal Cord Trauma**
Although spinal cord injury is not common in pediatric trauma patients, it is potentially devastating when it occurs. Cervical spine immobilization should be maintained until a spinal cord injury is ruled out. Cervical spine radiographs are not sufficient to rule out a spinal cord injury because the immature vertebral column in children may allow stretching of the cord or nerve roots with no radiologic abnormality (spinal cord injury without radiologic abnormality [SCIWORA]). SCIWORA may occur in a significant percentage of children with a spinal cord injury; when it is suspected, magnetic resonance imaging should be performed.

**Thoracic Trauma**
Thoracic injury is the second leading cause of trauma death. Pulmonary contusion, pneumothorax, and rib fractures occur most commonly, and patients may present without external signs of trauma. Patients with pulmonary parenchymal injury should receive supportive treatment to ensure adequate...
oxygenation and ventilation. Most pediatric blunt thoracic injuries can be managed without surgery. Injury to the heart and great vessels is rare but requires urgent diagnosis and treatment. Great vessel injury should be suspected if a widened mediastinum is seen on chest radiograph.

Abdominal Trauma
Injury to the abdomen occurs in approximately 8% of pediatric trauma patients and is the third leading cause of trauma death. The relative size and closer proximity of intra-abdominal organs in children increase the risk of significant injury after blunt trauma. Penetrating trauma may result in a child who is asymptomatic or who presents in hypovolemic shock.

Imaging studies such as abdominal CT and serial physical examinations are the primary methods of obtaining information on which to base decisions regarding operative intervention. Abdominal wall bruising is an important physical examination finding and is associated with significant intra-abdominal injury in more than 10% of patients. Operative intervention may be required in patients whose vital signs are persistently unstable in the face of aggressive fluid resuscitation, even in the absence of extravascular volume loss or an enlarging abdomen. The presence of peritoneal irritation or abdominal wall discoloration, together with signs of intravascular volume loss, indicates the need for laparotomy.

Most blunt solid organ injury is handled nonoperatively. Clinical observation is important, because most failures with nonoperative management occur in the first 12 hours.

Injury to the Spleen
The most frequently injured abdominal organ in children is the spleen. Suspicion of a splenic injury should be heightened if there are left upper quadrant abrasions or tenderness. A positive Kehr sign (pressure on the left upper quadrant eliciting left shoulder pain) is due to diaphragmatic irritation by the ruptured spleen and strongly suggests splenic injury. CT scans are used to identify and grade splenic injury.

Nonoperative management is the treatment of choice for most serious splenic injuries, unless there is continued large blood loss or hemodynamic instability. If a splenectomy is performed, patients should receive penicillin prophylaxis and Haemophilus influenzae vaccines to decrease the increased risk of overwhelming sepsis.

Liver Trauma
Major trauma to the liver is a serious cause of morbidity. Severe hemorrhage is more common in patients with liver injury than with other abdominal injuries because of its dual blood supply. Without significant vascular injury, hepatic injury presents and behaves clinically like a splenic injury. Nonoperative management is recommended but requires close clinical observation for signs of ongoing blood loss or hemodynamic instability. As with splenic injury, there is a grading system based on the pattern of injury.

Renal Injury
The kidney is less frequently injured than the liver or spleen, and when injured is often associated with other injuries. A young child's kidney is more vulnerable to trauma than an adult's because of a more compliant rib cage and relatively immature abdominal muscle development. The diagnosis of renal injury is based on history and physical examination coupled with urinalysis showing blood and increased protein levels. An ultrasound or CT may also be useful. Low-grade renal injury is usually managed conservatively, with bed rest, catheter drainage, and monitoring for resolution of injury by ultrasound or CT. Surgery may be required for falling hemoglobin levels, refractory shock, or urinary obstruction caused by clots.

Pancreatic Injury
Injuries of the pancreas are less common in children than in adults but are seen in bicycle handlebar injuries, motor vehicle crashes, and nonaccidental trauma. The diagnosis is difficult unless there is obvious injury to overlying structures, such as the stomach or duodenum. Diffuse abdominal tenderness, pain, and vomiting may be accompanied by elevations of amylose and lipase but may not occur until several days after the injury. Hemodynamic instability secondary to retroperitoneal hemorrhage may be the presenting sign. Nasogastric suction and parenteral nutrition are indicated in the management of these patients. Nonoperative management is appropriate for contusions, but surgical intervention may be required in patients with distal transection. Drainage of pseudocysts, in patients who develop them, may be required if they are unresponsive to bowel rest and parenteral nutrition.

Intestinal Injury
Injury to the intestine occurs less frequently than injury to solid intra-abdominal organs and varies with the amount of intestinal contents. A full bowel is likely to shear more easily than an empty bowel. Shearing occurs at points of fixation (the ligament of Treitz, the ileocecal valve, and the ascending and descending peritoneal reflections). Pneumoperitoneum should prompt surgical exploration. Serial physical examinations are useful when the clinical picture is uncertain.

Duodenal hematoma can occur in the absence of perforation. Duodenal hematomas result from blunt injury to the abdomen, and affected patients often present with persistent pain and bilious emesis. Most hematomas respond to nonoperative management with gastric decompression and parenteral nutrition.

COMPLICATIONS
Patients requiring hospitalization for multiple trauma are at risk for a variety of complications based on the type and severity of injury. Sepsis and multiple organ failure may occur in children with multiple trauma. Delays in enteral nutrition because of an ileus may further increase the risk of sepsis secondary to translocation of bacteria across the intestinal mucosa.

Renal failure secondary to myoglobinuria may be seen in children who sustain crushing or electrical injuries and burns. Deep venous thrombosis is less common in the pediatric population, but prophylaxis for children who will be immobilized because of injury is often provided.
PROGNOSIS
Unintentional injury is the leading cause of death for children ages 1 to 18; however, many of these deaths occur in the field, immediately after the injury. Once admitted to the hospital, mortality rates are much lower. Morbidities are numerous and include hypoxic-ischemic brain injury, loss of limbs, and psychological dysfunction.

PREVENTION
SEE CHAPTER 41.

DROWNING

ETIOLOGY
Drowning, as defined by the World Congress on Drowning in 2002, is the process of experiencing respiratory impairment from submersion/immersion in liquid. Drowning can further be categorized as fatal or nonfatal, but other terms such as near-drowning, secondary drowning, or dry drowning should be abandoned.

Initially, submersion or immersion results in aspiration of small amounts of fluid into the larynx, triggering breath holding or laryngospasm. In many cases, the laryngospasm resolves, and larger volumes of water or gastric contents are aspirated into the lungs, destroying surfactant and causing alveolitis and dysfunction of the alveolar-capillary gas exchange. The resulting hypoxemia leads to hypoxic brain injury that is exacerbated by ischemic injury after circulatory collapse.

EPIDEMIOLOGY
Drowning deaths overall have decreased over the past decade; however, drowning is still a significant cause of morbidity and mortality. In 2010, drowning was the leading cause of injury death for children 1 to 4 years of age and the second leading cause of injury death for children 1 to 18 years of age. Boys are four times more likely than girls to drown. The most common location of drowning varies by age, with drowning in natural bodies of water becoming more frequent in older age groups.

CLINICAL MANIFESTATIONS
Hypoxemia is the result of laryngospasm and aspiration during drowning. Victims may also develop respiratory distress secondary to pulmonary endothelial injury, increased capillary permeability, and destruction of surfactant. Clinical manifestations include tachypnea, tachycardia, increased work of breathing, and decreased breath sounds with or without crackles. The hypoxic-ischemic injury that may occur can lead to depressed myocardial function resulting in tachycardia, impaired perfusion, and potentially cardiovascular collapse. After resuscitation, acute respiratory distress syndrome is common. Altered mental status may be present and requires frequent monitoring of neurologic status. Following submersion in cold water, hypothermia may result in relative bradycardia and hypotension and place the child at risk for cardiac dysrhythmias.

LABORATORY AND IMAGING STUDIES
After resuscitation, arterial blood gas measurement assists in assessing pulmonary gas exchange. A chemistry profile may reveal elevated liver enzymes if hypoxemia and ischemia were of long duration and provide baseline renal functions. Electrolytes are often obtained, although alterations of serum electrolytes are minimal, even in freshwater drowning.

TREATMENT
Resuscitation of a drowning victim includes the basic ABCs (see Chapter 38). Victims of unwitnessed drowning require stabilization of the cervical spine because of the possibility of a fall or diving injury. Optimizing oxygenation and maintaining cerebral perfusion are two of the major foci of treatment. Rewarming the hypothermic patient requires careful attention to detail, including acid-base and cardiac status. Further treatment is based on the patient response to initial resuscitation. Some children begin breathing spontaneously and awaken before arrival at an emergency department. If the episode was significant, these children still require careful observation for pulmonary complications over the subsequent 6 to 12 hours. Children who have evidence of lung injury, cardiovascular compromise, or neurologic compromise should be monitored in an intensive care unit. Pulmonary dysfunction often results in hypoxemia. Oxygen supplementation should be implemented to maintain normal oxygen saturations. Mechanical ventilation may be needed in patients with significant pulmonary or neurologic dysfunction. Cardiovascular compromise is often the result of impaired contractility because of hypoxic-ischemic injury. The use of intracranial pressure monitoring devices and medical management with hypothermia and sedation is controversial and has not been shown to improve outcomes. Prophylactic antibiotics have not been shown to be beneficial and may increase the selection of resistant organisms.

PROGNOSIS
The outcome of drowning is determined by the success of immediate resuscitation efforts and the severity of the hypoxic-ischemic injury to the brain. Patients who have regained consciousness on arrival to the hospital will likely survive with intact neurologic function. Unfavorable prognostic markers include the need for CPR for more than 25 minutes, continued CPR at the hospital, Glasgow Coma Scale of 5 or less, fixed and dilated pupils, seizures, and coma for more than 72 hours.

PREVENTION
Despite the decreased incidence of drowning since the 1990s, few prevention strategies have been shown to be effective. Exceptions include implementation of mandatory four-sided
fencing around pools (decreasing the number of children <5 years of age who drown) and immediate provision of CPR to children who drown. The use of safety flotation devices in older children during water sport activities may be beneficial. Enhanced supervision is required to reduce the incidence of infants drowning in bathtubs.

**Chapter 44**

## BURNS

### ETIOLOGY

The pathophysiology of burn injury is caused by disruption of the three key functions of the skin: regulation of heat loss, preservation of body fluids, and barrier to infection. Burn injury releases inflammatory and vasoactive mediators resulting in increased capillary permeability, decreased plasma volume, and decreased cardiac output. The body then becomes hypermetabolic with increased resting energy expenditure and protein catabolism. This hypermetabolic state may continue for up to a year after injury.

Burns usually are classified on the basis of four criteria:

1. Depth of injury
2. Percent of body surface area involved
3. Location of the burn
4. Association with other injuries

### EPIDEMIOLOGY

More than 100,000 children sustain a burn injury each year. Burns are the third leading cause of injury-related death for children ages 1 to 9 and are a major cause of morbidity. Boys are more likely to sustain a burn injury, as are children age 6 and under. Scald burns are more common in younger children as compared to older children. Overall, thermal burns secondary to scald or flame are much more common than electrical or chemical burns. Most fire-related childhood deaths and injuries occur in homes.

### CLINICAL MANIFESTATIONS

The depth of injury should be assessed by the clinical appearance. Categories of first-degree, second-degree, and third-degree are commonly used; however, classification by depth (superficial, superficial partial-thickness, deep partial-thickness, and full-thickness) conveys more information about the structures injured and the likely need for surgical treatment and may be more clinically useful.

**Superficial** (first-degree) burns are red, painful, and dry. Commonly seen with sun exposure or mild scald injuries, these burns involve injury to the epidermis only. They heal in 2 to 5 days without scarring and are not included in burn surface area calculations. **Superficial partial-thickness** (second-degree) burns involve the entire epidermis and superficial dermis. These burns have fluid-containing blisters.

After debridement the underlying dermis will appear erythematos and wet, will be painful, and will blanch under pressure. Healing is dependent on the uninjured dermis and usually occurs within about 2 weeks without the need for skin grafting and without scarring. **Deep partial-thickness** (also second-degree) burns involve the entire epidermis and deeper portions of the dermis. These burns may also have blistering, but the dermal base is less blanching, mottled pink or white, and less painful than superficial partial-thickness burns. They behave more like full-thickness burns and will often require excision and grafting. **Full-thickness** (third-degree and fourth-degree) burns involve all skin layers. They appear dry, white, dark red, brown, or black in color. They do not blanch and are usually insensate. Full-thickness burns require surgical management. Fourth-degree burns involve underlying fascia, muscle, or bone and may require reconstruction in addition to grafting. **Inhalation injuries** should be suspected if there are facial burns, singed nasal hairs, or carbonaceous sputum. Hoarseness on vocalization also is consistent with a supraglottic injury. Inhalation injuries may result in bronchospasm, airway inflammation, and impaired pulmonary function.

There are multiple methods and charts available for calculating the percentage of skin surface involved in a burn. One method that may be used for children of various ages is presented in Figure 44-1. The extent of skin involvement of older adolescent and adult patients may be estimated as

### FIGURE 44-1

This chart of body areas, together with the table inserted in the figure showing the percentage of surface area of head and legs at various ages, can be used to estimate the surface area burned in a child. From Solomon JR: Pediatric burns, Crit Care Clin 1:159–174, 1985.
The location of the burn is important in assessing the risk of disability. The risk is greatest when the face, eyes, ears, feet, perineum, or hands are involved. Inhalation injuries not only cause respiratory compromise but also may result in difficulty in eating and drinking.

**LABORATORY AND IMAGING STUDIES**

Initial laboratory testing, including complete blood count, type and crossmatch for blood, coagulation studies, basic chemistry profile, arterial blood gas, and chest radiograph, can be helpful for patients with major burns. A carboxyhemoglobin assessment should be performed for any suspected inhalation exposure (a house or closed-space fire or a burn victim who requires cardiopulmonary resuscitation). Cyanide levels should be considered in children who sustain smoke inhalation and have altered mental status. Unusual patterns of burns may increase suspicion of child abuse and result in appropriate evaluation to assess for nonaccidental trauma to the skeleton or central nervous system.

**TREATMENT**

For severe burns, care is best managed by a multidisciplinary team in a qualified burn center. The American Burn Association criteria for patients who should be transferred to a burn center are: partial and full-thickness burns greater than 10% total body surface area (TBSA) in patients less than 10 years old or more than 50 years old, or greater than 20% TBSA in other age groups; partial and full-thickness burns involving the face, hands, feet, genitalia, perineum, or major joints; electrical burns; chemical burns; inhalation injury; burn injury in patients with preexisting medical conditions that could complicate management, prolong recovery, or increase mortality rate; any burn with concomitant trauma in which the burn injury poses the greatest risk; burn injury in children admitted to hospitals without qualified personnel or equipment for pediatric care; burn injury in patients requiring special social, emotional, or rehabilitative support, including child abuse cases.

Initial treatment should follow the ABCs of resuscitation. **Airway management** should include assessment for the presence of airway or inhalation injury, with early intubation if such an injury is suspected. Smoke inhalation may be associated with carbon monoxide toxicity; 100% humidified oxygen should be given if hypoxia or inhalation is suspected.

The systemic capillary leak that occurs after a serious burn response, the first 8 hours. (If resuscitation is delayed, half of the fluid replacement should be completed by the end of the eighth hour post-injury.) Fluids should be titrated to achieve adequate perfusion, one marker of which is urine output greater than 1 mL/kg/hour. Controversy exists over whether and when to administer colloid during fluid resuscitation. Colloid therapy may be needed for patients with extensive burns.

Because burn injury produces a hypermetabolic response, children with significant burns require immediate nutritional support. Enteral feeds should be started early unless there is a specific contraindication. Children with critical burn injury may require parenteral nutrition if unable to tolerate full enteral feeds. Consider supplementation of vitamins and trace elements. Factors that may modify the hypermetabolic state such as beta blockers, androgenic steroids, and others are being investigated.

**Wound care** starts with cleaning and debriding the wound. Effective pain control is important to allow for complete debridement. Topical agents and dressings are then applied to control bacterial colonization, decrease evaporative losses, and aid in pain control. Commonly used topical agents include silver sulfadiazine (Silvadene) or, if the burn is shallow, polymyxin B/bacitracin/neomycin (Neosporin) ointment. Silver nitrate and mafenide acetate (Sulfamylon) are alternative antimicrobial agents. Sulfamylon has the benefit of penetrating eschar, but it is painful and can cause metabolic acidosis. Silver nitrate is used less commonly because of poor tissue penetration and potential for electrolyte abnormalities. These agents

<table>
<thead>
<tr>
<th>Table 44-1</th>
<th>Complications of Burns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROBLEM</strong></td>
<td><strong>TREATMENT</strong></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Monitor for infection, avoid prophylactic antibiotics</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>Fluid replacement</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Adjust ambient temperature: dry blankets in field</td>
</tr>
<tr>
<td>Laryngeal edema</td>
<td>Endotracheal intubation, tracheostomy</td>
</tr>
<tr>
<td>Carbon monoxide poisoning</td>
<td>100% oxygen, hyperbaric oxygen</td>
</tr>
<tr>
<td>Cyanide poisoning</td>
<td>100% O₂ plus amyl nitrate, sodium nitrate, and sodium thiosulfate</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>Inotropic agents, diuretics</td>
</tr>
<tr>
<td>Gastric ulcers</td>
<td>H₂-receptor antagonist, antacids</td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>Escharotomy incision</td>
</tr>
<tr>
<td>Contractures</td>
<td>Physical therapy</td>
</tr>
<tr>
<td>Hypermetabolic state</td>
<td>Enteral and parenteral nutritional support</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Supportive care, dialysis</td>
</tr>
<tr>
<td>Transient antidiuresis</td>
<td>Expectant management</td>
</tr>
<tr>
<td>Anemia</td>
<td>Transfusions as indicated</td>
</tr>
<tr>
<td>Psychological trauma</td>
<td>Psychological rehabilitation</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td>PEEP, ventilation, oxygen</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Avoid overhydration, give diuretics</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>β-Agonist aerosols</td>
</tr>
</tbody>
</table>

**PEEP:** Positive end-expiratory pressure.
inhibit but do not prevent bacterial growth. Various grafts, such as cadaver allografts, porcine xenografts, or skin substitutes, have been used initially to cover wounds. For full-thickness burns, skin autografting and skin substitutes are required for eventual closure.

COMPLICATIONS
SEE TABLE 44-1.

PROGNOSIS
Most children who sustain burns recover without significant disability; however, burns remain the third leading cause of injury-related deaths in children ages 1 to 9. Estimation of morbidity is difficult to ascertain from databases. Physical scarring and emotional impact of disfiguring burns are long-term consequences of burn injuries.

PREVENTION
About 92% of burns occur in the home. Prevention is possible by using smoke and fire alarms, having identifiable escape routes and a fire extinguisher, and reducing hot water temperature to 49°C (120°F). Immersion full-thickness burns develop after 1 second at 70°C (158°F), after 5 seconds at 60°C (140°F), after 30 seconds at 54.5°C (130°F), and after 10 minutes at 49°C (120°F).

Chapter 45  •  Poisoning

POISONING

ETIOLOGY AND EPIDEMIOLOGY
The most common agents ingested by young children include cosmetics, personal care products, analgesics, and cleaning solutions. Fatal childhood poisonings are commonly caused by analgesics, antihistamines, sedative/hypnotics, and fumes/gases.

More than 2 million human exposures are called in to poison control centers in the United States each year. More than half of all exposures are in children (63% in 2010) with a male predominance in children under 13, but a female predominance in adolescence. Most ingestions in young children are unintentional, with intentional ingestions becoming more common in children 13 and older. Most ingestions occur at home (91%) and are single substance (90%).

CLINICAL MANIFESTATIONS
Any child who presents with unexplained symptoms including altered mental status, seizure, cardiovascular compromise, or metabolic abnormality should be considered to have ingested a poison until proven otherwise. A history and physical examination by someone who understands the signs and symptoms of various ingestions often provide sufficient clues to distinguish between toxic ingestion and organic disease (Table 45-1). Determination of all substances that the child was exposed to, type of medication, amount of medication, and time of exposure is crucial in directing interventions. Available data often are incomplete or inaccurate, requiring a careful physical examination and laboratory approach. A complete physical examination, including vital signs, is necessary. Certain complexes of symptoms and signs are relatively specific to a given class of drugs (toxidrome) (Table 45-2).

COMPLICATIONS
A poisoned child can exhibit any one of six basic clinical patterns: coma, toxicity, metabolic acidosis, heart rhythm aberrations, gastrointestinal symptoms, and seizures.

Coma
Coma is perhaps the most striking symptom of a poison ingestion, but it also may be seen as a result of several other causes including trauma, a cerebrovascular accident, asphyxia, or meningitis. A careful history and clinical examination are needed to distinguish among these alternatives.

Direct Toxicity
Hydrocarbon ingestion occasionally may result in systemic toxicity, but more often it leads to pulmonary toxicity. Hydrocarbons with low viscosity, low surface tension, and high volatility pose the greatest risk of producing aspiration pneumonia; however, when swallowed, they pose no risk unless emesis is induced. Emesis or lavage should not be initiated in a child who has ingested volatile hydrocarbons.

Caustic ingestions may cause dysphagia, epigastric pain, oral mucosal burns, and low-grade fever. Patients with esophageal lesions may have no oral burns or may have significant signs and symptoms. Treatment depends on the agent ingested and the presence or absence of esophageal injury. Alkali agents may be solid, granular, or liquid. Liquid agents are tasteless and produce full-thickness liquefaction necrosis of the esophagus or oropharynx. When the esophageal lesions heal, strictures form. Ingestion of these agents also creates a long-term risk of esophageal carcinoma. Treatment includes antibiotics if there are signs of infection and dilation of late-forming (2 to 3 weeks later) strictures.

Ingested button batteries also may produce a caustic mucosal injury. Batteries that remain in the esophagus may cause esophageal burns and erosion and should be removed with an endoscope. Acid agents can injure the lungs (with hydrochloric acid fumes), oral mucosa, esophagus, and stomach. Because acids taste sour, children usually stop drinking the solution, limiting the injury. Acids produce a coagulation necrosis, which limits the chemical from penetrating into deeper layers of the mucosa and damages tissue less severely than alkali. The signs, symptoms, and therapeutic measures are similar to those for alkali ingestion.

Metabolic Acidosis
A poisoned child may also have a high anion gap metabolic acidosis (mnemonic MUDPILES) (Table 45-3), which
### Table 45-1: Historical and Physical Findings in Poisoning

<table>
<thead>
<tr>
<th>ODOR</th>
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<tbody>
<tr>
<td>Bitter almonds</td>
<td>Cyanide</td>
</tr>
<tr>
<td>Acetone</td>
<td>Isopropyl alcohol, methanol, paraldehyde, salicylate</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Wintergreen</td>
<td>Methyl salicylate</td>
</tr>
<tr>
<td>Garlic</td>
<td>Arsenic, thallium, organophosphates, selenium</td>
</tr>
<tr>
<td>Violets</td>
<td>Turpentine</td>
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<table>
<thead>
<tr>
<th>OCULAR SIGNS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Miosis</td>
<td>Narcotics (except propoxyphene, meperidine, and pentazocine), organophosphates, muscarinic mushrooms, clonidine, phenothiazines, chloral hydrate, barbiturates (late)</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>Atropine, cocaine, amphetamines, antihistamines, cyclic antidepressants, PCP, LSD</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Phenytoin, barbiturates, ethanol, carbamazepine, PCP, ketamine, dextromethorphan</td>
</tr>
<tr>
<td>Lacrimation</td>
<td>Organophosphates, irritant gas or vapors</td>
</tr>
<tr>
<td>Retinal hyperemia</td>
<td>Methanol</td>
</tr>
<tr>
<td>Poor vision</td>
<td>Methanol, botulism, carbon monoxide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CUTANEOUS SIGNS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle tracks</td>
<td>Heroin, PCP, amphetamine</td>
</tr>
<tr>
<td>Dry, hot skin</td>
<td>Anticholinergic agents, botulism</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>Organophosphates, muscarinic mushrooms, aspirin, cocaine</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Thallium, arsenic, lead, mercury</td>
</tr>
<tr>
<td>Erythema</td>
<td>Boric acid, mercury, cyanide, anticholinergics</td>
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<table>
<thead>
<tr>
<th>ORAL SIGNS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Salivation</td>
<td>Organophosphates, salicylate, corrosives, strychnine, ketamine</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Amphetamines, anticholinergics, antihistamine</td>
</tr>
<tr>
<td>Burns</td>
<td>Corrosives, oxalate-containing plants</td>
</tr>
<tr>
<td>Gum lines</td>
<td>Lead, mercury, arsenic</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Corrosives, botulism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTESTINAL SIGNS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Antimicrobials, arsenic, iron, boric acid, cholinergics</td>
</tr>
<tr>
<td>Constipation</td>
<td>Lead, narcotics, botulism</td>
</tr>
<tr>
<td>Hematemesis</td>
<td>Corrosives, iron, salicylates, NSAIDs</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>CARDIAC SIGNS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia</td>
<td>Atropine, aspirin, amphetamine, cocaine, cyclic antidepressants, theophylline</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Digitalis, narcotics, clonidine, organophosphates, ß-blockers, calcium channel blockers</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Amphetamine, LSD, cocaine, PCP</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Phenothiazines, barbiturates, cyclic antidepressants, iron, ß-blockers, calcium channel blockers, clonidine, narcotics</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>RESPIRATORY SIGNS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed respiration</td>
<td>Alcohol, narcotics, barbiturates</td>
</tr>
<tr>
<td>Increased respiration</td>
<td>Amphetamines, aspirin, ethylene glycol, carbon monoxide, cyanide</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Hydrocarbons, organophosphates</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CENTRAL NERVOUS SYSTEM SIGNS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>Alcohol, barbiturates, anticholinergics, narcotics</td>
</tr>
<tr>
<td>Coma</td>
<td>Sedatives, narcotics, barbiturates, salicylate, cyanide, carbon monoxide, cyclic antidepressants, alcohol</td>
</tr>
<tr>
<td>Hyperpyrexia</td>
<td>Anticholinergics, salicylates, amphetamine, cocaine</td>
</tr>
<tr>
<td>Muscle fasciculation</td>
<td>Organophosphates, theophylline</td>
</tr>
<tr>
<td>Muscle rigidity</td>
<td>Cyclic antidepressants, PCP, phenothiazines, haloperidol</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>Lead, arsenic, mercury, organophosphates</td>
</tr>
<tr>
<td>Altered behavior</td>
<td>LSD, PCP, amphetamines, cocaine, alcohol, anticholinergics</td>
</tr>
</tbody>
</table>

LSD, Lysergic acid diethylamide; MSG, monosodium glutamate; NSAID, nonsteroidal anti-inflammatory drug; PCP, phencyclidine.
Chapter 45 ♦ Poisoning

is assessed easily by measuring arterial blood gases, serum electrolyte levels, and urine pH. An osmolar gap, if present, strongly suggests the presence of an unmeasured component, such as methanol or ethylene glycol. These ingestions require thorough assessment and prompt intervention.

**Dysrhythmias**

Dysrhythmias may be prominent signs of a variety of toxic ingestions, although ventricular arrhythmias are rare. Prolonged Q-T intervals may suggest phenothiazine or antihistamine ingestion, and widened QRS complexes are seen with ingestions of cyclic antidepressants and quinidine. Because many drug and chemical overdoses may lead to sinus tachycardia, this is not a useful or discriminating sign; however, sinus bradycardia suggests digoxin, cyanide, a cholinergic agent, or β-blocker ingestion (Table 45-4).

**Gastrointestinal Symptoms**

Gastrointestinal symptoms of poisoning include emesis, nausea, abdominal cramps, and diarrhea. These symptoms may be the result of direct toxic effects on the intestinal mucosa or of systemic toxicity after absorption.

**Seizures**

Seizures are the sixth major mode of presentation for children with toxic ingestions, but poisoning is an uncommon cause of afebrile seizures. When seizures do occur with intoxication, they may be life-threatening and require aggressive therapeutic intervention.

**Laboratory and Imaging Studies**

Laboratory studies helpful in initial management include specific toxin-drug assays; measurement of arterial blood gases and electrolytes, osmoles, and glucose; and calculation of the

<table>
<thead>
<tr>
<th>Table 45-2</th>
<th>Toxic Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGENT</strong></td>
<td><strong>MANIFESTATIONS</strong></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Nausea, vomiting, pallor, delayed jaundice–hepatic failure (72–96 hr)</td>
</tr>
<tr>
<td>Amphetamine, cocaine, and sympathomimetics</td>
<td>Tachycardia, hypertension, hyperthermia, psychosis and paranoia, seizures, mydriasis, diaphoresis, piloerection, aggressive behavior</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Mania, delirium, fever, red dry skin, dry mouth, tachycardia, mydriasis, urinary retention</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Headache, dizziness, coma, other systems affected</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Coma, convulsions, hyperpnea, bitter almond odor</td>
</tr>
<tr>
<td>Ethylene glycol (antifreeze)</td>
<td>Metabolic acidosis, hyperosmolarity, hypocalcemia, oxalate crystalluria</td>
</tr>
<tr>
<td>Iron</td>
<td>Vomiting (bloody), diarrhea, hypotension, hepatic failure, leukocytosis, hyperglycemia, radiopaque pills on KUB, late intestinal stricture, Yersinia sepsis</td>
</tr>
<tr>
<td>Narcotics</td>
<td>Coma, respiratory depression, hypotension, pinpoint pupils, bradycardia</td>
</tr>
<tr>
<td>Cholinergics (organophosphates, nicotine)</td>
<td>Miosis, salivation, urination, diaphoresis, lacrimation, bronchospasm (bronchorrhea), muscle weakness and fasciculations, emesis, defecation, coma, confusion, pulmonary edema, bradycardia</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Tachypnea, fever, lethargy, coma, vomiting, diaphoresis, alkalosis (early), acidosis (late)</td>
</tr>
<tr>
<td>Cyclic antidepressants</td>
<td>Coma, convulsions, mydriasis, hyperreflexia, arrhythmia (prolonged Q-T interval), cardiac arrest, shock</td>
</tr>
</tbody>
</table>

KUB, Kidney-ureter-bladder radiograph.

<table>
<thead>
<tr>
<th>Table 45-3</th>
<th>Screening Laboratory Clues in Toxicologic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANION GAP METABOLIC ACIDOSIS (MNEMONIC = MUDPILES)</strong></td>
<td></td>
</tr>
<tr>
<td>Methanol,* metformin</td>
<td></td>
</tr>
<tr>
<td>Uremia*</td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis*</td>
<td></td>
</tr>
<tr>
<td>Paraldehyde,* phenformin</td>
<td></td>
</tr>
<tr>
<td>Isoniazid, iron</td>
<td></td>
</tr>
<tr>
<td>Lactic acidosis (cyanide, carbon monoxide)</td>
<td></td>
</tr>
<tr>
<td>Ethanol,* ethylene glycol*</td>
<td></td>
</tr>
<tr>
<td>Salicylates, starvation, seizures</td>
<td></td>
</tr>
<tr>
<td><strong>HYPOGLYCEMIA</strong></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>Oral Hypoglycemic agents</td>
<td></td>
</tr>
<tr>
<td><strong>HYPERGLYCEMIA</strong></td>
<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Iron</td>
<td></td>
</tr>
<tr>
<td>Phenothiazines</td>
<td></td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td></td>
</tr>
<tr>
<td><strong>HYPOCALCEMIA</strong></td>
<td></td>
</tr>
<tr>
<td>Oxalate</td>
<td></td>
</tr>
</tbody>
</table>
| Ethylene glycol | *
| Fluoride | |
| **RADIOpaque SUBSTANCE ON KUB (MNEMONIC = CHIPPED)** | |
| Chlorhydrate, calcium carbonate | |
| Heavy metals (lead, zinc, barium, arsenic, lithium, bismuth as in Pepto-Bismol) | |
| Iron | |
| Phenothiazines | |
| Play-Doh, potassium chloride | |
| Enteric-coated pills | |
| Dental amalgam | |

KUB, Kidney-ureter-bladder radiograph.  
*Indicates hyperosmolar condition.
Section 8  ♦  The Acutely Ill or Injured Child

anion or osmolar gap. A full 12-lead electrocardiogram should be part of the initial evaluation in all patients suspected of ingesting toxic substances. Urine screens for drugs of abuse or to confirm suspected ingestion of medications in the home may be revealing.

Quantitative toxicology assays are important for some agents (Table 45-5), not only for identifying the specific drug, but also for providing guidance for therapy, anticipating complications, and estimating the prognosis.

**TREATMENT**

The four foci of treatment for poisonings are supportive care, decontamination, enhanced elimination, and specific antidotes.

**Supportive Care**

Supportive care is the mainstay of treatment in most cases. Prompt attention must be given to protecting and maintaining the airway, establishing effective breathing, and supporting the circulation. This management sequence takes precedence over other diagnostic or therapeutic procedures. If the level of consciousness is depressed, and a toxic substance is suspected, glucose (1 g/kg intravenously), 100% oxygen, and naloxone should be administered.

**Gastrointestinal Decontamination**

The intent of gastrointestinal decontamination is to prevent the absorption of a potentially toxic ingested substance and, in theory, to prevent the poisoning. There has been great controversy about which methods are the safest and most efficacious. Recommendations from the American Academy of Clinical Toxicology (AACT) and the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) follow. **Syrup of ipecac** should not be administered routinely to poisoned patients because of potential complications and lack of evidence that it improves outcome. Likewise, **gastric lavage** should not be used routinely, if ever, in the management of poisoned patients because of lack of efficacy and potential complications. **Single-dose activated charcoal** decreases drug absorption when used within 1 hour of ingestion; however, it has not been shown to improve outcome. Thus, it should

### Table 45-4  Drugs Associated with Major Modes of Presentation

<table>
<thead>
<tr>
<th>COMMON TOXIC CAUSES OF CARDIAC ARRHYTHMIA</th>
<th>Hypoglycemic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>Lead</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Lithium</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Methemoglobinemia*</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Narcotics</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Phencyclidine</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Phentolamine</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Cyanide</td>
<td>COMMON AGENTS CAUSING SEIZURES (MNEMONIC = CAPS)</td>
</tr>
<tr>
<td>Cyclic antidepressants</td>
<td>Camphor</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Freon</td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>Cyanide</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Aminophylline</td>
</tr>
<tr>
<td>Quinine, quinidine</td>
<td>Amphetamine</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Anticholinergics</td>
</tr>
<tr>
<td>CAUSES OF COMA</td>
<td>Antidepressants (cyclic)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Pb (lead) (also lithium)</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Pesticide (organophosphate)</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Phencyclidine</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Phenol</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Propoxyphene</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Cyclic antidepressants</td>
<td>Strychnine</td>
</tr>
</tbody>
</table>

*Causes of methemoglobinemia: amyl nitrite, aniline dyes, benzocaine, bismuth subnitrate, dapsone, primaquine, quinones, spinach, sulfonamides.
be used selectively in the management of a poisoned patient. Charcoal is ineffective against caustic or corrosive agents, hydrocarbons, heavy metals (arsenic, lead, mercury, iron, lithium), glycols, and water-insoluble compounds.

The administration of a cathartic (sorbitol or magnesium citrate) alone has no role in the management of the poisoned patient. The AACT has stated that based on available data, the use of a cathartic in combination with activated charcoal is not recommended.

Whole-bowel irrigation using polyethylene glycol (GoLYTELY) as a nonabsorbable cathartic may be effective for toxic ingestion of sustained-release or enteric-coated drugs. The AACT does not recommend the routine use of whole-bowel irrigation. However, there is theoretical benefit in its use for potentially toxic ingestions of iron, lead, zinc, or packets of illicit drugs.

**Enhanced Elimination**

**Multiple-dose activated charcoal** should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. **Alkalization of urine** may be helpful for salicylate or methotrexate ingestion. **Dialysis** may be used for substances that have a low volume of distribution, low molecular weight, low protein binding, and high degree of water solubility, such as methanol, ethylene glycol, salicylates, theophylline, bromide, and lithium.

**Specific Antidotes**

SEE TABLE 45-6.

When in doubt about therapy, contacting one of the U.S. Poison Control Centers (1-800-222-1222) can help to determine what additional treatment is necessary.

**PROGNOSIS**

Most poisonings result in minimal or no toxicity. Major toxicity is seen in fewer than 1% of ingestions, with fatality in fewer than 0.1%. Only 12% of children 12 and under with poisoning require treatment in a health care facility, compared with 48% of adolescents.

**PREVENTION**

Properly educating parents regarding safe storage of medications and household toxins is necessary for preventing ingestions. If a child has ingested poison, a poison control center should be called.

### Table 45-5 Drugs Amenable to Therapeutic Monitoring for Drug Toxicity

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIBIOTICS</strong></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides---gentamicin, tobramycin, and amikacin</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNOSUPPRESSION</strong></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td><strong>ANTIPYRETICS</strong></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
</tr>
<tr>
<td>Salicylate</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsant drugs</td>
<td></td>
</tr>
<tr>
<td>Serotonin uptake inhibitor agent</td>
<td></td>
</tr>
</tbody>
</table>

### Table 45-6 Specific Antidotes

<table>
<thead>
<tr>
<th>POISON</th>
<th>ANTIDOTE</th>
<th>DOSAGE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>N-Acetylcysteine</td>
<td>140 mg/kg PO initial dose, then 70 mg/kg PO q4hr × 17 doses</td>
<td>Most effective within 16 h of ingestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg/kg IV over 1 hr, followed by 50 mg/kg IV over 4 hr, followed by 100 mg/kg IV over 16 hr</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>Flumazenil</td>
<td>0.2 mg IV, may repeat to 1 mg max</td>
<td>Possible seizures, arrhythmias, DO NOT USE FOR UNKNOWN INGESTIONS</td>
</tr>
<tr>
<td>β-Blocking agents</td>
<td>Glucagon</td>
<td>0.15 mg/kg IV, followed by infusion of 0.05–0.15 mg/kg/hr</td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Oxygen</td>
<td>100%; hyperbaric O₂</td>
<td>Half-life of carboxyhemoglobin is 5 hr in room air but 1.5 hr in 100% O₂</td>
</tr>
<tr>
<td>Cyclic antidepressants</td>
<td>Sodium bicarbonate</td>
<td>1–2 mEq/kg IV, followed by continuous infusion; titrated to produce pH of 7.5–7.55</td>
<td>Follow potassium levels and replace as needed</td>
</tr>
<tr>
<td>Iron</td>
<td>Deferoxamine</td>
<td>Infusion of 5–15 mg/kg/hr IV (max 6 g/24 hr)</td>
<td>Hypotension (worse with rapid infusion rates)</td>
</tr>
</tbody>
</table>

Continued
SEDATION AND ANALGESIA

An acutely ill pediatric patient may have pain, discomfort, and anxiety resulting from injury, surgery, and invasive procedures (intubation, bone marrow aspiration, venous access placement) or during life-sustaining mechanical ventilation. Clear goals should be identified to allow provision of optimal analgesia or sedation without compromising the physiologic status of the patient. Anxiolysis, cooperation, amnesia, immobility, and lack of awareness all are goals of sedation and can be accomplished with various drugs (Table 46-1). Many of these goals can be achieved with behavioral techniques (preprocedural teaching), but sedation is often a necessary adjunct for painful procedures. Pain may be expressed by verbal or visible discomfort, crying, agitation, tachycardia, hypertension, and tachypnea. A variety of scales have been developed in an attempt to quantify pain and allow more directed therapy. Few of these scales are well validated, especially in populations of acutely ill children with physiologic derangements secondary to the underlying pathology. Pain caused by procedural interventions should always be treated with analgesics in addition to sedation (Table 46-2).

**Nonprocedural Sedation**

Many ventilated pediatric patients require sedation and some analgesia while intubated. The most common choice is a combination of a longer acting benzodiazepine and an opioid. Avoidance of oversedation is important. Use of appropriate pain and sedation scores allows for titration of medications to achieve goals of the sedation plan. Long-term use of benzodiazepines and opioids leads to tolerance, a problematic occurrence that must be considered as medications are added and weaned. True addiction is a rare occurrence, especially when medications are provided at the minimum level needed to achieve adequate sedation and pain control.

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**ASSESSMENT**

**Procedural Sedation**

A medical evaluation must be performed for any patient receiving procedural sedation to identify underlying medical conditions that may affect the choice of sedative agents. Specific attention must be paid to assessment of the airway (for ability to maintain a patent airway) and respiratory system (asthma, recent respiratory illness, loose teeth), cardiovascular status (especially adequacy of volume status), factors affecting drug metabolism (renal or liver disease), and risk of aspiration (adequate nothing-by-mouth status, gastroesophageal reflux). During the administration of procedural sedation, assessment of status must include monitoring of oxygen saturation, heart rate, and respiratory rate, as well as some assessment of effectiveness of ventilation. This assessment must be performed by someone who is not involved in the procedure; this person is also responsible for recording vital signs and drugs administered on a time-based graph. Monitoring must be continued until the child has returned to baseline. Patients who are receiving long-term sedation (e.g., to maintain endotracheal tube placement) may need only local anesthesia for painful procedures but may benefit from additional sedation or analgesia as well.

**Table 45-6**

<table>
<thead>
<tr>
<th>POISON</th>
<th>ANTIDOTE</th>
<th>DOSAGE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>Edetate calcium</td>
<td>35–50 mg/kg/day IV × 5 days; continuous</td>
<td>May cause sterile abscesses. Prepared in peanut oil, do not use in patients with peanut allergy.</td>
</tr>
<tr>
<td>BAL (British anti-Lewisite [dimercaprol])</td>
<td>3–5 mg/kg/dose IM q4h × 4–11 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succimer (2,3-dimercaptosuccinic acid [DMSA])</td>
<td>10 mg/kg/dose PO tid × 5 days, then 10 mg/kg/dose PO bid × 14 days</td>
<td>Few toxic effects, requires lead-free home plus compliant family</td>
<td></td>
</tr>
<tr>
<td>Nitrites/ methemoglobinemia*</td>
<td>Methylene blue</td>
<td>1–2 mg/kg IV, repeat q 30–60 min if needed; treat for levels &gt;30%</td>
<td>Exchange transfusion may be needed for severe methemoglobinemia; methylene blue overdose also causes methemoglobinemia</td>
</tr>
<tr>
<td>Opiates</td>
<td>Naloxone</td>
<td>0.1 mg/kg IV, ET, SC, IM for children, up to 2 mg, repeat as needed</td>
<td>Naloxone causes no respiratory depression</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>Atropine</td>
<td>0.05–0.1 mg/kg IV/ET, repeat every 5–10 minutes as needed</td>
<td>Physiologic: blocks acetylcholine</td>
</tr>
<tr>
<td></td>
<td>Pralidoxime (2 PAM; Protopam)</td>
<td>25–50 mg/kg IV over 5–10 min (max 200 mg/min); may repeat after 1–2 hr, then q10–12 h as needed</td>
<td>Specific: disrupts phosphate-cholinesterase bond</td>
</tr>
</tbody>
</table>

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*See Table 45-4 for causes of methemoglobinemia.
**Sedation and Analgesia**

**PAIN AND ANALGESIA**

The subjective aspect of pain requires that self-reporting be used for assessment. Visual analog scales, developed for adult patients (allowing patients to rate pain on a scale of 1 to 10), have been used for older children. Pain scales for younger children often incorporate behavioral and physiologic parameters, despite the imprecision of physiologic responses.

Local anesthetics, such as lidocaine, can be used for minor procedures. However, lidocaine requires subcutaneous or intradermal injection. The use of EMLA, a cream containing lidocaine and prilocaine, is less effective than intradermal lidocaine but is preferred by many patients.

Patient-controlled analgesia is an effective method for providing balanced analgesia care in older children and adolescents. Children using patient-controlled analgesia have better pain relief and experience less sedation than patients receiving intermittent, nurse-controlled, bolus analgesics. Analgesics can be administered through the patient-controlled analgesia pump with continuous basal infusions, bolus administration, or both. Morphine is the most frequent opioid used for patient-controlled analgesia.

Monitoring of oxygen saturations and respiratory rate are crucial with continuous opioid infusions because of the shift in CO₂ response curve and potential to decrease ventilatory response to hypoxia.

Epidural analgesia decreases the need for inhalation anesthetics during surgery and can provide significant analgesia without sedation in the postoperative period. Decreased costs and length of stay also may be benefits of epidural analgesic approaches. Medications used in epidurals include bupivacaine and morphine. Adverse effects include nausea and vomiting, motor blockade, and technical problems requiring catheter removal. Infection and permanent neurologic deficits are rare.

**Suggested Reading**


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**Table 46-1** Agents that Produce Sedation

<table>
<thead>
<tr>
<th>SEDATIVES</th>
<th>EFFECT</th>
<th>CONCERNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>Anxiolysis, sedation, muscle relaxation, amnesia</td>
<td>Tolerance is possible; apnea, hypotension, depressed myocardial function; short action</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Anxiolysis, sedation, muscle relaxation, amnesia</td>
<td>Same as midazolam; long action</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Sedation without respiratory depression</td>
<td>May cause bradycardia</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Anesthesia, analgesia, amnesia</td>
<td>Dissociative reactions, tachycardia, hypertension, increased bronchial secretions, emergent delirium, hallucinations; increases intracranial pressure</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Sedative</td>
<td>Emesis, hypotension, arrhythmias, hepatic dysfunction</td>
</tr>
<tr>
<td>Propofol</td>
<td>Rapid-onset sedative for induction and maintenance of anesthesia</td>
<td>Metabolic acidosis in children; may depress cardiac function</td>
</tr>
</tbody>
</table>

**Table 46-2** Agents that Produce Analgesia

<table>
<thead>
<tr>
<th>ANALGESIC</th>
<th>EFFECT</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen and NSAIDs</td>
<td>Moderate analgesia, antipyresis</td>
<td>Ceiling effect, requires PO administration NSAIDs—gastrointestinal bleed, ulceration</td>
</tr>
<tr>
<td>Opioids</td>
<td>No ceiling effect; respiratory depression, sedation, pruritus, nausea/vomiting, decreased gastric motility, urinary retention, tolerance with abuse potential</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Analgesia</td>
<td>May cause myocardial depression</td>
</tr>
<tr>
<td>Codeine</td>
<td>Analgesia</td>
<td>Nausea/vomitting</td>
</tr>
<tr>
<td>Fentanyl, alfentanil, sufentanil</td>
<td>Analgesia, sedation</td>
<td>No adverse effects on cardiovascular system; stiff chest syndrome</td>
</tr>
<tr>
<td>Methadone</td>
<td>Analgesia</td>
<td></td>
</tr>
</tbody>
</table>

NSAIDs, Nonsteroidal anti-inflammatory drugs; PO, oral.
Chapter 47

PATTERNS OF INHERITANCE

TYPES OF GENETIC DISORDERS
Among infants born in the United States, 2% to 4% have congenital malformations, abnormalities of form or function identifiable at birth. At 1 year of age, the number approaches 7%, because some anomalies may not be identifiable until after the neonatal period. The prevalence of congenital malformations is much greater in inpatient pediatric populations; 30% to 50% of hospitalized children have congenital anomalies or genetic disorders.

The clinical geneticist attempts to identify the etiology, mode of inheritance, and risk that a disorder might occur in the affected child's siblings. In evaluating children with congenital malformations, the patient's condition may be classified into one of five different categories:

1. Single-gene mutations, accounting for 6% of children with congenital anomalies
2. Chromosomal disorders, accounting for approximately 7.5%
3. Multifactorially inherited conditions, accounting for 20%
4. Disorders that show an unusual pattern of inheritance, accounting for 2% to 3%
5. Conditions caused by exposure to teratogens, accounting for 6%

INTRODUCTION TO GENETICS AND GENOMICS
DNA exists as multiple fragments that, together with a protein skeleton (chromatin), form chromosomes. Human cells have 23 pairs of chromosomes, with one copy of each chromosome inherited from each parent. Twenty-two pairs of chromosomes are autosomes; the remaining pair is called the sex chromosomes. Females have two X chromosomes; males have one X and one Y.

Spread along the chromosomes, like beads on a string, DNA sequences form genes, the basic units of heredity. A typical gene contains a promoter sequence, an untranslated region, and an open reading frame, all arrayed from the 5' to the 3' end of the DNA. In the open reading frame, every three nucleotides represent a single codon, coding for a particular amino acid. In this way, the sequence of bases dictates the sequence of amino acids in the corresponding protein. Some codons, rather than coding for a specific amino acid, act as a “start” signal, whereas others serve as “stop” signals. Between the start and stop codons, genes consist of two major portions: exons, regions containing the code that ultimately corresponds to a sequence of amino acids, and introns (intervening sequence), which do not become part of the amino acid sequence.

Genes are transcribed into messenger RNA (mRNA), then translated into proteins. During transcription, RNA is processed to remove introns. The mRNA serves as a template to construct the protein.

Human genetic material contains 3.1 billion bases. Less than 2% of the DNA codes for proteins, comprising the genome's approximately 21,000 genes. Through a mechanism called alternative splicing, these 21,000 genes may create more than 100,000 proteins. The remainder of the DNA, the portion not involved in protein formation, had been termed junk DNA, but a project called ENCODE (Encyclopedia of DNA Elements) found that much of this presumed junk DNA is functional and likely serves some regulatory function.

Disease may be caused by changes or mutations in the DNA sequence, with the point mutation, a change in a single DNA base, being the most common type. A point mutation that changes a codon and the resulting amino acid that goes into the protein is referred to as a missense mutation. A nonsense mutation is a point mutation that changes the codon to a “stop” codon so that transcription stops prematurely. A frameshift mutation often stems from the loss or addition of one or more DNA bases; this causes a shift in how the DNA is transcribed and generally leads to premature stop codons.
Pedigree Drawing

To identify specific patterns of inheritance, geneticists construct and analyze pedigrees, which are pictorial representations of a family history. Males are represented by squares and females by circles. Matings are connected with a solid line between each partner's symbols. Unmarried couples are often connected by a dashed line. Children from a couple are represented below their parents and are the next generation.

Grandparents, uncles, and aunts are added in similar fashion. Children of aunts and uncles also may be included. Ages or birthdays may be written next to or underneath each symbol. The proband (the patient who is the initial contact) is indicated with an arrow. Affected individuals are indicated by shading, or some other technique, which should be explained in a key. Carriers for a disorder (e.g., sickle cell disease) usually are indicated by a dot in the center of their symbol (Fig. 47-1).

To be useful, pedigrees should include representatives of at least three generations of family members.

Autosomal Dominant Disorders (AD)

If a single copy of a gene bearing a mutation is sufficient to cause disease and that gene is not on one of the sex chromosomes, that condition is inherited in an AD fashion (Table 47-1). In AD disorders, an affected parent has a 50% chance of passing the mutated gene to each child (Fig. 47-2; Table 47-2). Possessing one working gene and one nonworking gene is termed heterozygous. If both copies are the same, they are referred to as homozygous.

Some people who are obligate carriers of a mutation known to cause an AD disorder may not show clinical signs of the disorder, whereas other such individuals manifest symptoms. This phenomenon is referred to as penetrance. If all individuals who carry a mutation for an AD disorder show signs of that disorder, the gene is said to have complete penetrance. Many AD disorders show decreased penetrance.

Often, AD disorders show variability in symptoms expressed in different individuals carrying the same mutated gene. Some individuals have only mild clinical symptoms, whereas others have more severe disease. This phenomenon is referred to as variable expressivity.

AD disorders sometimes appear in a child of unaffected parents because of a spontaneous mutation. Known in some cases to be associated with advanced paternal age (>35 years of age), spontaneous mutations may account for most individuals with some disorders. Approximately 80% of patients with achondroplasia have a spontaneous mutation in the fibroblast growth factor receptor type 3 (FGFR3) gene. The following are examples of autosomal dominant disorders.

<table>
<thead>
<tr>
<th>Table 47-1</th>
<th>Autosomal Dominant Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISEASE</strong></td>
<td><strong>FREQUENCY</strong></td>
</tr>
<tr>
<td>Achondroplasia</td>
<td>~1:12,000</td>
</tr>
<tr>
<td>Thanatophoric dysplasia</td>
<td>1:3500</td>
</tr>
<tr>
<td>Crouzon syndrome with acanthosis nigricans</td>
<td>Genotype at birth, 1:33,000 Phenotype prevalence, 1:200,000</td>
</tr>
<tr>
<td>Nonsyndromic craniosynostosis</td>
<td>Neurofibromatosis 1</td>
</tr>
<tr>
<td>Neurofibromatosis 2 (NF2, bilateral acoustic neuromas, Merlin)</td>
<td>Genotype at birth, 1:33,000 Phenotype prevalence, 1:200,000</td>
</tr>
<tr>
<td>Huntington disease (HD)</td>
<td>1:10,000</td>
</tr>
<tr>
<td>Myotonic dystrophy (DM, Steinert disease)</td>
<td>1:500 in Quebec 1:25,000 Europeans</td>
</tr>
<tr>
<td>Marfan syndrome (FBN-1)</td>
<td>1:10,000</td>
</tr>
<tr>
<td>Hereditary angioneurotic edema (HANE) (C-1 esterase inhibitor that regulates the C-1 component of complement)</td>
<td>1:10,000</td>
</tr>
</tbody>
</table>
Achondroplasia
Caused by a defect in cartilage-derived bone, achondroplasia (ACH) is the most common skeletal dysplasia in humans. The bony abnormalities lead to short stature, macrocephaly, a flat midface with a prominent forehead, and rhizomelic shortening of the limbs. The disorder occurs in approximately 1 in 12,000 births.

ACH is caused by mutations in the *FGFR3* gene. Early in development, *FGFR3* is expressed during endochondral bone formation. More than 95% of cases of ACH are caused by one of two mutations in the same base pair (site 1138). This site, extremely active for mutations, is known as a mutational **hot spot**.

As they grow, children with ACH often develop associated medical and psychological problems. Hydrocephalus and central apnea may occur because of narrowing of the foramen magnum and compression of the brainstem and may present a life-threatening complication in infancy. Bowing of the legs may occur later in childhood because of unequal growth of the tibia and fibula. Dental malocclusion, obstructive apnea, and hearing loss due to middle ear dysfunction are common in later childhood. During later childhood and adolescence, the psychological effects of the short stature may manifest. In adulthood, further complications include compression of nerve roots and sciatica. People with ACH have normal life spans and normal intelligence.

The diagnosis of ACH is made on the basis of clinical findings; characteristic x-ray abnormalities confirm the diagnosis. Molecular testing is available but is usually reserved for cases that are difficult to diagnose or those in which prenatal diagnosis is requested. Prenatal diagnosis is possible by molecular testing, using fetal cells obtained through amniocentesis or chorionic villus sampling.

### Neurofibromatosis Type 1
One of the most common AD disorders, NF1 is estimated to be present in 1 in 3500 individuals. NF1 is caused by a mutation in the gene *NF1*, which codes for the protein neurofibromin.

Although the penetrance of NF1 is 100%, the expression is extremely variable. Many affected individuals have features so mild that they are never diagnosed.

SEE CHAPTER 186.

### Marfan Syndrome (MFS)
A condition that occurs in approximately 1 in 10,000 individuals, MFS shows pleiotropy, the condition in which abnormalities in multiple organ systems are caused by a mutation in a single gene. Caused by a mutation in the *FBN1* gene, clinical symptoms in MFS mostly involve three systems: **cardiac**, **ophthalmologic**, and **skeletal**. Skeletal findings include a tall, thin body habitus (dolichostenomelia), spider-like fingers and toes (arachnodactyly), abnormalities of the sternum (pectus excavatum or carinatum), scoliosis, pes planus, and joint laxity. Eye findings include high myopia, which can lead to vitreoretinal degeneration; an abnormal suspensory ligament of the lens, which can lead to ectopia lentis (dislocation of the lens); and cataracts. Cardiac findings include progressive dilatation of the aortic root. Aortic insufficiency followed by aortic dissection is a common complication. Other clinical features of MFS include dural ectasia, abnormal pulmonary septation, and striae. Diagnostic criteria for MFS are summarized in Table 47-3.

New mutations in *FBN1* account for 25% of cases of MFS. The gene is large and complex; more than 600 mutations have been identified in affected individuals. Many of the symptoms of MFS are caused not by the defect in the fibrillin protein itself but rather by an excess in transforming growth factor-beta (TGF-β), a protein usually bound by fibrillin. Losartan, an angiotensin II receptor antagonist that also lowers levels of TGF-β, may prevent aneurysms in patients with MFS.

### Autosomal Recessive Disorders (AR)
Disorders that are inherited in an AR manner manifest only when both copies of a gene pair located on a non-sex chromosome have a mutation (Tables 47-4, 47-5). Affected children usually are born to unaffected parents, each of whom carries one copy of the mutation. If both members of a couple are carriers (or heterozygotes) for this mutation, each of their offspring has a 25% chance of being affected (Fig. 47-3).

### Sickle Cell Disease
SEE CHAPTER 150.
### Table 47-3 Revised Ghent Nosology for the Diagnosis of Marfan Syndrome

<table>
<thead>
<tr>
<th>WITHOUT FAMILY HISTORY</th>
<th>WITHOUT FAMILY HISTORY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AORTIC ROOT DILATATION</strong> (Z ≥ 2SD) or AORTIC DISSECTION</td>
<td><strong>ECTOPIA LENS</strong></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
</tr>
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<td>-</td>
<td>+</td>
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<tr>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MVP</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>WITH FAMILY HISTORY</th>
</tr>
</thead>
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<tr>
<td>+</td>
</tr>
<tr>
<td>+</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>SCORING SYSTEM FOR SYSTEMIC FEATURES†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thumb AND Wrist Sign</td>
</tr>
<tr>
<td>Thumb OR Wrist Sign</td>
</tr>
<tr>
<td>Pectus Carinatum</td>
</tr>
<tr>
<td>Pectus Excavatum or Chest Asymmetry</td>
</tr>
<tr>
<td>Hindfoot Deformity</td>
</tr>
<tr>
<td>Pes Planus</td>
</tr>
<tr>
<td>Pneumothorax (History)</td>
</tr>
<tr>
<td>Dural Ectasia</td>
</tr>
<tr>
<td>Protrusio acetabuli</td>
</tr>
<tr>
<td>Decreased US/LS ratio AND increased Arm/Height BUT NO SCOLIOSIS</td>
</tr>
<tr>
<td>Scoliosis or Thoracolumbar kyphosis</td>
</tr>
<tr>
<td>Reduced Elbow Extension</td>
</tr>
<tr>
<td>Facial features (3 of 5)§</td>
</tr>
<tr>
<td>Skin Striae</td>
</tr>
<tr>
<td>Myopia &gt;3 diopters</td>
</tr>
<tr>
<td>Mitral Valve Prolapse</td>
</tr>
</tbody>
</table>


FGN1, Fibrillin-1; MASS, myopia, mitral valve prolapse, borderline aortic root dilatation (Z <2), striae, skeletal findings; MVPS, mitral valve prolapse syndrome.

* Aortic root dilatation (measured at the Sinuses of Valsalva).
† Loeys-Dietz syndrome (LDS), Shprintzen-Goldberg syndrome (SGS), and the vascular form of Ehlers Danlos (vEDS) should be excluded. If clinical features are suggestive, then DNA testing for TGFBR1, TGFBR2 (LDS), COL3A1 (vEDS) or collagen biochemistry should be done to help rule out these disorders.
‡ Maximum Total: 20 points; more than 7 points indicates systemic involvement.
§ Facial Features: Dolicocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia.

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**Tay-Sachs Disease**

SEE CHAPTERS 55 AND 185.

**X-Linked Disorders**

More than 1000 genes have been identified on the X chromosome, whereas males, who have one X chromosome and a Y chromosome, have only one copy of these genes. Early in female embryonic development, one X chromosome is randomly inactivated in each cell. There are many X-linked disorders (colorblindness, Duchenne muscular dystrophy, hemophilia A) in which heterozygous (carrier) females show some manifestations of the disorder due to skewed X chromosome inactivation.
X-Linked Recessive Inheritance
Most disorders involving the X chromosome are recessive. With only one copy of the X chromosome, males are more likely to manifest these diseases than females. Each son born to a female carrier of an X-linked recessive trait has a 50% chance of inheriting the trait, but none of this woman’s daughters would be affected (each daughter has a 50% chance of being a carrier). An affected father transmits the mutation to all of his daughters, who are carriers, but not to his sons; having received their father’s Y chromosome, they would not be affected (thus there is no male-to-male transmission) (Tables 47-6, 47-7 and Fig. 47-4).

Duchenne Muscular Dystrophy
SEE CHAPTER 182.

Hemophilia A
SEE CHAPTER 151.

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Table 47-4  Autosomal Recessive Diseases

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>FREQUENCY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal hyperplasia, congenital (CAH, 21-hydroxylase deficiency, CA21H, CYP21, cytochrome P450, subfamily XXI)</td>
<td>1:5000</td>
<td>Phenotype variation corresponds roughly to allelic variation. A deficiency causes virilization in females. The gene is located at 6p21.3 within the HLA complex and within 0.005 centimorgans (cM) of HLA B.</td>
</tr>
<tr>
<td>Phenylketonuria (PKU, phenylalanine hydroxylase deficiency, PAH)</td>
<td>1:12,000-1:17,000</td>
<td>There are hundreds of disease-causing mutations in the PAH gene located on chromosome 12q22-q24.1. The first population-based newborn screening was a test for PKU because the disease is treatable by diet. Women with elevated phenylalanine have infants with damage to the central nervous system because high phenylalanine is neurotoxic and teratogenic.</td>
</tr>
<tr>
<td>Cystic fibrosis (CF)</td>
<td>1:2500 whites</td>
<td>The gene CF transmembrane conductance regulator (CFTR) is on chromosome 7q31.2.</td>
</tr>
<tr>
<td>Friedreich ataxia (FA, frataxin)</td>
<td>1:25,000</td>
<td>Frataxin is a mitochondrial protein involved with iron metabolism and respiration. The gene is on chromosome 9q13-q21, and the common mutation is a GAA expanded triplet repeat located in the first intron of the gene. FA does not show anticipation.</td>
</tr>
<tr>
<td>Gaucher disease, all types (glucocerebrosidase deficiency, acid β-glucosidase deficiency) (a lysosomal storage disease)</td>
<td>1:2500 Ashkenazi Jews</td>
<td>The gene is located on chromosome 1q21. There are many mutations; some mutations lead to neuropathic disease, but most are milder in expression. The phenotypes correspond to the genotypes, but the latter are difficult to analyze.</td>
</tr>
<tr>
<td>Sickle cell disease (hemoglobin beta locus, beta 6 glu -&gt; val mutation)</td>
<td>1:625 African Americans</td>
<td>This is the first condition with a defined molecular defect (1959). A single base change results in an amino acid substitution of valine for glutamic acid at position 6 of the beta chain of hemoglobin, with resulting hemolytic anemia. The gene is on chromosome 11p15.5. Penicillin prophylaxis reduces death from pneumococcal infections in affected persons, especially in infants.</td>
</tr>
</tbody>
</table>

Table 47-5  Rules of Autosomal Recessive Inheritance

| Trait appears in siblings, not in their parents or their offspring |
| On average, 25% of siblings of the proband are affected (at the time of conception, each sibling has a 25% chance of being affected) |
| A normal sibling of an affected individual has a two thirds chance of being a carrier (heterozygote) |
| Males and females are likely to be affected equally |
| Rare traits are likely to be associated with parental consanguinity |
| Traits generally involve mutations in genes that code for enzymes (e.g., phenylalanine hydroxylase–deficient in PKU) and are associated with serious illness and shortened life span |

PKU, Phenylketonuria.

X-Linked Dominant Inheritance
Only a few X-linked dominant disorders have been described. Both males and females are affected by this group of disorders, but females have less severe symptoms due to X-chromosome inactivation. This is the case for X-linked vitamin D–resistant rickets (hypophosphatemic rickets), a disorder in which the kidney’s ability to reabsorb phosphate is impaired. Phosphate levels and resulting rickets are not as severe in females as in males.

However, many X-linked dominant disorders are lethal in males. Affected mothers can have affected or normal daughters but only normal sons. Affected sons die in utero. This is the case in incontinentia pigmenti, which has a characteristic swirling skin pattern of hyperpigmentation that develops after a perinatal skin rash with blistering. Affected females also have variable involvement of the central nervous system, hair, nails,
teeth, and eyes. In Rett syndrome, caused by mutations in the MECP2 gene, females are normal at birth, but later in the first year of life develop microcephaly and developmental regression and plateau. About 50% of patients develop seizures. Girls often adopt a hand-washing posture that causes them to lose all purposeful hand movements.

**OTHER TYPES OF GENETIC DISORDERS**

**Multifactorial Disorders**

Often termed polygenic inheritance, multifactorially inherited disorders result from the interplay of genetic and environmental factors. In addition to 20% of congenital malformations, including cleft lip and palate and spina bifida, most common disorders of childhood and adult life, such as asthma, atherosclerosis, diabetes, and cancer, result from an interaction between genes and the environment. These disorders do not follow simple mendelian modes of inheritance; rather, affected individuals tend to cluster in families. The disorders occur more often in first- and second-degree relatives than would be expected by chance, and...
they are more likely to be concordant (although not 100%) in monozygotic twins than in dizygotic twins.

**Hypertrophic Pyloric Stenosis**

Occurring in about 1 in 300 children, hypertrophic pyloric stenosis (HPS) is five times more likely to occur in males than in females. When a child with HPS is born, the recurrence risk in future progeny is 5% to 10% for males and 1.5% to 2% for females. In adulthood, the risk of an affected male having an affected child is markedly increased over the general population: 4% of sons and 1% of daughters of such men would be likely to be affected. Even more striking is the risk to children born to affected females: 17% to 20% of sons and 7% of daughters are affected.

The thickness of the pyloric muscle may be distributed across a bell-shaped curve; the position on the bell-shaped curve is determined by many factors, including the expression of multiple, unknown genes. HPS may result when an individual's genetic and environmental influences cause him or her to fall to an extreme position on this curve, past a certain point, which is called a *threshold*. In HPS, this threshold is farther to the left for males than it is for females.

**Neural Tube Defects**

Before 1998, myelomeningocele affected 1 in 1000 liveborn infants in the United States. Anencephaly occurred with a similar frequency, although most infants were either stillborn or died in the neonatal period. Since 1998, because of the supplementation of food staples with folic acid, both of these conditions have become far less frequent. Multiple genetic and nongenetic factors dictate the speed with which the neural tube closes, as follows:

1. The frequency of neural tube defects (NTDs) varies greatly in different ethnic groups. NTDs are more common in the British Isles, where, in 1990, they occurred in 1 in 250 live births, and far less common in Asia, where the frequency was 1 in 4000. These ethnic differences suggest a genetic component.
2. Couples from the British Isles who move to the United States have a risk intermediate between the risks in the United Kingdom and the United States, suggesting an environmental component.
3. The occurrence of NTDs exhibits seasonality. In the United States, affected infants are more likely to be born during late fall and early winter, again suggesting an environmental component.
4. Periconceptual supplementation with folic acid has significantly lowered the risk of having an infant with an NTD. This nutritional influence suggests an environmental component.
5. Parents who have one child with an NTD are 20 to 40 times more likely to have a second affected child; this provides further evidence of a genetic component.

**Disorders with Unusual Patterns of Inheritance**

**Mitochondrial Inheritance**

Human cells contain non-nuclear DNA; a single chromosome is present in each mitochondrion, and mutations within this DNA are associated with a group of diseases.

Mitochondrial DNA (mtDNA), which is circular and 16.5 kb in length, replicates independently of nuclear DNA. Involved in energy production used to run the cell, mtDNA codes for a few respiratory chain proteins (most mitochondrial proteins are coded on nuclear DNA) and for a set of transfer RNAs unique to mitochondrial protein synthesis. Virtually all mitochondria are supplied by the oocyte, which means that mtDNA is maternally derived. A woman with a mutation in mtDNA passes this mutation to all of her children. More than one population of mitochondria may be present in the oocyte, a phenomenon called heteroplasmy. The mtDNA mutation may be present in a few or many mitochondria. When the fertilized egg divides, mitochondria are distributed randomly. The presence of symptoms in the offspring, and their severity, depends on the ratio of mutant to wild-type mtDNA present in a particular tissue. If an abundance of mutant mitochondria exists in tissue that has high energy requirements (brain, muscle, and liver), clinical symptoms occur. If fewer mutant mitochondria are present, few clinical symptoms may be seen.

**MELAS** (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes) is an example of a mitochondrial disorder. Normal in early childhood, individuals affected with MELAS develop episodic vomiting, seizures, and recurrent cerebral insults that resemble strokes between 5 and 10 years of age. In 80% of cases, analysis of the mtDNA reveals a specific mutation (A3242G) in *MTTL1*, a gene that codes for a mitochondrial transfer RNA.

In families in which MELAS occurs, a range of symptoms is seen in first-degree relatives, including progressive external ophthalmoplegia, hearing loss, cardiomyopathy, and diabetes mellitus. Although all offspring of a woman who carries a mutation would be affected, because of heteroplasmy, the severity of disease varies, depending on the percentage of mitochondria bearing the mutation that are present.

**Uniparental Disomy**

Evaluation of a child with uniparental disomy (UPD) reveals a normal karyotype. However, chromosomal markers for one particular chromosome are identical to the markers found on the chromosomes of the patient’s mother or father (but not both). In UPD, the individual inherits two copies of one parent’s chromosome and no copy from the other parent. UPD probably occurs through a few mechanisms, but the most common results from a spontaneous rescue mechanism. At the time of conception, through nondisjunction, the fertilized egg is trisomic for a particular chromosome, with two copies of one parent’s chromosome and one copy of the other parent’s chromosome; conceptuses with trisomy often miscarry early in development. Fetuses with UPD survive because they spontaneously lose one of three copies of the affected chromosome. If the single chromosome from one parent is lost, the patient has UPD.

An alternate explanation involves monosomy for a chromosome rather than trisomy. Had the conceptus, at the time of conception, inherited only a single copy of a chromosome,
spontaneous duplication of the single chromosome would lead to UPD.

Prader-Willi and Angelman Syndromes

**Prader-Willi syndrome (PWS)**, which occurs in approximately 1 in 10,000 infants, is characterized by hypotonia of prenatal onset; postnatal growth delay; a characteristic appearance, including almond-shaped eyes and small hands and feet; developmental disability; hypogonadotropic hypogonadism; and obesity after infancy. Early in life, affected infants are so hypotonic that they cannot consume enough calories to maintain their weight. Nasogastric feeding is invariably necessary, and failure to thrive is common. During the first year of life, muscle tone improves and children develop a voracious appetite. Some 60% to 70% of individuals with PWS have a small deletion of chromosome 15 (15q11). In individuals without a deletion, 20% have UPD of chromosome 15.

**Angelman syndrome (AS)** is a condition with moderate to severe mental retardation, absence of speech, ataxic movements of the arms and legs, a characteristic craniofacial appearance, and a seizure disorder that is characterized by inappropriate laughter. AS is also characterized by a deletion in the 15q11 region in 70% of affected individuals; UPD for chromosome 15 can be demonstrated in approximately 10% of AS patients.

If the deletion occurs in paternal chromosome 15, the affected individual has PWS, whereas AS results from a deletion occurring only in the maternal chromosome 15. When UPD is responsible, maternal UPD results in PWS, whereas paternal UPD results in AS. To summarize, if a copy of paternal chromosome 15q11.2 is lacking, PWS occurs; if maternal chromosome 15q11.2 is lacking, AS results.

This phenomenon is explained by genomic imprinting. Imprinting is an epigenetic phenomenon, a nonheritable change in the DNA that causes an alteration in gene expression based on parental origin of the gene. PWS is caused by deficiency of the protein product of the gene SNRPN (small nuclear ribonucleoprotein). Although present on both maternally and paternally derived chromosome 15, SNRPN is expressed only in the paternally derived chromosome. Expression is blocked in the maternal chromosome because the bases of the open reading frame are methylated; this physical change in the DNA prevents gene expression. PWS results whenever a paternal chromosome 15 is missing, either through deletion or through UPD.

AS results from a lack of expression of ubiquitin-protein ligase E3A (UBE3A), a second gene in the chromosome 15q11.2 region. UBE3A is normally expressed only in the maternally derived chromosome 15. Although present in paternal chromosome 15, UBE3A is methylated, and gene expression is blocked. Therefore, if either the critical region of maternal chromosome 15 is deleted, or paternal UPD occurs, the individual will manifest symptoms of AS.

Expansion of a Trinucleotide Repeat

More than 50% of human DNA appears as repeat sequences, two or three bases repeated over and over again. Disorders caused by expansion of trinucleotide repeats include Fragile X syndrome, Huntington disease, myotonic dystrophy, Friedreich ataxia, and the spinocerebellar ataxias. Although an increase in the number of the three repeated bases is at the heart of each disorder, the molecular mechanism differs.

**Fragile X syndrome (FRAX)**, which occurs with a frequency of approximately 1 in 2000 children, is the most common cause of inherited intellectual disability. Features include characteristic craniofacial findings (large head; prominent forehead, jaw, and ears); macro-orchidism with testicular volume twice normal in adulthood; a mild connective tissue disorder, including joint laxity, patulous eustachian tubes, and mitral valve prolapse; and a characteristic neurobehavioral profile, including intellectual disability (ranging from mild to profound) and autism spectrum disorders.

Positional cloning in the Xq27 region identified a triplet repeat region composed of one cytosine and two guanine residues (CGG). These repeats occur in the CpG island, a part of the promoter region of a gene that has been called FMR1. Unaffected individuals who have no family history of FRAX have 0 to 45 CGG repeats (most have 25 to 35). In individuals with FRAX, the number of repeats is greater than 200; such people are said to have a full mutation. Between these two categories, a third group has 56 to 200 repeats; always phenotypically normal, these individuals are premutation carriers.

FRAX results from a failure to express FMRP, the protein product of the FMR1 gene. "Fragile X Mental Retardation Protein" (FMRP) shuttles mRNA between the nucleus and cytoplasm in the central nervous system and other areas (e.g., the developing testis) during early embryonic development. Although FMRP is produced in unaffected individuals and premutation carriers, in those with the full mutation, FMRP transcription of the protein is blocked because the large number of CGG repeats in the CPG island become methylated (an epigenetic phenomenon). Thus, FRAX occurs as a consequence of a loss-of-function mutation—the failure of expression of FMRP because of methylation of the promoter sequence.

In female premutation carriers, an expansion in the number of repeats from the premutation to the full mutation range may occur during gametogenesis. The cause of this expansion is not understood. Although these females do not have symptoms and signs of FRAX, premutation carriers may manifest premature ovarian failure and/or a neurologic condition known as fragile X tremor/ataxia syndrome later in life.

**TERATOGENIC AGENTS**

Approximately 6.5% of all birth defects are attributed to teratogens—chemical, physical, or biologic agents that have the potential to damage embryonic tissue and result in congenital malformations. Agents known to be teratogenic
include drugs (prescription and nonprescription); intrauterine infections (rubella); maternal diseases, such as diabetes mellitus; and environmental substances, such as alcohol and heavy metals. Knowledge of teratogenic agents and their effect on the developing fetus is important, because limiting exposure to these agents is an effective way to prevent birth defects (see Chapters 58, 59, and 60).

**Maternal Infections**
Rubella was the first maternal infection known to cause a pattern of malformations in fetuses affected in utero. Cytomegalovirus, Toxoplasma gondii, herpes simplex, and varicella are additional potentially teratogenic in utero infections (see Chapter 66).

**Maternal Disease**
Maternal diabetes mellitus and maternal phenylketonuria can result in congenital anomalies in the fetus. Strict control of these disorders before and during pregnancy protects the developing child (see Chapter 59).

**Medications and Chemicals**
**Fetal alcohol spectrum disorder**, which occurs in 10 to 20 per 1000 children, may be the most common teratogenic syndrome. Features include prenatal and postnatal growth deficiency, developmental disabilities, microcephaly, skeletal and cardiac anomalies, and a characteristic facial appearance. To cause the full-blown fetal alcohol syndrome, pregnant women must drink alcohol throughout the pregnancy. Lesser consumption during all or part of the gestation will lead to milder symptoms. Warfarin, retinoic acid, and phenytoin are additional teratogenic agents (see Chapter 59).

**Radiation**
High-dose radiation exposure during pregnancy in Hiroshima and Nagasaki, Japan, was shown to increase the rate of spontaneous abortion and result in children born with microcephaly, mental retardation, and skeletal malformations. Estimates of exposure to cause these effects were approximately 25 rad. The dose from routine radiologic diagnostic examinations is in the millirad range.

**PRECONCEPTION AND PREGNATAL COUNSELING**

**Familial Factors**
Families with relatives affected with genetic disorders may have questions about how a disorder is inherited. The inheritance pattern and the risk of having an affected child can be discussed with a geneticist.

In some cultures, it is common for relatives to mate. This relatedness or consanguinity does not increase the likelihood of offspring having any particular single genetic disorder, but it may increase the chance that a child will be born with a rare autosomal recessive (AR) condition, as the mutated gene segregates through that family. Generally, the closer the relation between the partners, the greater the chance that the couple shares one or more mutated genes in common, increasing the risk that offspring will have an AR disorder. The risk of first cousins producing a child with an AR disorder is 1 in 64. In evaluating these couples, it is important to determine which ethnic group they belong to and to test for conditions commonly found in that group.

**Screening**
It is common for couples to be screened for disorders that may occur more commonly in their particular ethnic group. People of Ashkenazi Jewish background may choose to be screened for heterozygosity for a panel of AR disorders, including Tay-Sachs disease, Niemann-Pick disease, Bloom syndrome, Canavan disease, Gaucher syndrome, cystic fibrosis, Fanconi anemia, and familial dysautonomia. People of African-American ancestry may choose to be screened for sickle cell anemia. People whose ancestors originated in the Mediterranean basin may be screened for thalassemia.

Historically, prenatal screening involved maternal serum screening for α-fetoprotein (AFP), a protein secreted during fetal life by the liver, gastrointestinal tract, and yolk sac. Some of the AFP crosses the placenta and enters the maternal circulation. Although maternal serum screening was initially used to detect high levels of AFP associated with neural tube defects (NTDs) and the disruption of fetal integument such as omphalocele or gastroschisis, low levels of AFP were found to be associated with fetal aneuploidy. Approximately 50% of fetuses with autosomal trisomies (Down syndrome, trisomy 18, trisomy 13) will be detected by low maternal serum AFP levels. Three other proteins—unconjugated estriol (uE3), inhibin A, and human chorionic gonadotropin (HCG)—were added to the maternal serum screening to create the **quad screen**. The addition of these compounds increased the detection rate to about 80%.

The quad screen is done in the second trimester. During the first trimester, measurement of a fluid collection of the posterior neck of the developing fetus is termed nuchal translucency. An increase in the nuchal translucency is a marker for chromosomal anomalies as well as genetic and structural abnormalities in the fetus. This association provided a noninvasive first trimester marker. Once standardization of nuchal translucency measurements was done, the detection rate for aneuploidy approached 70%. Testing for abnormalities with two first trimester analytes, free β-HCG and PAPP-A (pregnancy associated plasma protein) has enhanced first trimester screening to a detection rate of almost 90%.

**GENETIC ASSESSMENT**

Individuals referred to a geneticist because of suspicion of a genetic disorder are called **probands**; individuals who come for genetic counseling are **consultands**. Referral for genetic evaluation may be made for a wide variety of reasons and at different stages of life (fetus, neonate, childhood, pregnancy).
Although the risk of nondisjunction resulting in aneuploidy rises as a woman gets older (and more so for women older than 35 years of age), all pregnant women should be individually counseled as to their risk for aneuploidy and other fetal abnormalities. A combination of first and second trimester screening together with the women's age produces an individualized risk factor. It is important to emphasize that both of these first and second trimester screening tests are just screens to identify increased risk. If this risk is high, or if there is concern about fetal anomalies from family history, ultrasound, or serum screening, then a more definitive test, either chorionic villus sampling (CVS) or amniocentesis, is offered as further testing. Fetal cells are usually tested for chromosomal abnormalities by cytogenetic techniques, but the use of chromosomal microarray is becoming more common. Biochemical testing for a known family history of an inherited metabolic disorder can also be done on the fetal cells, as well as molecular screening for familial mutations for known disorders.

Historically, serum screening has required the use of invasive testing follow-up to confirm findings. Because invasive testing carries a small but real risk of pregnancy loss, many women were not willing to submit to an amniocentesis or CVS. What has been needed is a noninvasive definitive test, one in which fetal risk is negligible. Recently, the search for such a noninvasive test has been successful.

Prenatal diagnosis using cell-free fetal DNA in maternal blood offers the ability to detect trisomies in fetuses using nothing more than a sample of the mother's blood. Although still in the research stage, this technique is being piloted in high-risk pregnancies. It is common for pregnant women to have a screening sonogram at 18 weeks' gestation. An anatomy scan is done to look for congenital anomalies. Brain, heart, kidneys, lungs, and spine are examined.

**Maternal Factors**

The presence of either acute or chronic maternal illness during pregnancy may lead to complications in the developing fetus. Chronic conditions may expose the fetus to maternal medications that are potentially teratogenic. Acute illnesses such as varicella, Lyme disease, and cytomegalovirus expose the fetus to infectious agents that may cause birth defects. Other factors, such as maternal smoking, alcohol use, and maternal exposure to radiation or chemicals, may also necessitate genetic counseling.

**Postnatal—Newborn and Infant**

Two percent to four percent of newborns have a genetic abnormality or birth defect. This broad definition of a birth defect includes not only a visible malformation but also functional defects that might not be apparent at birth.

Birth defects have a significant impact on childhood morbidity and mortality. Almost 11% of childhood deaths can be traced to a genetic cause. If contributing genetic factors related to childhood deaths are considered, this increases to almost 25%. Consultation with a geneticist for a newborn or infant may be prompted by many different findings, including the presence of a malformation, abnormal results on a routine newborn screening test, abnormalities in growth (e.g., failure to gain weight, increase in length, or abnormal head growth), developmental delay, blindness or deafness, and the knowledge of a family history of a genetic disorder or chromosomal abnormality or (as a result of prenatal testing) the presence of a genetic disorder or chromosomal abnormality in the infant.

**Adolescent and Adult**

Adolescents and adults may be seen by a geneticist for evaluation of a genetic disorder that has late onset. Some neurodegenerative disorders, such as Huntington disease and adult-onset spinal muscular atrophy, present later in life. Some forms of hereditary blindness (retinal degenerative diseases) and deafness (Usher syndrome, neurofibromatosis type 2) may not show significant symptoms until adolescence or early adulthood. Genetic consultation also may be prompted for a known family history of a hereditary cancer syndrome (breast, thyroid, colon, and ovarian cancers). Individuals may wish to have testing done to determine if they carry a mutation for these syndromes and would be at risk for developing certain types of cancers. A known family history or personal history of a genetic disorder or chromosomal abnormality might prompt testing in anticipation of pregnancy planning.

**GENERAL APPROACH TO PATIENTS**

**Family History**

A pedigree usually is drawn to help visualize various inheritance patterns. Answers to questions about the family help determine if there is an autosomal dominant, AR, X-linked, or sporadic disorder. When a child is affected with the new onset of an AD disorder, it is necessary to closely examine the parents to check for the presence of manifestations. If the parents are unaffected, the child's condition is most likely the result of a new mutation; the risk of recurrence is extremely low (although not 0, because of the possibility of gonadal mosaicism in one of the parents). When one parent is affected (even mildly so due to varying penetrance), the recurrence risk rises to 50%. With X-linked disorders, the focus is on the maternal family history to determine if there is a significant enough risk to warrant testing.

Questions about the couple's age are important to ascertain the risk related to maternal age for chromosome abnormalities and paternal age for new mutations leading to AD and X-linked disorders. A history of more than two spontaneous abortions increases the risk that one of the parents has a balanced translocation and the spontaneous abortions are due to chromosomal abnormalities in the fetus.

**Pregnancy**

During a genetic consultation, it is important to gather information about the pregnancy (see Chapters 58, 59, and 60). A maternal history of a chronic medical condition, such as a seizure disorder or diabetes, has known consequences in the fetus. Medication used in pregnancy can be teratogenic; the pregnant woman's exposure to toxic chemicals (work related) or use of alcohol, cigarettes, or drugs of abuse can have serious effects on the developing fetus. Maternal infection during pregnancy with varicella, Toxoplasma, cytomegalovirus, and parvovirus B19, among others, has been found to cause malformations in the fetus.
Follow-up is needed if an amniocentesis or CVS reveals abnormal results. A fetal ultrasound may detect a malformation that needs follow-up when the infant is born. Often hydronephrosis is detected prenatally. These infants need a repeat ultrasound soon after birth.

**Delivery and Birth**

An infant born prematurely is likely to have more complications than a term infant. An infant can be small, appropriate, or large for his or her gestational age; each of these has implications for the child (see Chapters 58, 59, and 60). In general, the finding that an infant is small for gestational age is suggestive of exposure to a teratogen or the presence of a chromosomal abnormality.

**Medical History**

Children with inborn errors of metabolism who have intermittent symptoms often have a history of multiple hospitalizations for dehydration or vomiting. Children with neuromuscular disorders may have a normal period followed by increasing weakness or ataxia. Children with lysosomal storage diseases, such as the mucopolysaccharidoses, often have recurrent ear infections and can develop sleep apnea.

**Development**

Many genetic disorders are associated with developmental disabilities. However, the onset of the disability may not always be present from the newborn period; many inborn errors of metabolism, including storage disorders, cause developmental manifestations after a period of normal development (see Chapters 7 and 8). Some adult-onset disorders have no symptoms until the teens or later. Assessing school problems is important. The type of learning problem, age at onset, and whether there is improvement with intervention or continued decline all are important for proper assessment.

**Physical Examination**

A careful and thorough physical examination is necessary for all patients with signs, symptoms, or suspicion of genetic disease. Sometimes subtle clues may lead to an unsuspected diagnosis. Features suggestive of a syndrome are discussed in more detail in Chapter 50.

**Laboratory Evaluation**

**Chromosome Analysis**

An individual's chromosomal material, known as the karyotype, can be analyzed using cells capable of dividing. In pediatrics, lymphocytes obtained from peripheral blood are the usual source for such cells, but cells obtained from bone marrow aspiration, skin biopsy (fibroblasts), or, prenatally, from amniotic fluid or chorionic villi also can be used. Cells are placed in culture medium and stimulated to grow; their division is arrested in either metaphase or prophase, slides are made, the chromosomes are stained with Giemsa or other dyes, and the chromosomes are analyzed.

In metaphase, chromosomes are short, squat, and easy to count. Metaphase analysis should be ordered in children whose features suggest a known aneuploidy syndrome, such as a trisomy or monosomy. Chromosomes analyzed in prophase are long, thin, and drawn out; analysis gives far more details than are seen in metaphase preparations. Prophase analysis is ordered in individuals with multiple congenital anomalies without an obvious disorder.

**Fluorescent In Situ Hybridization**

Fluorescent in situ hybridization (FISH) allows the identification of the presence or absence of a specific region of DNA. A complementary DNA probe specific for the region in question is generated, and a fluorescent marker is attached. The probe is incubated with cells from the subject and viewed under a microscope. The bound probe fluoresces, allowing the number of copies of the DNA segment in question to be counted. This technique is useful in Prader-Willi syndrome and Angelman syndrome, in which a deletion in a segment of 15q11.2 occurs, and in velocardiofacial (DiGeorge) syndrome, which is associated with a deletion of 22q11.2.

**Microarray Comparative Genomic Hybridization**

Microarray comparative genomic hybridization (array CGH) has supplanted prophase analysis in cases in which a subtle chromosomal deletion or duplication (copy number variant) is suspected. In array CGH, DNA from the individual being studied and a normal control is labeled with fluorescent markers and hybridized to thousands of FISH-like probes for sequences spread around the genome. The probes are derived from known genes and noncoding regions. By analyzing the ratio of intensity of the fluorescent marker at each site, it is possible to determine whether the individual in question has any difference in copy number compared with the control DNA.

**Direct DNA Analysis**

Direct DNA analysis allows identification of mutations in a growing number of genetic disorders. Using polymerase chain reaction, the specific gene in question can be amplified and analyzed. The website www.genetests.org lists disorders in which direct DNA analysis is available and identifies laboratories performing such testing.

**Errors that occur in meiosis during the production of gametes can lead to abnormalities of chromosome structure or number. Syndromes caused by chromosomal abnormalities include trisomy 21 (Down syndrome or DS), trisomy 13, trisomy 18, Turner syndrome (TS), and Klinefelter syndrome (KS), as well as rarer chromosomal duplications, deletions, or inversions.**
Chromosomal abnormalities occur in approximately 8% of fertilized ova but in only 0.6% of liveborn infants. Fifty percent of spontaneous abortuses have chromosomal abnormalities, the most common being 45,X (TS); an estimated 99% of 45,X fetuses are spontaneously aborted. The fetal loss rate for DS, the most viable of the autosomal aneuploidies, approaches 80%. Most other chromosomal abnormalities also adversely affect fetal viability. In newborns and older children, features that suggest the presence of a chromosome anomaly include low birth weight (small for gestational age), failure to thrive, developmental delay, and the presence of three or more congenital malformations.

**ABNORMALITIES IN NUMBER (ANEUPLOIDY)**

During meiosis or mitosis, failure of a chromosomal pair to separate properly results in nondisjunction. **Aneuploidy** is a change in the number of chromosomes that results from nondisjunction. A cell may have one (**monosomy**) or three (**trisomy**) copies of a particular chromosome.

### Trisomies

**Down Syndrome**

DS is the most common abnormality of chromosomal number. It occurs in 1 of every 1000 births. Most cases (92.5%) are due to nondisjunction; in 68%, the nondisjunctional event occurs in maternal meiosis phase I. As a result of nondisjunction, there are three copies of chromosome 21 (trisomy 21); using standard cytogenetic nomenclature, trisomy 21 is designated 47,XX,+21 or 47,XY,+21. In 4.5% of cases, the extra chromosome is part of a ** robertsonian translocation**, which occurs when the long arms (q) of two acrocentric chromosomes (numbers 13, 14, 15, 21, or 22) fuse at the centromeres, and the short arms (p), containing copies of ribosomal RNA, are lost. The most common robertsonian translocation leading to DS involves chromosomes 14 and 21; standard nomenclature is 46,XX,t(14q21q) or 46,XY,t(14q21q). The parents of DS infants with translocations should have a karyotype to exclude a balanced translocation.

In approximately 1% to 2% of children with DS, **mosaicism** occurs. These individuals have two populations of cells: one with trisomy 21 and one with a normal chromosome complement. Mosaicism results from a either a nondisjunctional event that occurs after fertilization and after a few cell divisions, or from **trisomic rescue**. The loss of this aneuploidy returns the cell to 46,XX or 46,XY. In either case, the individual is referred to as a mosaic for these two populations of cells and is designated 47,XX, +21/46XX or 47,XY, +21/46,XY. Although it is widely believed that individuals with mosaic DS are more mildly affected, there are wide variations in the clinical findings.

Children with DS are most likely diagnosed in the newborn period. These infants tend to have normal birth weight and length, but are hypotonic. The characteristic facial appearance, with brachycephaly, flattened occiput, hypoplastic midface, flattened nasal bridge, upslanting palpebral fissures, epicanthal folds, and large protruding tongue, is apparent at birth. Infants also have short broad hands, often with a single transverse palmar crease, and a wide gap between the first and second toes. The severe hypotonia may cause feeding problems and decreased activity.

Approximately 50% of children with DS have **congenital heart disease**, including atroventricular canal, ventriculo- or atrioseptal defects, and valvular disease. Approximately 10% of newborns with DS have **gastrointestinal tract anomalies**. The three most common defects are duodenal atresia, annular pancreas, and imperforate anus.

Four percent to 18% of infants with DS are found to have congenital hypothyroidism, which is identified as part of the newborn screening program. Acquired hypothyroidism is a more common problem. Thyroid function testing must be monitored periodically during the child’s life.

Polycythemia at birth (hematocrit levels >70%) is common and may require treatment. Some infants with DS show a leukemoid reaction, with markedly elevated white blood cell counts. Although this resembles congenital leukemia, it is a self-limited condition, resolving on its own over the first month of life. Nonetheless, children with DS also have an increased risk of **leukemia**, with a 10- to 20-fold increase in risk compared with individuals without DS. In children with DS younger than 2 year of age, the type is generally acute megakaryoblastic leukemia; in individuals older than 3 years of age, the types of leukemia are similar to those of other children, with acute lymphoblastic leukemia being the predominant type.

Children with DS are more susceptible to infection, more likely to develop cataracts, and approximately 10% have atlantoaxial instability, an increased distance between the first and second cervical vertebrae that may predispose to spinal cord injury. Many individuals older than 35 years of age develop Alzheimer-like features.

The recurrence risk for parents who have had a child with DS depends on the child’s cytogenetic findings. If the child has trisomy 21, the empiric recurrence risk is 1% (added to the age-specific risk for women up to 40 years of age; after 40, the age-specific risk alone is used for subsequent pregnancies). If the child has a robertsonian translocation, chromosomal analysis of both parents must be performed. In approximately 65% of cases, the translocation is found to have arisen de novo (i.e., spontaneously, with both parents having normal karyotypes), and in 35% of cases, one parent has a balanced translocation. The recurrence risk depends on which parent is the carrier: if the mother is the carrier, the risk is 10% to 15%; if the father is the carrier, the recurrence risk is 2% to 5%.

### Trisomy 18

Trisomy 18 (47,XX,+18 or 47,XY,+18) is the second most common autosomal trisomy, occurring in approximately 1 in 7500 live births. More than 95% of conceptuses with trisomy 18 are spontaneously aborted in the first trimester. Trisomy 18 is usually lethal; fewer than 10% of affected infants survive until their first birthday. Most infants with trisomy 18 are small for gestational age. Clinical features include hypotonia, prominent occiput, micrognathia, low-set and malformed ears, short
Trisomy 13

The third of the common trisomies, trisomy 13 (47,XX,+13 or 47,XY,+13) occurs in 1 in 12,000 live births. It is usually fatal in the first year of life; only 8.6% of infants survive beyond their first birthday.

Infants with trisomy 13 have numerous malformations (see Table 49-1). These infants are small for gestational age and microcephalic. Midline facial defects such as cyclopia (single orbit), cebocephaly (single nostril), and cleft lip and palate are common, as are midline central nervous system anomalies, such as alobar holoprosencephaly. The forehead is generally sloping, ears are often small and malformed, and microphthalmia or anophthalmia may occur. Postaxial polydactyly of the hands is common, as is clubfeet or rocker-bottom feet. Hypospadias and cryptorchidism are common in boys, whereas girls generally have hypoplasia of the labia minora. Most infants with trisomy 13 also have congenital heart disease. Many infants with this condition have a punched-out scalp lesion over the occiput called aplasia cutis congenita; when seen in conjunction with polydactyly and some or all of the facial findings, this finding is essentially pathognomonic for the diagnosis of trisomy 13.

<table>
<thead>
<tr>
<th>Head and face</th>
<th>Possible Clinical Findings in Trisomy 13 and Trisomy 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp defects (e.g., cuts, aplasia)</td>
<td>Small and premature appearance</td>
</tr>
<tr>
<td>Microphthalmia, corneal abnormalities</td>
<td>Tight palpebral fissures</td>
</tr>
<tr>
<td>Cleft lip and palate in 60%–80% of cases</td>
<td>Narrow nose and hypoplastic nasal alae</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>Narrow bifrontal diameter</td>
</tr>
<tr>
<td>Sloping forehead</td>
<td>Prominent occiput</td>
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<tr>
<td>Holoprosencephaly (arhinencephaly)</td>
<td>Micrognathia</td>
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<tr>
<td>Capillary hemangiomas</td>
<td>Cleft lip or palate</td>
</tr>
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<tr>
<th>Chest</th>
<th>Congenital heart disease (e.g., VSD, PDA, and ASD) in 80% of cases</th>
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</thead>
<tbody>
<tr>
<td>Congenital heart disease (e.g., VSD, PDA, and ASD)</td>
<td>Short sternum, small nipples</td>
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<thead>
<tr>
<th>Extremities</th>
<th>Overlapping fingers and toes (clinodactyly)</th>
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<tbody>
<tr>
<td>Polydactyly</td>
<td>Limited hip abduction</td>
</tr>
<tr>
<td>Hypoplastic nails, hyperconvex nails</td>
<td>Clinodactyly and overlapping fingers; index over third, fifth over fourth</td>
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<tr>
<th>General</th>
<th>Severe developmental delays and prenatal and postnatal growth retardation</th>
</tr>
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<tbody>
<tr>
<td>Renal abnormalities</td>
<td>Premature birth, polyhydramnios</td>
</tr>
<tr>
<td>Nuclear projections in neutrophils</td>
<td>Inguinal or abdominal hernias</td>
</tr>
<tr>
<td>Only 5% live &gt;6 mo</td>
<td>Only 5% live &gt;1 yr</td>
</tr>
</tbody>
</table>

Klinefelter Syndrome

Occurring in 1 in 500 male births, KS is the most common genetic cause of hypogonadism and infertility in men. It is caused by the presence of an extra X chromosome (47,XXY) (see Chapter 174). The extra X chromosome arises from a nondisjunction in either the sperm or the egg. About 15% of boys with features of KS are found to be mosaic, with 46,XY/47,XXY mosaicism being the most common. Before puberty, boys with KS are notypically indistinguishable from the rest of the population.

The diagnosis is often made when the boy is 15 or 16 years of age. At that point, the finding of the progressive development of pubic and axillary hair in the presence of testes that remain infantile in volume should alert the clinician to the disorder. Adolescents and young adults with KS tend to be tall, with long limbs. During adolescence or adulthood, gynecomastia occurs.

Because of failure of growth and maturation of the testes, males with KS have testosterone deficiency and failure to produce viable sperm. Low production of testicular testosterone results in failure to develop later secondary sexual characteristics, such as facial hair, deepening of the voice, and libido. In adulthood, osteopenia and osteoporosis develop. Because of these findings, testosterone supplementation is indicated.

Most men with KS are infertile because they produce few viable sperm. Through the use of isolation of viable sperm through testicular biopsy, coupled with in vitro fertilization and intracytoplasmic sperm injection, it is possible for men with KS to father children; all children born to these men using this technology have had a normal chromosome complement.

Monosomies

Turner Syndrome

TS is the only condition in which a monosomic conceptus survives to term; however, 99% of embryos with 45,X are spontaneously aborted. The most common aneuploidy found in conceptuses (accounting for 1.4%), 45,X is seen in 13% of first-trimester pregnancy losses. Occurring in 1 in 3200 live-born females, TS is notable for its spectrum of relatively mild physical and developmental findings. Affected women tend to have normal intelligence and life expectancy.

Females with TS typically have a characteristic facial appearance with low-set, mildly malformed ears, triangular face, flattened nasal bridge, and epicantial folds. There is webbing of the neck, with or without cystic hygroma, a shield-like chest with widened internipple distance, and puffiness of the hands.
and feet. Internal malformations may include congenital heart defect (in 45%, coarctation of the aorta is the most common anomaly, followed by bicuspid aortic valve; later in life, poststenotic aortic dilation with aneurysm may develop). Renal anomalies, including horseshoe kidney, are seen in more than 50% of patients. Short stature is a cardinal feature of this condition, and acquired hypothyroidism is estimated to occur five times more frequently in women with TS than in the general population.

The presence of streak gonads (gonadal dysgenesis) instead of well-developed ovaries leads to estrogen deficiency, which prevents these women from developing secondary sexual characteristics and results in amenorrhea. Although 10% of women with TS may have normal pubertal development and are even fertile, most affected women require estrogen replacement to complete secondary sexual development.

Infertility in these women is not corrected by estrogen replacement. Assisted reproductive technology using donor ova has allowed women with TS to bear children. During pregnancy, these women must be followed carefully, because poststenotic dilation of the aorta, leading to dissecting aneurysm, may occur.

Many girls with TS escape detection during the newborn period because phenotypic features are subtle. About 33% of children with TS are diagnosed during the newborn period because of the presence of heart disease and physical features; another 33% are diagnosed in childhood, often during a workup for short stature (and receive growth hormone therapy); the final 33% are diagnosed during adolescence when they fail to develop secondary sexual characteristics.

The karyotypic spectrum in girls with TS is wide. Only 30% have a 45,X karyotype; 15% have an isochromosome Xq [46,X,t(Xq)]; in which one X chromosome is represented by two copies of the long arm (leading to a trisomy of Xq and a monosomy of Xp); and approximately 25% are mosaic (45,X/46,XX or 45,X/46,XY). Deletions involving the short (p) arm of the X chromosome (Xp22) produce short stature and congenital malformations, whereas deletions of the long arm (Xq) cause gonadal dysgenesis.

Although monosomy X is caused by nondisjunction, TS is not associated with advanced maternal age. Rather, it is believed that the 45,X karyotype results from a loss of either an X or a Y chromosome after conception; that is, it is a postconceptual mitotic (rather than meiotic) nondisjunctional event.

**SYNDROMES INVOLVING CHROMOSOMAL DELETIONS**

**Cri du Chat Syndrome**

A deletion in the short arm of chromosome 5 is responsible for cri du chat syndrome, with its characteristic catlike cry during early infancy, the result of tracheal hypoplasia. Other clinical features include low birth weight and postnatal failure to thrive, hypotonia, developmental disability, microcephaly, and craniofacial dysmorphism, including ocular hypertelorism, epicanthic folds, downward obliquity of the palpebral fissures, and low-set malformed ears. Clefts of the lip and palate, congenital heart disease, and other malformations may be seen.

The clinical severity of cri du chat syndrome depends on the size of the chromosomal deletion. Larger deletions are associated with more severe expression. Most cases arise de novo; the deletion is usually in the chromosome 5 inherited from the father.

**Williams Syndrome**

Williams syndrome is due to a small deletion of chromosome 7q11.2. Congenital heart disease is seen in 80% of affected children, with supravalvular aortic-valve and pulmonic-valve stenosis and peripheral pulmonic stenosis being the most common anomalies. Although these children often have normal birth weight, they have growth delay, manifesting short stature. They have a distinctive facial appearance (“elfin facies”), with median flare of the eyebrows, fullness of the perioral and periorbital region, blue irides with a stellate pattern of pigment, and depressed nasal bridge with anteverision of the nares. Moderate intellectual disability (average IQ in the 50 to 60 range) is common, but developmental testing reveals strength in personal social skills and deficiencies in cognitive areas. Hypercalcemia is present in neonates.

Individuals with Williams syndrome often have a striking personality. Loquacious and gregarious, they are frequently described as having a cocktail party personality. However, approximately 10% of children with Williams syndrome have features of autism spectrum disorder. Patients occasionally have unusual musical ability (about 20% have absolute or perfect pitch). Most children with Williams syndrome have a de novo deletion. In rare cases, the deletion is inherited from a parent in an autosomal dominant pattern.

**Aniridia Wilms Tumor Association**

WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) is caused by a deletion of 11p13 and is generally a de novo deletion. Genitourinary abnormalities include cryptorchidism and hypospadias. Patients often have short stature, and half may have microcephaly. Wilms tumor develops in 50% of patients with aniridia, genitourinary abnormalities, and mental retardation (see Chapter 159).

**Prader-Willi Syndrome**

SEE CHAPTER 47.

**Angelman Syndrome**

SEE CHAPTER 47.

**Chromosome 22q11.2 Deletion Syndromes**

Deletions of chromosome 22q11.2 are responsible for a group of findings that have been called by several names, including velocardiofacial syndrome, conotruncal anomaly face syndrome, Shprintzen syndrome, and DiGeorge syndrome.
These conditions represent a continuum of findings, virtually all of which are due to the chromosomal deletion.

Although chromosome 22q11.2 deletions can be inherited in an autosomal dominant fashion, most cases arise de novo. Common features include clefting of the palate with velopharyngeal insufficiency; conotruncal cardiac defects (including truncus arteriosus, ventriculoaseptal defect, tetralogy of Fallot, and right-sided aortic arch); and a characteristic facial appearance, including a prominent nose and a broad nasal root. Speech and language difficulties are common, as is mild intellectual impairment. More than 200 additional abnormalities have been identified in individuals with these conditions. About 70% have immunodeficiencies, largely related to T-cell dysfunction. A wide spectrum of psychiatric disturbances, including schizophrenia and bipolar disorder, has been seen in more than 33% of affected adults.

Damage to the third and fourth pharyngeal pouches, embryonic structures that form parts of the cranial portion of the developing embryo, leads to abnormalities in the developing face (clefting of the palate, micrognathia), the thymus gland, the parathyroid glands, and the conotruncal region of the heart. This spectrum of findings, called the DiGeorge malformation sequence, is an important chromosome 22 deletion syndrome.

The deletion that occurs in chromosome 22q11 is usually too small to be seen by standard chromosome analysis; either fluorescent in situ hybridization or chromosomal microarray is needed to identify the deletion. A gene called TBX1 is within the deleted sequence. It is believed that deletion of one copy of TBX1 is responsible for many of the features of the various 22q11 deletion syndromes.

**SYNDROMES INVOLVING CHROMOSOME DUPLICATION**

Duplications and deletions occur secondary to misalignment and unequal crossing over during meiosis. Small extra chromosomes are found in a small percentage of the population (0.06%). These “marker” chromosomes sometimes are associated with mental retardation and other abnormalities, and other times they have no apparent phenotypic effects.

**Inverted Duplication Chromosome 15**

Chromosome 15 is the most common of all marker chromosomes, and its inverted duplication accounts for almost 40% of this group of chromosomal abnormalities. Features seen in children with 47,XX,+inv dup (15q) or 47,XY,inv dup(15q) depend on the size of the extra chromosomal material present: the larger the region, the worse the prognosis. Children with this disorder tend to have a variable degree of developmental disability and autism spectrum disorders; seizures are common, as are behavior problems. The phenotype shows minimal dysmorphic features, with a sloping forehead, short and downward-slanting palpebral fissures, a prominent nose with a broad nasal bridge, a long and well-defined philtrum, a midline crease in the lower lip, and micrognathia.

**Cat Eye Syndrome**

Named for the iris coloboma that gives patients’ eyes a catlike appearance, cat eye syndrome is due to a small, supernumerary chromosome with an inversion duplication of 22q11. The two copies of 22q11 on this extra chromosome plus the two normal copies of chromosome 22 result in four copies of this region. Although the colobomas name the syndrome, they occur in fewer than 50% of individuals with the marker chromosome. Other clinical features include mild mental retardation, behavioral disturbances, mild ocular hypertelorism, downward-slanting palpebral fissures, micrognathia, auricular pits and/or tags, anal atresia with rectovestibular fistula, and renal agenesis.

**THE APPROACH TO THE DYSMORPHIC CHILD**

Dysmorphology is the recognition of the pattern of congenital malformations (often multiple congenital malformations) and dysmorphic features that characterize a particular syndrome. Syndromes are collections of abnormalities, including malformations, deformations, dysmorphic features, and abnormal behaviors that have a unifying, identifiable etiology. This etiology may be the presence of a mutation in a single gene, as is the case in Rett syndrome, a disorder that is caused by a mutation in the MECP2 gene on Xq28; by the deletion or duplication of chromosomal material, as is the case in Prader-Willi syndrome, which is caused by the deletion of the paternal copy of the imprinted SNRPN gene on chromosome 15q11.2; or by exposure to a teratogenic substance during embryonic development, as in fetal alcohol spectrum disorder.

**DEFINITIONS**

Congenital malformations are defined as clinically significant abnormalities in either form or function. They result from localized intrinsic defects in morphogenesis, which were caused by an event that occurred in embryonic or early fetal life. This event may have been a disturbance of development from some unknown cause, but often mutations in developmental genes led to the abnormality. Extrinsic factors may cause disruptions of development by disturbing the development of apparently normal tissues. These disruptions may include amniotic bands, disruption of blood supply to developing tissues, or exposure to teratogens. A malformation sequence is the end result of a malformation that has secondary effects on later developmental events. An example is the Pierre Robin sequence. The primary malformation, failure of the growth of the mandible during the first weeks of gestation, results in micrognathia, which forces the normal-sized tongue into an unusual position. The abnormally placed tongue blocks the fusion of the palatal shelves, which normally come together in the midline to produce the hard and soft palate; this leads to the presence of a U-shaped cleft palate. After delivery, the normal-sized tongue in the smaller than normal oral cavity leads to airway obstruction, a potentially life-threatening
complication. Pierre Robin sequence comprises a triad of anomalies (micrognathia, U-shaped cleft palate, and obstructive apnea) which results from a single malformation, the failure of the jaw to grow at a critical time during gestation. Many children with Pierre Robin syndrome have Stickler syndrome, an autosomal dominant disorder caused by mutations in collagen genes. Stickler syndrome also manifests with ocular and musculoskeletal abnormalities.

Deformations arise as a result of environmental forces acting on normal structures. They occur later in pregnancy or after delivery. For instance, plagiocephaly (rhomboid shaped head) may result from intrauterine positioning or from torticollis experienced in the newborn period. Deformations often resolve with minimal intervention, but malformations often require surgical and medical management.

Minor malformations, variants of normal that occur in less than 3% of the population, include findings such as single transverse palmar creases, low-set ears, or hypertelorism; when isolated, they have no clinical significance. A multiple malformation syndrome is the recognizable pattern of anomalies that results from a single identifiable underlying cause. It may involve a series of malformations, malformation sequences, and deformations. These syndromes often prompt a consultation with a clinical geneticist. Dysmorphology is the specialty focusing on recognition of patterns of malformations that occur in syndromes (Table 50-1).

An association differs from a syndrome in that in the former, no single underlying etiology explains the recognizable pattern of anomalies that occur together more often than would be expected by chance alone. The VACTERL association (vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb anomalies) is an example of a group of malformations that occur more commonly together than might be expected by chance. No single unifying etiology explains this condition, so it is considered an association.

In approximately 50% of children noted to have one or more congenital malformations, only a single malformation is identifiable; in the other 50%, multiple malformations are present. About 6% of infants with congenital malformations have chromosomal defects, 7.5% have a single gene disorder, 20% have conditions that are due to multifactorial effects (an interplay between genetic and environmental factors), and approximately 7% are due to exposure to a teratogen. In more than 50% of cases, no cause can be identified.

### HISTORY AND PHYSICAL EXAMINATION

#### Pregnancy History

The history of the pregnancy and birth can reveal multiple risk factors that are associated with dysmorphology. Small for gestational age infants may have a chromosome anomaly or may have been exposed to a teratogen. Large for gestational age infants may be infants of diabetic mothers or have an overgrowth syndrome, such as Beckwith-Wiedemann syndrome. When evaluating an older child with intellectual disabilities, complications of extreme prematurity may account for the child’s problems. Postmaturity also is associated with some chromosome anomalies (e.g., trisomy 18) and anencephaly. Infants born from breech presentation are more likely to have congenital malformations.

As a woman gets older there is increased risk of nondisjunction leading to trisomies. Advanced paternal age may be associated with the risk of a new mutation leading to an autosomal dominant trait. Maternal medical problems and exposures (medications, drugs, cigarette smoking, and alcohol use) are associated with malformations (see Chapters 47 and 48).

An increased amount of amniotic fluid may be associated with intestinal obstruction or a central nervous system anomaly that leads to poor swallowing. A decreased amount of fluid may be the result of a chronic amniotic fluid leak or point to a urinary tract abnormality that results in a failure to produce urine.

#### Family History

A pedigree comprising at least three generations should be constructed, searching for similar or dissimilar abnormalities in first- and second-degree relatives. A history of pregnancy...
or neonatal losses should be documented. For a more detailed discussion of pedigrees, see Chapter 47.

Physical Examination
When examining children with dysmorphic features, the following approach should be used.

Growth
The height (length), weight, and head circumference should be measured carefully and plotted on appropriate growth curves. Small size or growth restriction may be secondary to a chromosomal abnormality, skeletal dysplasia, or exposure to toxic or teratogenic agents. Larger than expected size suggests an overgrowth syndrome (Sotos or Beckwith-Wiedemann syndrome) or, in the newborn period, might suggest a diabetic mother.

The clinician should note if the child is proportionate. Limbs that are too short for the head and trunk imply the presence of a short-limbed bone dysplasia, such as achondroplasia. A trunk and head that are too short for the extremities suggest a disorder affecting the vertebrae, such as spondyloepiphyseal dysplasia.

Craniofacial
Careful examination of the head and face is crucial for the diagnosis of many congenital malformation syndromes. Head shape should be carefully assessed; if the head is not normal in size and shape (normocephalic), it may be long and thin (dolichocephalic), short and wide (brachycephalic), or asymmetric or lopsided (plagiocephalic).

Any asymmetry of facial features should be noted. Asymmetry may be due to a deformation related to intrauterine position or a malformation of one side of the face. The face should be divided into four regions, which are evaluated separately. The forehead may show overt prominence (achondroplasia) or deficiency (often described as a sloping appearance, which occurs in children with primary microcephaly). The midface, extending from the eyebrows to the upper lip and from the outer canthi of the eyes to the commissures of the mouth, is especially important. Careful assessment of the distance between the eyes (inner canthal distance) and the pupils (interpupillary distance) may confirm the impression of hypotelorism (eyes that are too close together), which suggests a defect in midline brain formation, or hypertelorism (eyes that are too far apart). The length of the palpebral fissure should be noted and may help define whether the opening for the eye is short, as is found with fetal alcohol syndrome, or excessively long, as in Kabuki makeup syndrome (short stature, mental retardation, long palpebral fissures with syndrome, or excessively long, as in Kabuki makeup syndrome—should be noted.

The malar region of the face is examined next. It extends from the ear to the midface. The ears should be checked for size (measured and checked against appropriate growth charts), shape, position (low-set ears are below a line drawn from the outer canthus to the occiput), and orientation (posterior rotation is where the ear appears turned toward the rear of the head). Ears may be low set because they are small (or microtic) or because of a malformation of the mandibular region.

The mandibular region is the area from the lower portion of the ears bounded out to the chin by the mandible. In most newborns, the chin is often slightly retruded (that is, slightly behind the vertical line extending from the forehead to the philtrum). If this retrusion is pronounced, the child may have the Pierre Robin malformation sequence. In addition, the mouth should be examined. The number and appearance of the teeth should be noted, the tongue should be observed for abnormalities, and the palate and uvula checked for defects.

Neck
Examination of the neck may reveal webbing, a common feature in Turner syndrome and Noonan syndrome, or shortening, as is seen occasionally in some skeletal dysplasias and in conditions in which anomalies of the cervical spine occur, such as Klippel-Feil syndrome. The position of the posterior hairline also should be evaluated. The size of the thyroid gland should be assessed.

Trunk
The chest may be examined for shape (shield-like chest in Noonan syndrome and Turner syndrome) and for symmetry. The presence of a pectus deformity should be noted and is common in Marfan syndrome. The presence of scoliosis should be assessed; it is common in Marfan syndrome and many other syndromes.

Extremities
Many congenital malformation syndromes are associated with anomalies of the extremities. All joints should be examined for range of motion. The presence of single or multiple joint contractures suggests either intrinsic neuromuscular dysfunction, as in some forms of muscular dystrophy, or external deforming forces that limited motion of the joint in utero. Multiple contractures also are found with arthrogryposis multiplex congenita and are due to a variety of causes. Radial or ulnar synostosis, an inability to pronate or supinate the elbow, occurs in fetal alcohol spectrum disorder and in some X chromosome aneuploidy syndromes.

Examination of the hands is important. Polydactyly (the presence of extra digits) usually occurs as an isolated autosomal dominant trait but also can be seen in trisomy 13. Oligodactyly (a deficiency in the number of digits) is seen in Fanconi syndrome (anemia, leukopenia, thrombocytopenia, and associated heart, renal, and limb anomalies—usually radial aplasia and thumb malformation or aplasia), in which it is generally part of a more severe limb reduction defect, or secondary to intrauterine amputation, which may occur with amniotic band disruption sequence. Syndactyly (a joining of
two or more digits) is common to many syndromes, including Smith-Lemli-Opitz syndrome (see Chapters 199 and 201).

Dermatoglyphics include palmar crease patterns. A transverse palmar crease, indicative of hypotonia during early fetal life, is seen in approximately 50% of children with Down syndrome (and 10% of individuals in the general population). A characteristic palmar crease pattern is also seen in fetal alcohol spectrum disorder.

Genitalia

Genitalia should be examined closely for abnormalities in structure. In boys, if the penis appears short, it should be measured and compared with known age-related data. Ambiguous genitalia often are associated with endocrinologic disorders, such as congenital adrenal hyperplasia (girls have masculinized external genitalia, but male genitalia may be unaffected), or chromosomal disorders such as 45,X/46,XY mosaicism or possibly secondary to a multiple congenital anomaly syndrome (see Chapters 174 and 177). Although hypospadias, which occurs in 1 in 300 newborn boys, is a common congenital malformation that often occurs as an isolated defect, if it is associated with other anomalies, especially cryptorchidism, there is a strong possibility of a syndrome.

LABORATORY EVALUATION

Chromosome analysis should be ordered for children with multiple congenital anomalies, the involvement of one major organ system and the presence of multiple dysmorphic features, or the presence of mental retardation. In recent years, microarray comparative genomic hybridization has supplanted routine or high-resolution chromosome analysis in most situations. For a complete discussion of chromosome analysis, see Chapter 48.

Direct DNA analysis can be performed to identify specific mutations. It is necessary to use Web-based resources to keep up-to-date. An extremely helpful website is www.genetests.org, which provides information about the availability of testing for specific conditions and identifies laboratories performing the testing.

Radiologic imaging plays an important role in the evaluation of children with dysmorphic features. Individuals found to have multiple external malformations should have a careful evaluation to search for the presence of internal malformations. Testing might include ultrasound evaluations of the head and abdomen to look for anomalies in the brain, kidney, bladder, liver, and spleen. Skeletal radiographs should be performed if there is concern about a possible skeletal dysplasia. The presence of a heart murmur should trigger a cardiology consultation; an electrocardiogram and echocardiogram may be indicated. Magnetic resonance imaging may be indicated in children with neurologic abnormalities or a spinal defect. The presence of craniosynostosis may indicate a computed tomography scan of the head.

For those patients for whom testing does not yield a diagnosis, whole-exome sequencing or whole-genome sequencing is becoming a powerful tool.

DIAGNOSIS

Although the presence of characteristic findings may make the diagnosis of a malformation syndrome straightforward, in most cases no specific diagnosis is immediately evident. Some constellations of findings are rare, and finding a “match” may prove difficult. In many cases, all laboratory tests are normal, and confirmation relies on subjective findings. Clinical geneticists have attempted to resolve this difficulty by developing scoring systems, cross-referenced tables of anomalies that help in the development of a differential diagnosis, and computerized diagnostic programs. An accurate diagnosis is important for the following reasons:

1. It offers an explanation to the family why their child was born with congenital anomalies. This may help allay guilt for parents, who often believe they are responsible for their child’s problem.
2. With well-described natural histories of many disorders, a diagnosis allows anticipation of medical problems associated with a particular syndrome and appropriate screening. It also provides reassurance that other medical problems are no more likely to occur than they might with other children who do not have the diagnosis.
3. It permits genetic counseling to be done to identify the risk to future children and permits prenatal testing to be done for the disorders for which it is available.

Diagnosis enables the clinician to provide the family with educational materials about the diagnosis and facilitate contact with support groups for particular disorders. The Internet has become an important source for such information. Care should be exercised, as information on the Internet is not subject to editorial control and may be inaccurate. A good site is the National Organization for Rare Disorders (www.rarediseases.org), a clearinghouse for information about rare diseases and their support groups. Genetic testing information is available at the Genetests website (www.genetests.org). This site provides information on available clinical and research testing for many diseases.

Suggested Reading

Optimal outcomes for children with inborn errors of metabolism (IEMs) depend upon recognition of the signs and symptoms of metabolic disease, and prompt evaluation and referral to a center familiar with their management. Delay in diagnosis may result in end organ damage including progressive neurologic injury or death.

With the exception of phenylketonuria (PKU), and medium chain acyl-CoA dehydrogenase (MCAD) deficiency, most metabolic disorders are individually rare, having an incidence of less than 1 per 100,000 births in the United States. When considered collectively, the incidence may approach 1 in 800 to 2500 births (Table 51-1) with the prevalence of a confirmed metabolic disorder detected by newborn screening in 1 in 4000 live births (about 12,500 diagnoses each year) in the United States. This is comparable with the 1 in 1000 infants who have early-onset bacterial sepsis and the 1 in 3000 infants who have invasive group B streptococcal infections.

IEMs are frequent causes of sepsis-like presentations, mental retardation, seizures, sudden infant death, and neurologic impairment; 20% of admissions to a regional children’s hospital are for genetic disorders.

Metabolic disorders can be classified using a variety of schemes based on the clinical presentation, including the age of onset, the tissues or organ systems involved, the defective metabolic pathways, or the subcellular localization of the underlying defect. These classification schemes have differing utility when considering approach to diagnosis, management, and screening strategies. The clinical presentation and long-term prognosis have the most bearing on management of children with genetic metabolic disorders.

Genetic metabolic disorders result from the deficiency of an enzyme, its cofactors, or biochemical transporters that lead to the deficiency of a required metabolite, the buildup of a toxic compound, or a combination of both processes (Fig. 51-1, Table 51-2). Understanding which of these mechanisms is involved and if the effects are systemic or restricted to the local tissue enables a rational approach to diagnosis, therapy, and management.

The signs and symptoms of an inborn error are diverse and can involve any organ system. The presentation varies among age groups. Inborn errors of metabolism often present a few hours to weeks after birth, often mimicking late-onset sepsis. Infants who survive the neonatal period without developing recognized symptoms often experience intermittent illness separated by periods of being well. While pursuing the evaluation of the specific clinical presentations (e.g., the approach to the sick newborn, irritable child, or child with liver dysfunction), the hypoglycemic and intoxicating (encephalopathy) metabolic disorders should be considered in all neonates presenting with lethargy, poor tone, poor feeding, hypothermia, irritability, or seizures. In most cases these should be evaluated for by assessment of plasma ammonia, blood glucose, and anion gap (Fig. 51-2). Significant ketosis in the neonate is unusual and suggests

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**Table 51-1**

| Disorders Diagnosed or Followed at Specialized Clinics per 100,000 Population |
|-----------------------------|-----------------------------|
| Amino acid disorders         | 7.5                         | 19                        |
| (excluding phenylketonuria)  |                             |                           |
| Lysosomal storage diseases   | 7.5                         | 19                        |
| Phenylketonuria              | 7.5                         | 8                         |
| Organic acidemias            | 4                           | 12.5                      |
| Peroxisomal disorders        | 3.5                         | 7.5                       |
| Mitochondrial diseases       | 3                           | 20                        |
| Glycogen storage diseases    | 2                           | 7                         |
| Urea cycle diseases          | 2                           | 4.5                       |

*Populations in British Columbia, Canada (a predominantly white population), between 1969 and 1996, and in the West Midlands of the United Kingdom (which has a diverse ethnic breakdown) between 1999 and 2003.
an organic acid disorder. Similarly specific metabolic disorders predispose to cardiomyopathy, myopathy, hepatopathy, developmental delay, sepsis and developmental regression; appropriate evaluation should be tailored to the clinical presentation.

Introduction of new foods or metabolic stress associated with fasting or fever may unmask an inborn error of metabolism during infancy or in older children. The introduction of fructose or sucrose in the diet may lead to decompensation in hereditary fructose intolerance. In older children, increased protein intake may unmask disorders of ammonia detoxification.

**TYPES OF CLINICAL PRESENTATION OF INBORN ERRORS**

**Toxic Presentation**

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>DEFICIENCY OF A REQUIRED COMPOUND</th>
<th>ACCUMULATION OF TOXIC COMPOUND</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOGLYCEMIC DISORDERS</td>
<td>Fat for energy</td>
<td>Long-chain fats</td>
<td>Use of glucose with consequent hypoglycemia; mitochondrial dysfunction in liver, heart, etc., leading to organ dysfunction</td>
</tr>
<tr>
<td></td>
<td>Glucose to prevent fasting hypoglycemia</td>
<td>Glycogen resulting in storage in liver, muscle, heart</td>
<td>Risk of hypoglycemic brain injury and storage tissue dysfunction</td>
</tr>
<tr>
<td>INTOXICATING DISORDERS (ENCEPHALOPATHY)</td>
<td>Ketones</td>
<td>Risk of hypoglycemic brain injury; profound metabolic acidosis and reversible neurologic dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galactose</td>
<td>Elevated galactose leads to severe hepatic dysfunction, neurologic injury, and impaired immune response</td>
<td></td>
</tr>
<tr>
<td>CELLULAR COMPARTMENT DISORDERS</td>
<td>Leucine</td>
<td>Leucine toxicity leading to cerebral edema</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>Deficiency of ATP (energy) in affected tissues</td>
<td>Failure of affected tissues to carry out normal functions, e.g., muscle weakness, failure of relaxation of blood vessel muscles</td>
<td></td>
</tr>
<tr>
<td>Peroxisomal disorders</td>
<td>Deficiency of VLCFA and steroid hormones necessary for signaling</td>
<td>Aberrant embryonic patterning and hormone deficiency, defects in maintenance of myelin and white matter</td>
<td></td>
</tr>
<tr>
<td>Lysosomal storage disorders</td>
<td>Tissue-specific accumulation of compound not metabolized by lysosome</td>
<td>Cell type–specific damage and dysfunction as a result of lysosomal failure and reaction to waste product buildup</td>
<td></td>
</tr>
<tr>
<td>OTHER</td>
<td>Deficiency of cerebral creatine</td>
<td>Accumulation of guanidinoacetate in AGAT deficiency leads to seizures</td>
<td>Global brain energy defect leads to severe cognitive delays</td>
</tr>
<tr>
<td>Disorders of creatine biosynthesis</td>
<td>Deficiency of steroid hormones</td>
<td>Endocrinopathies; disordered cellular signaling</td>
<td></td>
</tr>
</tbody>
</table>
Hyperammonemia in infants

- Prematurity, respiratory distress early onset
- Possible inborn error of metabolism

Transient hyperammonemia

Metabolic acidosis
- Ketosis
- Organic aciduria

Lactic acidosis
- PDH
- PC – pyruvate dehydrogenase deficiency
- Mitochondrial disorders

Organic aciduria
- Propionic acidemia
- Methylmalonic acidemia
- Isovaleric acidemia
- Multiple carboxylase deficiency
- Glutaric acidemia
- 3-Methyl-3-OH-glutarlyl-CoA lyase deficiency

Fatty acid oxidation defects
- Short, medium and long chain acyl-CoA dehydrogenase deficiencies
- Carnitine disorders

No acidosis or ketosis
- Respiratory alkalosis
- Low BUN

Urea cycle detects
- Plasma citrulline

Marked elevation
- Citrullinemia

Elevated with ASA in plasma, urine
- Argininosuccinic aciduria

Absent, trace
- Urine orotic acid

Elevated
- OTC deficiency
- CPS or NAGS deficiency

Normal or reduced
- Plasma arginine

Elevated urine lysine, ornithine, arginine

Normal, low
- Elevated plasma ornithine, urine homocitrulline

Elevated plasma
- Lysinuric protein intolerance
- Hyperornithinemia, hyperammonemia, homocitrullinuria syndrome

Figure 51-2 Algorithm for the approach to hyperammonemia infants. ASA, Argininosuccinic acid; BUN, blood urea nitrogen; CPS, carbamylphosphate synthase; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase; PC, pyruvate carboxylase deficiency; PDH, pyruvate dehydrogenase deficiency.
The toxic presentation often presents as an encephalopathy. Fever, infection, fasting, or other catabolic stresses may precipitate the symptom complex. A metabolic acidosis, vomiting, lethargy, and other neurologic findings may be present. Diagnostic testing is most effective when metabolites are present in highest concentration in blood and urine at presentation. Abnormal metabolism of amino acids, organic acids, ammonia, or carbohydrates may be at fault. Hyperammonemia is an important diagnostic possibility if an infant or child presents with features of toxic encephalopathy (see Fig. 51-2). Symptoms and signs depend on the underlying cause of the hyperammonemia, the age at which it develops, and its degree. The severity of hyperammonemia may provide a clue to the etiology (Tables 51-3 and 51-4).

Severe Neonatal Hyperammonemia

Infants with genetic defects in urea synthesis, transient neonatal hyperammonemia, and impaired synthesis of urea and glutamine secondary to genetic disorders of organic acid metabolism can have levels of blood ammonia (>1000 μmol/L) more than 10 times normal in the neonatal period. Poor feeding, hypotonia, apnea, hypothermia, and vomiting rapidly give way to coma and occasionally to intractable seizures. Respiratory alkalosis is common. Death occurs in hours to days if the condition remains untreated.

Moderate Neonatal Hyperammonemia

Moderate neonatal hyperammonemia (range, 200 to 400 μmol/L) is associated with depression of the central nervous system, poor feeding, and vomiting. Seizures are not characteristic. Respiratory alkalosis may occur. This type of hyperammonemia may be caused by partial or more distal blocks in urea synthesis and commonly is caused by disorders of organic acid metabolism (producing a metabolic acidosis) that secondarily interfere with the elimination of nitrogen.

Clinical Hyperammonemia in Later Infancy and Childhood

Infants who are affected by defects in the urea cycle may continue to do well while receiving the low-protein intake of breast milk, developing clinical hyperammonemia when dietary protein is increased or when catabolic stress occurs. Vomiting and lethargy may progress to coma. Seizures are not typical. During a crisis, the plasma ammonia level is usually 200 to 500 μmol/L. However, as the ammonia level decreases with decreased protein intake, the condition may go unrecognized for years, especially in the absence of central nervous system symptoms. If a crisis occurs during an epidemic of influenza, the child mistakenly may be thought to have Reye syndrome.

### Table 51-3

<table>
<thead>
<tr>
<th>GENERALIZED SEIZURES</th>
<th>ENCEPHALOPATHIC COMA WITH OR WITHOUT SEIZURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>All disorders that cause hypoglycemia:</td>
<td>Mitochondrial disease:</td>
</tr>
<tr>
<td>Most hepatic glycogen storage diseases</td>
<td>POLG deficiency</td>
</tr>
<tr>
<td>Galactosemia, hereditary fructose intolerance</td>
<td>Iron-sulfur cluster disease</td>
</tr>
<tr>
<td>Fructose-1,6-bisphosphatase deficiency</td>
<td>Maple syrup urine disease</td>
</tr>
<tr>
<td>Disorders of fatty acid beta oxidation</td>
<td>Nonketotic hyperglycinemia</td>
</tr>
<tr>
<td>Glucose transporter deficiency</td>
<td>Diseases producing extreme hyperammonemia:</td>
</tr>
<tr>
<td>Disorders of the propionate pathway</td>
<td>Disorders of the urea cycle</td>
</tr>
<tr>
<td>HMG-CoA lyase deficiency</td>
<td>Disorders of the propionate pathway</td>
</tr>
<tr>
<td>Menkes disease</td>
<td>Disorders of beta oxidation</td>
</tr>
<tr>
<td>Pyruvate carboxylase deficiency (PCD)</td>
<td>Congenital lactic acidosis (PCD)</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td></td>
</tr>
</tbody>
</table>

**SEIZURES AND/OR POSTURING**

- Nonketotic hyperglycinemia
- Maple syrup urine disease

### Table 51-4

<table>
<thead>
<tr>
<th>ETIOLOGY OF HYPERAMMONEMIA</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorders of the urea cycle</td>
<td>Lethal hyperammonemia is common</td>
</tr>
<tr>
<td>Disorders of the propionate pathway</td>
<td>Severe hyperammonemia may precede acidosis</td>
</tr>
<tr>
<td>Disorders of fatty acid catabolism and of ketogenesis</td>
<td>Reye-like syndrome possible</td>
</tr>
<tr>
<td>Transient neonatal hyperammonemia</td>
<td>Idiopathic, self-limited</td>
</tr>
<tr>
<td>Portal-systemic shunting</td>
<td>Thrombosis of portal vein, cirrhosis, hepatitis</td>
</tr>
<tr>
<td>Mitochondrial DNA depletion</td>
<td>Typically associated with elevated lactate level</td>
</tr>
<tr>
<td>Drug intoxication: salicylate, valproic acid, acetaminophen</td>
<td>Obtain drug levels</td>
</tr>
<tr>
<td>Hyperinsulinism/hyperammonemia syndrome</td>
<td>Clinical hypoglycemia, subclinical hyperammonemia</td>
</tr>
<tr>
<td>Non-metabolic liver disease including infections such as herpes, cytomegalovirus</td>
<td>Ensure evaluation of hepatic function and appropriate infectious disease workup</td>
</tr>
</tbody>
</table>

**HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA.**
Older children may have neuropsychiatric or behavioral abnormalities (see Fig. 51-2).

**Specific Organ Presentation**

Any organ or system can be injured by toxic accumulation of any of the metabolites involved in inborn errors. Symptoms relate to organ-specific or system-specific toxicity and injury. Examples include nervous system (seizures, coma, ataxia), liver (hepatocellular damage), eye (cataracts, dislocated lenses), renal (tubular dysfunction, cysts), and heart (cardiomyopathy, pericardial effusion) (Table 51-5).

**Energy Deficiency**

Disorders whose pathophysiology results in energy deficiency (e.g., disorders of fatty acid oxidation, mitochondrial function/oxidative phosphorylation, or carbohydrate metabolism) may manifest myopathy; central nervous system dysfunction, including mental retardation and seizures; cardiomyopathy; vomiting; hypoglycemia; or renal tubular acidosis.

**Ketosis and Ketotic Hypoglycemia**

Acidosis is often found in children without metabolic diseases and may be due to fasting associated with anorexia, vomiting, diarrhea, and dehydration in the course of a viral illness. In this normal result of fasting, the blood glucose is relatively low; a mild acidosis and ketonuria may be present. Administration of carbohydrate restores balance. Severe ketosis may also be the result of disorders of ketone utilization such as ketothiolase deficiency or SCOT (succinyl-CoA:3 ketoacid CoA transferase) deficiency. In these conditions, which frequently present in the context of fasting, infection with fever, or decreased intake secondary to vomiting and diarrhea, hypoglycemia may be profound; the ketosis resolves slowly. As ketone bodies accumulate, cyclic vomiting may ensue. Ketotic hypoglycemia is a common condition in which tolerance for fasting is impaired. Symptomatic hypoglycemia with seizures or coma occurs when the child encounters a catabolic stress. The stress may be significant (viral infection with vomiting) or minor (a prolongation by several hours of the normal overnight fast). Ketotic hypoglycemia first appears in the second year of life and occurs in otherwise healthy children. It is treated by frequent snacks and the provision of glucose during periods of stress. The pathophysiology is poorly understood (see Chapter 172). Although ketonuria is a normal response to prolonged (not overnight) fasting in older infants and children, it indicates metabolic disease in neonates. A high anion gap metabolic acidosis with or without ketosis suggests a metabolic disorder (Table 51-6). Although ketone production may be reduced in some fatty acid oxidation disorders, the presence of ketonuria does not exclude this group of disorders.

**Disorders Associated with Dysmorphic Findings**

Congenital malformations or dysmorphic features are not intuitively thought of as symptoms and signs of inborn errors. Conditions that cause congenital malformations include carbohydrate-deficient glycoprotein syndrome, disorders of cholesterol biosynthesis (Smith-Lemli-Opitz syndrome), disorders of copper transport (Menkes syndrome, occipital horn syndrome), maternal phenylketonuria syndrome, glutaric aciduria II (also called multiple acyl-coenzyme A [CoA] dehydrogenase deficiency), and several storage diseases.

**Storage Disorders**

Storage disorders are caused by accumulation of incompletely metabolized macromolecules. This storage often occurs in subcellular organelles, such as lysosomes. The glycogen storage diseases and mucopolysaccharide disorders are examples of storage disorders.

<table>
<thead>
<tr>
<th>Table 51-5</th>
<th>Inborn Errors of Metabolism Presenting with Hepatomegaly or Hepatic Dysfunction in Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEPATOMEGALY</td>
<td>HEPATIC FAILURE</td>
</tr>
<tr>
<td>GSD I</td>
<td>Citrin deficiency</td>
</tr>
<tr>
<td></td>
<td>Galactosemia</td>
</tr>
<tr>
<td>GSD III</td>
<td>Hereditary fructose intolerance</td>
</tr>
<tr>
<td>Mucopolysaccharidosis I and II</td>
<td>Tyrosinemia type 1 (fumarylacetoacetate hydratase deficiency)</td>
</tr>
<tr>
<td>Gaucher and Niemann-Pick diseases</td>
<td>GSD IV (slowly evolving)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GSD, Glycogen storage disease.
lack of appropriate ketosis
hypoglycemia, ketosis (or metabolic emergency often presents with vomiting, acidosis, or laboratory findings demands urgent metabolic evaluation. A laboratory testing to confirm the diagnosis.

generate a differential diagnosis and a list of more specific lab-

define the metabolic derangement (Table 51-7). The results

vidual) and clinical evaluation. Clinical laboratory testing can

The assessment begins with a careful history (family and individual) and clinical evaluation. Clinical laboratory testing can define the metabolic derangement (Table 51-7). The results generate a differential diagnosis and a list of more specific laboratory testing to confirm the diagnosis.

The combination of symptoms and abnormal clinical laboratory findings demands urgent metabolic evaluation. A metabolic emergency often presents with vomiting, acidosis, hypoglycemia, ketosis (or lack of appropriate ketosis), intercurrent infection, anorexia/failure to feed, lethargy proceeding to coma, and hyperventilation or hypoventilation. Clinical evaluation should focus on the cardiac, renal, neurologic, and developmental assessment as well as looking for changes in mental status, seizures, abnormal tone, visual symptoms, poor developmental progress, global developmental delay, loss of developmental milestones (regression), cardiomyopathy, cardiac failure, cystic renal malformation, and renal tubular dysfunction.

Clinical laboratory testing should begin with tests that are available in most hospital clinical laboratories. Care in the collection and handling of laboratory specimens is crucial to obtaining accurate results. Plasma measurements of lactate and ammonia are particularly subject to spurious results if not handled correctly. Significant ketosis in the neonate is unusual and suggests an organic acid disorder. Ketosis out of proportion to fasting status in an older child occurs in disorders of ketone usage. Lack of severe ketosis in an older child under conditions of metabolic stress is a feature of fatty acid oxidation disorders. In some disorders, such as urea cycle disorders, ketone utilization disorders, milder forms of fatty acid oxidation defects, and intermittent maple syrup urine disease, the laboratory abnormalities may be present only during an acute presentation. Therefore, normal testing in the well state does not rule out a metabolic disorder.

Table 51-6 Etiologies of Metabolic Acidosis Caused by Inborn Errors of Metabolism in Infants

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylmalonicemia (MMA)</td>
<td>Hyperammonemia, ketosis, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Propionic acidemia</td>
<td>Similar to MMA</td>
</tr>
<tr>
<td>Isovaleric acidemia</td>
<td>Similar to MMA; odor of sweaty feet</td>
</tr>
<tr>
<td>Pyruvate dehydrogenase deficiency</td>
<td>Lactic acidosis, hyperammonemia</td>
</tr>
<tr>
<td>Pyruvate carboxylase deficiency</td>
<td>Lactic acidosis, hypoglycemia, and ketosis</td>
</tr>
<tr>
<td>Respiratory chain (mitochondrial) disorders</td>
<td>Lactic acidosis, ketosis occasionally seen</td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)</td>
<td>Moderate acidosis, hypoglycemia, decreased ketosis, possible hyperammonemia</td>
</tr>
<tr>
<td>Other fatty acid oxidation defects</td>
<td>Similar to MCAD, with potential hepatic and cardiac disease</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Renal tubular acidosis, <em>Escherichia coli</em> neonatal sepsis, hypoglycemia</td>
</tr>
<tr>
<td>3-Hydroxy-3-methylglutaryl-CoA lyase deficiency</td>
<td>Severe lactic acidosis, hyperammonemia, hypoglycemia</td>
</tr>
<tr>
<td>Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria 2)</td>
<td>Metabolic acidosis, hypoglycemia, lethal renal malformations</td>
</tr>
</tbody>
</table>

Table 51-7 Initial Diagnostic Evaluation for a Suspected Inborn Error of Metabolism*

<table>
<thead>
<tr>
<th>BLOOD AND PLASMA</th>
<th>URINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gas</td>
<td>Glucose</td>
</tr>
<tr>
<td>Electrolytes—anion gap</td>
<td>pH</td>
</tr>
<tr>
<td>Glucose</td>
<td>Ketones</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Reducing substances</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>Organic acids</td>
</tr>
<tr>
<td>Complete blood count, differential,† and platelet count</td>
<td>Acylglycines</td>
</tr>
<tr>
<td>Lactate, pyruvate</td>
<td>Orotic acid</td>
</tr>
<tr>
<td>Organic acids</td>
<td></td>
</tr>
<tr>
<td>Amino acids</td>
<td></td>
</tr>
<tr>
<td>Acylcarnitines</td>
<td></td>
</tr>
<tr>
<td>Carnitine</td>
<td></td>
</tr>
</tbody>
</table>

*Organ-specific evaluation is indicated for specific symptoms (e.g., cranial magnetic resonance imaging for coma or seizures; echocardiography for cardiomyopathy; cerebrospinal fluid amino acids by column chromatography if nonketotic hyperglycemia is suspected).
†Thrombocytopenia and neutropenia are seen in organic acidurias; vacuolated lymphocytes and metachromatic granules are seen in lysosomal disorders.

CLINICAL ASSESSMENT AND LABORATORY TESTING

The assessment begins with a careful history (family and individual) and clinical evaluation. Clinical laboratory testing can define the metabolic derangement (Table 51-7). The results generate a differential diagnosis and a list of more specific laboratory testing to confirm the diagnosis.

Besides the metabolic emergency already described, a metabolic acidosis may be a feature of fatty acid oxidation disorders. In some disorders, such as urea cycle disorders, ketone utilization disorders, milder forms of fatty acid oxidation defects, and intermittent maple syrup urine disease, the laboratory abnormalities may be present only during an acute presentation. Therefore, normal testing in the well state does not rule out a metabolic disorder.

GENETIC ASPECTS OF INBORN ERRORS

Mechanisms of Inheritance

Although all of the classic mechanisms of inheritance are represented, most inborn errors of metabolism are autosomal recessive. Isolation or founder effect may make a specific recessive condition common in some populations (e.g., maple syrup urine disease in the Old Order Mennonite population in Pennsylvania). X-linked conditions exhibit increased prevalence in males. In general, carriers of recessive or X-linked (females) diseases are asymptomatic. However, in ornithine transcarbamylase deficiency, females can be symptomatic if they have a low proportion of normal cells in the liver. Most mitochondrial disorders in children are a result of mutations in autosomal genes, although there are X-linked forms. Mutations in the mitochondrial DNA also lead to mitochondrial disease. In this situation the type and severity of the presentation depend on the specific defects and the tissue specific ratio of normal to abnormal copies of the mitochondrial DNA (the degree of heteroplasmy).

Identification of Molecular Pathology

If the molecular basis of an inborn error of metabolism is known (i.e., the gene or genes have been mapped and mutations defined), specific genetic testing may be clinically available. In some disorders, there is a good correlation between specific mutations and clinical outcome. Genetic testing in other at-risk family members can provide important genetic information for them, enabling decision making throughout the rest of the family.
IDENTIFICATION OF INBORN ERRORS BY NEONATAL SCREENING

Disorders Identified by Neonatal Screening

In the United States the majority of infants diagnosed with a treatable metabolic disorder will be identified as a result of an abnormal newborn screen. Most states use tandem mass spectrometry to screen for a core panel of 29 disorders (Table 51-8). In most states, biotinidase deficiency and galactosemia are typically screened for by evaluating enzyme function.

Strategy of Neonatal Screening

The purpose of neonatal screening is the early detection and rapid treatment of disorders before the onset of symptoms, thus preventing morbidity and mortality. In most states, infants are tested at 24 to 48 hours (see Chapter 58). A positive test demands prompt evaluation. Specific follow-up testing and treatment of an affected child depends on the disorder. Consistent with most screening tests, a significant proportion of infants who have a positive neonatal screening test do not have a metabolic disorder.

Confirmatory Testing Principles

Neonatal screening is designed to maximize detection of affected infants but is not diagnostic. “Cutoff values” for each test are established carefully to identify infants with an elevated concentration of the substance or decreased activity of an enzyme with an acceptable number of false-positive results. A positive screening test must be followed by prompt clinical assessment as recommended by the screening program and metabolic specialist. In many cases children will also be provided therapy until the completion of definitive testing.

A positive screening test result causes anxiety for new parents; management of such anxiety is essential to minimize the harm of the program. In addition, definitive testing must be carried out promptly and accurately. If an inborn error of metabolism is excluded, parents need a thorough explanation of the results and reassurance that the infant is well. Such explanations will frequently require the expertise of a metabolic specialist or genetic counselor in the newborn period but may require reassessment by the primary care physician in the long term.

Specialized Laboratory and Clinical Testing

Specialized testing for inherited disorders of metabolism is effective in confirming a diagnosis suspected on the basis of an abnormal newborn screening result or on the basis of clinical suspicion. The tests that are helpful and examples of diagnoses made using these measurements depend on the deficient pathway in the disorder under consideration (Table 51-9).

Amino acid analysis is performed in plasma, urine, and cerebrospinal fluid. The plasma amino acid profile is most useful in identifying disorders of amino acid catabolism. Amino acids in the deficient pathway of the organic acid disorders may be abnormal, but often they are normal or may not be diagnostic.

Table 51-8 | Disorders Identified by Newborn Screening Programs in the United States

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>METHODS</th>
<th>CONFIRMATORY TESTING</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMINO ACID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylketonuria (PKU)</td>
<td>Guthrie*, MS/MS</td>
<td>Plasma phenylalanine, mutation testing</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>Guthrie, MS/MS</td>
<td>Plasma amino acid profile, urine succinylacetone</td>
</tr>
<tr>
<td>Maple syrup urine disease (MSUD)</td>
<td>Guthrie, MS/MS</td>
<td>Plasma amino acid profile, look for alloisoleucine</td>
</tr>
<tr>
<td>ORGANIC ACID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propionic acidemia</td>
<td>MS/MS</td>
<td>Urine organic acid profile</td>
</tr>
<tr>
<td>Methylmalonic acidemias</td>
<td>MS/MS</td>
<td>Urine organic acid profile, plasma amino acid profile, plasma homocysteine</td>
</tr>
<tr>
<td>Isovaleric acidemia</td>
<td>MS/MS</td>
<td>Urine organic acid profile</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>Enzyme measurement</td>
<td>Quantitative biotinidase measurement, DNA mutations</td>
</tr>
<tr>
<td>FATTY ACID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)</td>
<td>MS/MS</td>
<td>Urine organic acid profile, urine acylglycine profile, plasma acylcarnitine profile</td>
</tr>
<tr>
<td>Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)</td>
<td>MS/MS</td>
<td>Urine organic acid profile, urine acylglycine profile, plasma acylcarnitine profile</td>
</tr>
<tr>
<td>Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)</td>
<td>MS/MS</td>
<td>Urine organic acid profile, urine acylglycine profile, plasma acylcarnitine profile</td>
</tr>
<tr>
<td>CARBOHYDRATE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galactosemia</td>
<td>GALT enzyme measurement</td>
<td>GALT enzyme measurement, DNA mutations, galactose-1-P measurement</td>
</tr>
<tr>
<td>UREA CYCLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MS/MS</td>
<td>Plasma amino acid profile, DNA mutations</td>
</tr>
</tbody>
</table>
The urine amino acid profile is helpful in diagnosing primary disorders of renal tubular function, such as Lowe syndrome and cystinuria, as well as secondary disorders of renal tubular function, such as cystinosis and Fanconi syndrome of any cause. The urine amino acid profile is not the test of choice for diagnosing disorders of amino acid or organic acid metabolism.

Markers of disordered fatty acid oxidation are measured in urine and plasma. Excessive intermediates of fatty acid oxidation and organic acid catabolism are conjugated with glycine and carnitine. The urine acylglycine profile and the plasma acylcarnitine profile reflect this accumulation. In organic acid disorders and fatty acid oxidation disorders, measurement of plasma carnitine may reveal a secondary deficiency of carnitine and abnormal distribution of free and acylated carnitine. The plasma free fatty acid profile is helpful in diagnosis of disorders of fatty acid oxidation. Excess 3-OH-butyrate suggests a disorder of ketone metabolism; absence of ketones or decreased amounts of 3-OH-butyrate suggests a fatty acid oxidation disorder. Profiling of fatty acid intermediates in cultured skin fibroblasts may be informative.

Disorders of organic acid metabolism, such as propionic acidemia and methylmalonic acidemia, have typical urine organic acid profiles. Although analysis of blood and urine usually suggest the specific diagnosis, more targeted testing is typically needed by measuring enzymatic activity in the pathway or establishing DNA changes in the gene.

Disorders of creatine biosynthesis are reflected by a reduction in creatine in cerebrospinal fluid (CSF) and, in one form, an increase in guanidinoacetic acid in blood and urine. Disorders of purine and pyrimidine metabolism are suggested by the presence of an abnormal urinary profile of purines, such as xanthine, hypoxanthine, inosine, guanosine, adenosine, adenosine, or succinyladenosine. Similarly, disorders of pyrimidine metabolism are identified by an abnormal profile of pyrimidines, including uracil, uridine, thymine, thymidine, orotic acid, orotidine, dihydrouracil, dihydrothymine, pseudouridine, N-carbamoyl-β-alanine, or N-carbamoyl-β-aminoisobutyrate, in the urine.

Storage disorders show abnormalities in urine mucopolysaccharides (glycosaminoglycans, glycoproteins), sialic acid, heparan sulfate, dermatan sulfate, or chondroitin sulfate. Specific enzymology depends on the disorder; tissue can be either white blood cells or cultured skin fibroblasts, depending on assay. In several disorders, CSF is the most helpful specimen, including glycine encephalopathy (CSF amino acid profile when compared to concurrent plasma amino acids), disorders of neurotransmitter synthesis (biogenic amine profile), glucose transporter (GLUT1) deficiency (plasma-to-cerebrospinal fluid glucose ratio), and serine synthesis defect (amino acid profile).

In many disorders, an abnormal metabolic profile is consistently present during illness and when the child is well. In some cases, it is only diagnostic during an episode of illness.

**OVERVIEW OF TREATMENT**

There are several basic principles for treatment of inborn errors of metabolism. Syndromes with toxicity often present with encephalopathy; removal of toxic compounds is the first goal of therapy. Strategies include hemodialysis, hemovenovenous filtration, and administration of alternate pathway agents (see Chapter 53). A second strategy is to enhance deficient enzyme activity through administration of enzyme cofactors (e.g., pyridoxine in homocystinuria, tetrahydrobiopterin in PKU). If deficiency of a pathway product plays an important role, providing missing products is helpful (e.g., tyrosine in the treatment of phenylketonuria). A major principle is to decrease flux through the deficient pathway by restricting precursors in the diet. Examples include the restriction of protein in disorders of ammonia detoxification and of amino acid precursors in the organic acid disorders.
CARBOHYDRATE DISORDERS

GLYCOGEN STORAGE DISEASES

Many glycogen storage diseases are characterized by hypoglycemia and hepatomegaly (Table 52-1). Glycogen, the storage form of glucose, is found most abundantly in the liver (where it modulates blood glucose levels) and in muscles (where it facilitates anaerobic work). Glycogen is synthesized from uridine diphosphoglucose through the concerted action of glycogen synthetase and brancher enzyme (Fig. 52-1). The accumulation of glycogen is stimulated by insulin. Glycogenolysis occurs through a cascade initiated by epinephrine accumulation of glycogen is stimulated by insulin. Glycogen is synthesized from uridine diphosphoglucose through the concerted action of glycogen synthetase and brancher enzyme (Fig. 52-1). The accumulation of glycogen is stimulated by insulin. Glycogenolysis occurs through a cascade initiated by epinephrine.

The diagnosis of type I or type III glycogen storage disease is suggested by an elevated uric acid, lactate, and triglycerides in blood. For all forms, a diagnosis can normally be confirmed by DNA mutation testing in white blood cells. When this is feasible, invasive procedures, such as muscle and liver biopsy, can be avoided. When mutation testing is not available or is inconclusive, enzyme measurements in tissue from the affected organ confirm the diagnosis. If the diagnosis cannot be established, metabolic challenge and exercise testing may be needed. Treatment of hepatic glycogen storage disease is aimed at maintaining satisfactory

<table>
<thead>
<tr>
<th>Table 52-1 Glycogen Storage Diseases*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISEASE</strong></td>
</tr>
<tr>
<td>Type 1a: von Gierke</td>
</tr>
<tr>
<td>Type 1b</td>
</tr>
<tr>
<td>Type II: Pompe</td>
</tr>
<tr>
<td>Type III: Forbes</td>
</tr>
<tr>
<td>Type IV: Andersen</td>
</tr>
<tr>
<td>Type V: McArdle</td>
</tr>
<tr>
<td>Type VI: Hers</td>
</tr>
<tr>
<td>Type VII: Tarui</td>
</tr>
<tr>
<td>Type VIII</td>
</tr>
</tbody>
</table>

*Except for one form of hepatic phosphorylase kinase, which is X-linked, these disorders are autosomal recessive.
blood glucose levels or supplying alternative energy sources to muscle. In glucose-6-phosphatase deficiency (type I), the treatment usually requires nocturnal intragastric feedings of glucose during the first 1 or 2 years of life. Thereafter, snacks or nocturnal intragastric feedings of uncooked cornstarch may be satisfactory; hepatic tumors (sometimes malignant) are a threat in adolescence and adult life. No specific treatment exists for the diseases of muscle that impair skeletal muscle ischemic exercise. Enzyme replacement early in life is effective in Pompe disease (type II), which involves cardiac and skeletal muscle.

**GALACTOSEMIA**

Galactosemia is an autosomal recessive disease caused by deficiency of galactose-1-phosphate uridylyltransferase (Fig. 52-2). Clinical manifestations are most striking in a neonate who, when fed milk, generally exhibits evidence of liver failure (hyperbilirubinemia, disorders of coagulation, hypoglycemia), disordered renal tubular function (acidosis, glycosuria, aminoaciduria), and cataracts. The neonatal screening test must have a rapid turnaround time because affected infants may die in the first week of life. Affected infants are at increased risk for severe neonatal Escherichia coli sepsis. Major effects on liver and kidney function and the development of cataracts are limited to the first few years of life; older children may have learning disorders despite dietary compliance. Girls usually develop premature ovarian failure despite treatment.

**Laboratory manifestations** of galactosemia depend on dietary galactose intake. When galactose is ingested (as lactose), levels of plasma galactose and erythrocyte galactose 1-phosphate are elevated. Hypoglycemia is frequent, and albuminuria is present. Galactose frequently is present in the urine and can be detected by a positive reaction for reducing substances without a reaction with glucose oxidase on urine strip tests. The absence of urinary reducing substances cannot be relied on to exclude the diagnosis. The diagnosis is made by showing extreme reduction in erythrocyte galactose-1-phosphate uridylyltransferase activity. DNA testing for the mutations in galactose-1-phosphate uridylyltransferase confirms the diagnosis and may be useful in predicting prognosis. Renal tubular dysfunction may be evidenced by a normal–anion-gap hyperchloremic metabolic acidosis. **Treatment** by the elimination of dietary galactose results in rapid correction of abnormalities but infants who are extremely ill before treatment may die before therapy is effective.

**Galactokinase deficiency**, an autosomal recessive disorder, also leads to the accumulation of galactose in body fluids (see Fig. 52-2), which results in the formation of galactitol (dulcitol) through the action of aldose reductase. Galactitol, acting as an osmotic agent, can be responsible for cataract formation and, rarely, for increased intracranial pressure. These are the only clinical manifestations. Individuals homozygous for galactokinase deficiency usually develop cataracts after the
neonatal period, whereas heterozygous individuals may be at risk for cataracts as adults.

Hereditary fructose intolerance, in many ways, is analogous to galactosemia. When fructose is ingested, deficiency of fructose-1-phosphate aldolase leads to the intracellular accumulation of fructose 1-phosphate with resultant emesis, hypoglycemia, and severe liver and kidney disease. Elimination of fructose and sucrose from the diet prevents clinical disease. Fructosuria is caused by fructokinase deficiency, but its deficiency is not associated with clinical consequences.

**Chapter 53**

**AMINO ACID DISORDERS**

**DISORDERS OF AMINO ACID METABOLISM**

Disorders of amino acid metabolism are the result of the inability to catabolize specific amino acids derived from protein. Usually a single amino acid pathway is involved. This amino acid accumulates in excess and is toxic to various organs, such as the brain, eyes, skin, or liver. Treatment is directed at the specific pathway and usually involves dietary restriction of the offending amino acid and supplementation with special medical foods (formulas) that provide the other amino acids and other nutrients. Confirmatory testing includes quantitative specific plasma amino acid profiles along with specific mutation testing and sometimes enzymology.

**PHENYLKETONURIA**

Phenylketonuria (PKU), an autosomal recessive disease, primarily affects the brain and occurs in 1 in 10,000 persons. Classic PKU is the result from a defect in the hydroxylation of phenylalanine to form tyrosine (Fig. 53-1); the activity of phenylalanine hydroxylase in the liver is absent or greatly reduced. Affected infants are normal at birth, but if untreated, severe mental retardation (IQ 30) develops in the first year of life. A positive newborn screening test must be followed up by performing quantitative plasma amino acid analysis. A plasma phenylalanine value of greater than 360 μM (6 mg/dL) is consistent with the diagnosis of one of the hyperphenylalaninemias and demands prompt evaluation and treatment. Untreated, classic PKU is characterized by blood phenylalanine concentrations higher than 600 μM. Milder forms of hyperphenylalaninemia are indicated by values of plasma phenylalanine lower than this but higher than 360 μM. A significant percentage of premature infants and a few full-term infants have transient elevations in phenylalanine. Short-term follow-up usually identifies these infants promptly. A small percentage of infants diagnosed with PKU (≤2% in the United States) have a defect in the synthesis or metabolism of tetrahydrobiopterin, the cofactor for phenylalanine hydroxylase and for other enzymes involved in the intermediary metabolism of aromatic amino acids. Such disorders in biopterin metabolism are diagnosed by measuring dihydrobiopterin reductase in erythrocytes and by analyzing biopterin metabolites in urine. This testing should be carried out in all hyperphenylalaninemic infants.

Treatment is designed to maintain plasma phenylalanine values in the therapeutic range of 120 to 360 mM using a diet specifically restricted in phenylalanine but otherwise nutritionally complete. Since the early 1980s, treatment for life is recommended to reduce the risks of long-term neuropsychiatric problems and reduce the risk of maternal PKU syndrome.

Outcome of treatment in classic PKU is excellent. Most infants with classic PKU who are treated within the first...
10 days of life achieve normal intelligence. However, learning problems and problems with executive function are more frequent than in unaffected peers. The safe concentration of phenylalanine in older children and adults with PKU has not been clearly established. Reversible cognitive dysfunction is associated with acute elevations of plasma phenylalanine in adults and children with PKU. If the elevated level has been sustained, the dysfunction may not be reversible. Treatment with modified preparation of tetrahydrobiopterin has shown good responses in some individuals with PKU.

Females with PKU and their families must be educated on the risks and prevention of “maternal PKU syndrome.” Maternal hyperphenylalaninemia requires rigorous management before conception and throughout pregnancy to prevent fetal brain damage, congenital heart disease, and microcephaly.

TYROSINEMIAS
Tyrosinemia is identified in neonatal screening programs using tandem mass spectrometry methods to detect elevated tyrosine and/or succinylacetone. Elevated tyrosine levels also occur as a nonspecific consequence of severe liver disease or transient tyrosinemia of the newborn, which responds to ascorbic acid treatment. The inherited disorders of tyrosine metabolism are the target of neonatal screening. Tyrosinemia Type I, which is due to fumarylacetoacetate hydrolase deficiency (see Fig. 53-1), is a rare disease in which accumulated metabolites produce severe liver disease associated with bleeding disorder, hypoglycemia, hypoalbuminemia, elevated transaminases, and defects in renal tubular function. Hepatocellular carcinoma may eventually occur. Quantitative measurement of plasma tyrosine and blood or urine succinylacetone is performed after a positive neonatal screen. The diagnosis of tyrosinemia I is confirmed by an increased concentration of succinylacetone; DNA testing is available for some mutations. Treatment with nitisinone (NTBC) (an inhibitor of the oxidation of parahydroxyphenylpyruvic acid) effectively eliminates the production of the toxic succinylacetone. A low-phenylalanine, low-tyrosine diet may also play a role. These treatments have obviated the immediate need for liver transplantation in children identified by neonatal screening. Whether they completely eliminate the occurrence of hepatocellular carcinoma is unknown.

Tyrosinemias II and III are more benign forms of hereditary tyrosinemia. Blocked metabolism of tyrosine at earlier steps in the pathway is responsible, and succinylacetone is not produced. The clinical features include hyperkeratosis of palms and soles and keratitis, which can cause severe visual disturbance. Poor dietary compliance with type II tyrosinemia is associated with mild cognitive impairment. Treatment with a phenylalanine- and tyrosine-restricted diet is effective.

HOMOCYSTINURIA
Homocystinuria, an autosomal recessive disease (1:200,000 live births) involving connective tissue, the brain, and the vascular system, is caused by a deficiency of cystathionine β-synthase. In the normal metabolism of the sulfur amino acids, methionine gives rise to cysteine; homocysteine is a pivotal intermediate (Fig. 53-2). When cystathionine β-synthase is deficient, homocysteine accumulates in the blood and appears in the urine. Another result is enhanced reconversion of homocysteine to methionine, resulting in an increase in the concentration of methionine in the blood. The neonatal screening test most commonly used measures methionine. An excess of homocysteine produces a slowly evolving clinical syndrome that includes dislocated ocular lenses; long, slender extremities; malar flushing; and livedo reticularis. Arachnodactyly, scoliosis, pectus excavatum or carinatum, and genu valgum are skeletal features. Mental retardation, psychiatric illness, or both may be present. Major arterial or venous thromboses are a constant threat.

Confirmation of the diagnosis requires demonstration of elevated total homocysteine in the blood. A plasma amino acid profile reveals hypermethioninemia. Measurement of cystathionine β-synthase is not clinically available, but numerous mutations in the gene are known and can be tested.

There are two clinical forms of homocystinuria. In one form, activity of the deficient enzyme can be enhanced by the administration of large doses of pyridoxine (100 to 1000 mg/day). Folate supplementation is added to overcome folate deficiency if folate is trapped in the process of remethylation of homocysteine to methionine. This pyridoxine-responsive form comprises about 50% of cases and is the more likely form to be missed by neonatal screening because the methionine concentrations are not always above the screening cutoff. The second form is not responsive to pyridoxine therapy. The accumulation of homocysteine is controlled with a methionine-restricted diet and cystine and folate supplementation. The use of supplemental betaine (trimethylglycine), a donor of methyl groups for remethylation of homocysteine to methionine, also has a role in the management of pyridoxine-unresponsive patients. Diet and betaine are sometimes required to control plasma homocysteine, even in pyridoxine-responsive patients. The prognosis is good for infants whose plasma homocysteine concentration is controlled.

![Figure 53-2 Metabolism of methionine and homocysteine.](image-url)
MAPLE SYRUP URINE DISEASE

Maple syrup urine disease (MSUD) is an autosomal recessive disease, also called branched chain ketoaciduria. A deficiency of the decarboxylase initiates the degradation of the keto-acid analogs of the three branched chain amino acids—leucine, isoleucine, and valine (Fig. 53-3). Classic MSUD is rare (1:250,000) in the general population but much more common in some population isolates (Pennsylvania Mennonites 1:150). The American College of Medical Genetics neonatal screening panel includes MSUD.

Although MSUD does have intermittent-onset and late-onset forms, clinical manifestations of the classic form typically begin within 1 to 4 weeks of birth. Poor feeding, vomiting, and tachypnea commonly are noted, but the hallmark of the disease is profound depression of the central nervous system, associated with alternating hypotonia and hypertonia (extensor spasms), opisthotonos, and seizures. The urine has the odor of maple syrup.

Laboratory manifestations of MSUD include hypoglycemia and a variable presence of metabolic acidosis, with elevation of the undetermined anions; the acidosis is caused, in part, by plasma branched chain organic acids and, in part, by the usual ketone bodies, β-hydroxybutyrate and acetoacetate. Branched-chain ketoacids in urine (but not β-hydroxybutyrate or acetoacetate) react immediately with 2,4-dinitrophenylhydrazine to form a copious, white precipitate.

The definitive diagnosis of MSUD generally is made by showing large increases in plasma leucine, isoleucine, and valine concentrations and identification of alloisoleucine in the plasma in excess. The urinary organic acid profile is usually abnormal and shows the ketoacid derivatives of the branched chain amino acids.

Provision of adequate calories and protein, with restriction of leucine, is crucial for acute and chronic management. Hemodialysis, hemoftltration, or peritoneal dialysis can be lifesaving during acidotic crises in addition to close monitoring and therapy for cerebral edema. Ordinary catabolic stresses, such as moderate infections or labor and delivery in a pregnant mother with MSUD, can precipitate clinical crises. Liver transplantation effectively treats MSUD.

DISORDERS OF AMMONIA DISPOSAL

Inherited enzymatic deficiencies have been described for each of the steps of urea synthesis (Fig. 53-4). Neonatal screening does not currently detect all of the disorders in the urea cycle.

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**Figure 53-3** Metabolism of the branched chain amino acids. (1) Aminotransferases, (2) α-ketoacid dehydrogenase complex.

**Figure 53-4** The urea cycle. Site of enzymatic defects: (1) N-acetylglutamate synthase (N-AG), (2) carbamoyl phosphate synthetase, (3) ornithine carbamoyltransferase, (4) argininosuccinate acid synthetase, (5) argininosuccinate acid lyase, (6) arginase. Transporters (star), (7) citrin, (8) ornithine translocator (star). AKG, Alpha ketoglutarate.
Clinically the two most frequent disorders in the United States are ornithine carbamoyltransferase (OTC) deficiency and argininosuccinate lyase (ASL) deficiency.

**Ornithine carbamoyltransferase (OTC) deficiency** is X-linked. Gene mutations include both deletions and point mutations. If the enzyme is nonfunctional, there is no OTC activity in affected males, who are likely to die in the neonatal period. Affected females are heterozygous and, because of lyonization, may have a significant degree of enzyme deficiency and may be clinically affected at any time in life. **Clinical manifestations** range from lethal disease in the male (coma, encephalopathy) to clinical normalcy in a high percentage of females. Late-onset forms in males also occur. Manifestations in clinically affected females include recurrent emesis, lethargy, seizures, developmental delay, mental retardation, or episodic confusion. Affected females may spontaneously limit their protein intake.

Confirmatory testing for OTC includes a plasma amino acid profile, which may show reduced citrulline and arginine concentrations with increased glutamate and alanine. A urine organic acid profile shows increased excretion of orotic acid after protein loading or with concurrent administration of allopurinol. Mutation testing, deletion testing, and sequencing of the entire coding region of the related genes are available as clinical tests.

Argininosuccinate lyase (ASL) deficiency is autosomal recessive, and most children in the United States are detected as a result of an elevated citrulline on newborn screening. The diagnosis is confirmed by the detection of elevated argininosuccinic acid in the urine.

**Treatment of Hyperammonemia**

During episodes of symptomatic hyperammonemia, protein intake is reduced, and intravenous glucose is given in sufficient quantity to suppress catabolism of endogenous protein. Ammonia can be eliminated by use of the following agents, sodium benzoate and sodium phenylacetate, which are excreted in the urine as conjugates of glycine and glutamine. Arginine, which is usually deficient, is supplied. When ammonia levels are very high (>1000 µM) or refractory to therapy, direct removal of ammonia using hemodialysis or hemofiltration, but not peritoneal dialysis, is required. The neurologic status must be followed closely and cerebral edema treated promptly. Despite successful management of hyperammonemnic crises, the long-term outcome for males with severe neonatal OTC deficiency and all children with severe ASL deficiency is guarded. Early liver transplantation has increased survival, especially in males with severe OTC deficiency.

Restriction of dietary protein intake to daily needs is the mainstay of ongoing treatment for urea cycle defects. Crystalline essential amino acids can be supplied in amounts just sufficient to support protein synthesis. Arginine is an essential amino acid when arginine synthesis via the urea cycle is grossly impaired; thus arginine must be supplied except in the case of arginase deficiency. Citrulline needs to be supplied for some urea cycle disorders. For OTC deficiency and carbamoyl phosphate synthase deficiency, treatment with phenylbutyrate (which is metabolized to phenylacetate) prevents accumulation of ammonia.

**Disorders of Amino Acid Transport That Affect Specific Transport Mechanisms in the Kidney and Intestine**

Cystinuria is a disorder of renal tubular transport of cystine, lysine, arginine, and ornithine. Although intestinal transport is affected in some genetic forms, the symptoms are largely due to the renal transport abnormality. The concentration of cystine exceeds its solubility product and results in significant renal stones. Evaluation and diagnosis are based on the pattern of amino acid excretion in the urine. Mutation testing can be done. Treatment is based on increasing the solubility of cystine by complexing it with compounds such as penicillamine.

Intestinal transport of tryptophan is impaired in Hartnup syndrome; pellagra-like symptoms result from this deficiency. Diagnosis is based on the amino acid pattern in urine. Treatment with tryptophan is successful.

**Organic Acid Disorders**

**Disorders of Organic Acid Metabolism**

Organic acid disorders result from a block in the pathways of amino acid catabolism. Occurring after the amino moiety has been removed, they result in the accumulation of specific organic acids in the blood and urine. Treatment is directed at the specific abnormality, with restriction in precursor substrates and administration of enzyme cofactors, when available. Outcome is generally poor for children with neonatal-onset propionic or methylmalonic acidemia but is influenced by frequency and severity of crises and is optimal when diagnosis is made before the onset of the first episode. Liver transplantation has been used in some patients with early indicators of success. Confirmatory testing begins with a urine organic acid profile and plasma amino acid profile. More specific testing often requires enzyme measurements in appropriate tissues. When abnormal results suggest a specific disorder, DNA testing may identify the mutations involved.

**Propionic Acidemia and Methylmalonic Acidemia**

Propionic acidemia and methylmalonic acidemia result from defects in a series of reactions called the propionate pathway (Fig. 54-1). Defects in these steps produce ketosis and hyperglycinemia. Propionic acidemia and methylmalonic acidemia are identified by neonatal screening with tandem mass spectrometry methods. The clinical manifestations of both of these disorders in the neonatal period consist of tachypnea, vomiting, lethargy, coma, intermittent ketoacidosis, hyperglycinemia, neutropenia, thrombocytopenia, hyperammonemia,
and hypoglycemia. If these disorders are not identified by neonatal screening, intermittent episodes of metabolic acidosis occur. Crises occur during periods of catabolic stress, such as fever, vomiting, and diarrhea; they also may occur without an apparent precipitating event. During periods of neutropenia, the risk of serious bacterial infection is increased. Failure to thrive and impaired development are common.

**Propionic acidemia** results from deficiency in propionyl CoA-carboxylase, an enzyme that has two pairs of identical subunits. All forms of propionic acidemia are inherited in an autosomal recessive manner and are due to mutations in one of the subunits. **Methylmalonic acidemia** results from deficiency in methylmalonyl mutase; this may be caused by mutations in the gene for the mutase protein itself or in one of the steps of the synthesis of the cobalamin cofactors for the enzyme. A complex set of defects in cobalamin metabolism results in other forms of methylmalonic acidemia, some of which are associated with hyperhomocystinemia. **Treatment** with massive doses of hydroxocobalamin (the active form of vitamin B12) is helpful in some cases of methylmalonic acidemia. For propionic acidemia and the vitamin B12–unresponsive forms of methylmalonic acidemia, management includes the restriction of dietary protein and addition of a medical food deficient in the specific amino acid precursors of propionyl-CoA (isoleucine, valine, methionine, and threonine). Carnitine supplementation is often needed because it is lost in the urine as acylcarnitines. Intestinal bacteria produce a significant quantity of propionate; thus, antibacterial treatment to reduce the population of bacteria in the gut has some beneficial effect in propionic acidemia and vitamin B12–unresponsive methylmalonic acidemia.

**ISOVALERIC ACIDEMIA**

Isovaleric acidemia results from a block in the catabolism of leucine. Its clinical manifestations are similar to those of defects in the propionate pathway. The strong odor of isovaleric acid results in **sweaty feet odor** in untreated infants. Therapy involves restricting the intake of leucine, and providing glycine as an alternate pathway therapy that conjugates isovaleric acid (Fig. 54-2) and is then excreted in the urine.

**GLUTARIC ACIDEMIA I**

Glutaric acidemia I results from a deficiency at the end of the lysine catabolic pathway. It is an autosomal recessive disease produced by deficiency of glutaryl-CoA dehydrogenase activity (Fig. 54-3). **Clinical manifestations** include macrocephaly, which may be present at birth, with fever and metabolic distress. Before the advent of newborn screening, more than 70% of children had metabolic stroke-like episodes associated with infarction of the basal ganglia and dystonia, which characteristically develops after an episode of intercurrent illness, although it may reflect birth stress or prenatal insults. **Treatment** includes a protein-restricted diet accompanied by a medical food deficient in lysine and aggressive management of intercurrent illness. Despite this treatment as many as one third of children still develop neurologic symptoms.

**BIOTINIDASE DEFICIENCY AND HOLOCARBOXYLASE DEFICIENCY**

Biotin is a ubiquitous vitamin that is covalently linked to many carboxylases and cannot be recycled from its attachment to
the carboxylases. Thus, inherited biotinidase deficiency greatly increases the dietary requirement for biotin. Affected individuals become biotin deficient while consuming normal diets. Clinical disease can appear in the neonatal period or be delayed until later infancy, depending on the degree of deficiency.

Clinical manifestations of biotin deficiency vary greatly (seizures, hypotonia, sensory neural deafness, alopecia, skin rash, metabolic acidosis, immune deficits) and depend on which enzymes in which tissues have the most biotin depletion. Carboxylation is a crucial reaction in the metabolism of organic acids; most patients with biotinidase deficiency excrete abnormal amounts of several organic acids, among which \( \beta \)-methyl-crotonylglycine is prominent. In addition to biotinidase deficiency, an inherited deficiency of holoenzyme synthetase gives rise to severe disease and to similar patterns of organic aciduria. Both conditions respond well to treatment with large doses of biotin (10 to 40 mg/day). Confirmatory testing is accomplished with quantitative measurement of biotinidase activity.

![Figure 54-3](image) Scheme of flavoprotein metabolism with reference to glutaric aciduria types I and II. (1) Glutaryl-CoA dehydrogenase (deficient in glutaric aciduria type I), (2) fatty acyl-CoA dehydrogenases, (3) other flavoprotein dehydrogenases, (4) ETF (deficiency results in glutaric aciduria type II), (5) ETF-ubiquinone oxidoreductase (deficiency results in glutaric aciduria type II). CoA, Coenzyme A; ETF, electron transfer flavoprotein.

**Chapter 55**

**FAT METABOLIC DISORDERS**

**DISORDERS OF FATTY ACID OXIDATION**

Fatty acids are derived from hydrolysis of triglycerides and catabolism of fat. The catabolism of fatty acids (Fig. 55-1) proceeds through the serial, oxidative removal of two carbons at a time as acetyl groups (each as acetyl-CoA). The reactions are catalyzed by a group of enzymes that exhibit specificities related to the chain length and other properties of the fatty acids: very long chain acyl-CoA dehydrogenase (VLCAD), long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) or trifunctional protein, medium-chain acyl-CoA dehydrogenase (MCAD), and short-chain acyl-CoA dehydrogenase (SCAD).

MCAD deficiency is the most common inborn error of \( \beta \)-oxidation. Hypoketotic hypoglycemia is a common manifestation, as is Reye syndrome–like illness with hypoglycemia and elevated liver enzymes. Fatty infiltration of the liver also occurs. True hepatic failure is rare. Episodes may be recurrent in the patient or the family. Sudden infant death syndrome is reported in infants with MCAD deficiency, perhaps related to hypoglycemia. Treatment requires avoidance of fasting and provision of calories with fever or other metabolic stress. Medium-chain triglycerides must be avoided.

VLCAD deficiency and LCHAD (trifunctional protein) deficiency result in significant myopathy and cardiomyopathy. LCHAD deficiency is accompanied by a retinopathy in later childhood. In all of the disorders of \( \beta \)-oxidation, carnitine depletion can occur through excessive urinary excretion of carnitine esters of the incompletely oxidized fatty acids. Measurement of plasma carnitine is helpful in monitoring for this deficiency, which results in weakness and muscle pain, along with myoglobinuria in some people.

Hydroxymethylglutaryl-CoA lyase deficiency, although not a disorder of \( \beta \)-oxidation, interferes profoundly with hepatic adaptation to fasting by impairing ketogenesis (see Fig. 55-1). The clinical manifestations are those of MCAD deficiency, except that carnitine depletion is less prominent.

The diagnosis of disorders involving a deficiency of \( \beta \)-oxidation is suggested by the clinical picture and by hypoketotic hypoglycemia. The diagnosis is confirmed by analysis of urinary organic acid and acylglycine profiles, along with plasma acylcarnitine and free fatty acid profiles. Enzyme measurements and DNA testing complete the confirmatory testing. The profile of acylcarnitines in cultured skin fibroblasts may be helpful if other testing is not conclusive. In MCAD deficiency, a single mutation 985 A–G accounts for a significant percentage of cases. Treatment includes avoidance of fasting, as well as fluid and calorie supplementation during periods of metabolic stress, such as fever. In MCAD deficiency, medium-chain triglycerides must be avoided. In the long-chain fatty acid metabolic disorders, provision of medium-chain fatty acids improves muscle energy metabolism.

**GLUTARIC ACIDURIA TYPE II**

Glutaric aciduria type II (multiple acyl-CoA dehydrogenase deficiency) is a clinical disease produced by a defect in the transfer of electrons from flavine adenine nucleotides to the electron transport chain (electron transfer flavoprotein [ETF], or ETF dehydrogenase); this defect results in glutaric aciduria type II. The diagnosis of disorders involving a deficiency of glutaric aciduria is suggested by the clinical picture and by hypoketotic hypoglycemia. The diagnosis is confirmed by analysis of urinary organic acid and acylglycine profiles, along with plasma acylcarnitine and free fatty acid profiles. Enzyme measurements and DNA testing complete the confirmatory testing. The profile of acylcarnitines in cultured skin fibroblasts may be helpful if other testing is not conclusive. In MCAD deficiency, a single mutation 985 A–G accounts for a significant percentage of cases. Treatment includes avoidance of fasting, as well as fluid and calorie supplementation during periods of metabolic stress, such as fever. In MCAD deficiency, medium-chain triglycerides must be avoided. In the long-chain fatty acid metabolic disorders, provision of medium-chain fatty acids improves muscle energy metabolism.
It should not be confused with glutaric acidemia type I (see Chapter 54). When the enzyme essentially is nonfunctional, congenital anomalies are common, including renal cysts, facial abnormalities, rocker-bottom feet, and hypospadias. Severely affected infants have nonketotic hypoglycemia, metabolic acidosis, and the odor of sweaty feet soon after birth; these infants may die within the neonatal period. Less severely affected infants may have a more episodic, Reye syndrome–like illness. Skeletal and cardiac myopathy can be prominent in this complex, multisystemic disease. Onset in later childhood may be marked by recurrent hypoglycemia and myopathy. Treatment has not been effective in infants with complete deficiency. Milder forms respond to avoidance of fasting and caloric support during metabolic stress. Some patients respond to administration of riboflavin. Glutaric aciduria type II exhibits autosomal recessive inheritance. Confirmatory testing is similar to that for the other fatty acid oxidation disorders.

CARNITINE DEFICIENCY
Carnitine is a crucial cofactor in the transport of long-chain fatty acids across the mitochondrial inner membrane (see Fig. 55-1). It is synthesized from lysine by humans and is present in dietary red meat and dairy products. Carnitine deficiency is either primary (caused by failure of intake, synthesis, or transport of carnitine) or secondary (caused by the excretion of excessive amounts of carnitine as carnitine esters in patients with other inborn errors of metabolism; treatment with drugs that complex carnitine, such as valproic acid; or as a result of renal replacement therapy). Primary systemic carnitine deficiency is rare and results from inadequate renal reabsorption of carnitine secondary to a mutation in the sodium-dependent carnitine transporter. It responds well to carnitine supplementation. There are numerous examples of secondary carnitine deficiency among the organic acidurias, most prominently in disorders of the propionate pathway and in disorders of the β-oxidation of long-chain and medium-chain fatty acids. Clinical manifestations of carnitine deficiency include hypoketotic hypoglycemia, lethargy, lassitude, muscle weakness, sudden death, and cardiomyopathy.

FIGURE 55-1 Scheme of fatty acid and catabolism and ketone body formation. (1) Carnitine acyl-CoA dehydrogenases, (2) long-chain fatty acyl-CoA dehydrogenase (trifunctional protein), (3) medium-chain fatty acyl-CoA dehydrogenase, (4) short-chain fatty acyl-CoA dehydrogenase, (5) β-ketothiolase, (6) β-hydroxy-β-methylglutaryl-CoA synthase, (7) β-hydroxy-β-methylglutaryl-CoA lyase, (8) β-hydroxybutyrate dehydrogenase. CoA, Coenzyme A.

LYSOSOMAL AND PEROXISOMAL DISORDERS

PEROXISOMAL DISORDERS
Peroxisomes are subcellular organelles involved in metabolism and biosynthesis of bile acids, membrane phospholipids, and some β-oxidation of long-chain fatty acids. Disorders include conditions caused by abnormal peroxisomal enzyme function and abnormal peroxisomal biogenesis. Clinical symptoms are diverse and frequently include developmental delay and dysmorphic features that can involve the skeleton and the head. Zellweger syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease are examples of disorders of peroxisome biogenesis. Zellweger syndrome, an autosomal recessive disease (1:100,000 births), is also called cerebrohepatorenal syndrome. Peroxisomes are virtually absent, as are normal peroxisomal functions, which include the oxidation of very long chain fatty acids. Affected infants have high
# Lysosomal and Peroxisomal Disorders

## Table 56-1: Lysosomal Storage Diseases

<table>
<thead>
<tr>
<th>DISEASE (EPONYM)</th>
<th>ENZYME DEFIENCY</th>
<th>CLINICAL ONSET</th>
<th>DYSOSTOSIS MULTIPLEX</th>
<th>CORNEA</th>
<th>RETINA</th>
<th>LIVER, SPLEEN</th>
<th>CNS FINDINGS</th>
<th>STORED MATERIAL IN URINE</th>
<th>WBC/BONE MARROW</th>
<th>COMMENT</th>
<th>MULTIPLE FORMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MUCOPOLYSACCHARIDOSES (MPS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPS I (Hurler)</td>
<td>α-L-Iduronidase</td>
<td>–1 yr</td>
<td>Yes</td>
<td>Cloudy</td>
<td>—</td>
<td>Both enlarged</td>
<td>Profound loss of function</td>
<td>Acid mucopolysaccharide</td>
<td>Alder-Reilly bodies (WBC)</td>
<td>Kyphosis</td>
<td>Yes—Scheie and compounds</td>
</tr>
<tr>
<td>MPS II (Hunter)</td>
<td>Iduronate-2-sulfatase</td>
<td>1–2 yr</td>
<td>Yes</td>
<td>Clear</td>
<td>Retinal degeneration, papilledema</td>
<td>Both enlarged</td>
<td>Slow loss of function</td>
<td>Acid mucopolysaccharide</td>
<td>Alder-Reilly bodies (WBC)</td>
<td>X-linked</td>
<td>Yes</td>
</tr>
<tr>
<td>MPS III (Sanfilippo)</td>
<td>One of several</td>
<td>2–6 yr</td>
<td>Mild</td>
<td>Clear</td>
<td>Liver ± enlarged</td>
<td>Rapid loss of function</td>
<td>Acid mucopolysaccharide</td>
<td>Alder-Reilly bodies (WBC)</td>
<td>—</td>
<td>Several types biochemically</td>
<td></td>
</tr>
<tr>
<td>MPS IV (Morquio)</td>
<td>Galactose-6-sulfatase or β-galactosidase</td>
<td>2 yr</td>
<td>No, dwarfism deformities</td>
<td>Faint clouding</td>
<td>—</td>
<td>—</td>
<td>Normal</td>
<td>Acid mucopolysaccharide</td>
<td>Alder-Reilly bodies (WBC)</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>MPS VI (Maroteaux-Lamy)</td>
<td>N-Acetylgalactosamine-4-sulfatase</td>
<td>2 yr</td>
<td>Yes</td>
<td>Cloudy</td>
<td>—</td>
<td>Normal in size</td>
<td>Normal</td>
<td>Acid mucopolysaccharide</td>
<td>Alder-Reilly bodies (WBC)</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>MPS VII (Sly)</td>
<td>β-Glucuronidase</td>
<td>Variable neonatal</td>
<td>Yes</td>
<td>± Cloudy</td>
<td>—</td>
<td>Both enlarged</td>
<td>± Affected</td>
<td>Acid mucopolysaccharide</td>
<td>Alder-Reilly bodies (WBC)</td>
<td>Nonimmune hydrops</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>LIPIDOSES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucosylceramide lipidosis (Gaucher 1)</td>
<td>Glucocerebrosidase</td>
<td>Any age</td>
<td>No</td>
<td>Clear</td>
<td>Normal</td>
<td>Both enlarged</td>
<td>Normal</td>
<td>No</td>
<td>Gaucher cells in marrow</td>
<td>Bone pain fractures</td>
<td>Variability is the rule</td>
</tr>
<tr>
<td>Glucosylceramide lipidosis 2 (Gaucher 2)</td>
<td>Glucocerebrosidase</td>
<td>Fetal life to 2nd year</td>
<td>No</td>
<td>Clear</td>
<td>Normal</td>
<td>Both enlarged</td>
<td>Profound loss of function</td>
<td>No</td>
<td>Gaucher cells in marrow</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>Sphingomyelin lipidosis A (Niemann-Pick A)</td>
<td>Sphingomyelinase</td>
<td>1st mo</td>
<td>No</td>
<td>Clear</td>
<td>Cherry-red spots (50%)</td>
<td>Both enlarged</td>
<td>Profound loss of function</td>
<td>No</td>
<td>Foam cells in marrow</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Sphingomyelin lipidosis B (Niemann-Pick B)</td>
<td>Sphingomyelinase</td>
<td>1st mo or later</td>
<td>No</td>
<td>Clear</td>
<td>Normal</td>
<td>Both enlarged</td>
<td>Normal</td>
<td>No</td>
<td>Foam cells in marrow</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>Niemann-Pick C</td>
<td></td>
<td>Fetal life to adolescence</td>
<td>No</td>
<td>Clear</td>
<td>Normal</td>
<td>Enlarged</td>
<td>Vertical ophthalmoplegia, dystonia, cataplexy, seizures</td>
<td>No</td>
<td>Foam cells and sea-blue histiocytes in marrow</td>
<td>Pathogenesis not as for NP-A and NP-B</td>
<td>Lethal neonatal to adolescent onset</td>
</tr>
<tr>
<td>GM1 gangliosidosis (Tay-Sachs)</td>
<td>Hexosaminidase A</td>
<td>3–6 mo</td>
<td>No</td>
<td>Clear</td>
<td>Cherry-red spots</td>
<td>Normal</td>
<td>Profound loss of function</td>
<td>No</td>
<td>Normal</td>
<td>Sandhoff disease related</td>
<td>Yes</td>
</tr>
<tr>
<td>Generalized gangliosidosis (infantile) (GM1)</td>
<td>β-Galactosidase</td>
<td>Neonatal to 1st mo</td>
<td>Yes</td>
<td>Clear</td>
<td>Cherry-red spots (50%)</td>
<td>Both enlarged</td>
<td>Profound loss of function</td>
<td>No</td>
<td>Inclusion in WBC</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Arylsulfatase A</td>
<td>1–2 yr</td>
<td>No</td>
<td>Clear</td>
<td>Normal</td>
<td>Normal</td>
<td>Profound loss of function</td>
<td>No</td>
<td>Normal</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>α-Galactosidase A (cerebrosidase)</td>
<td>Childhood, adolescence</td>
<td>No</td>
<td>Cloudy by slit lamp</td>
<td>—</td>
<td>Liver may be enlarged</td>
<td>Normal</td>
<td>No</td>
<td>Normal</td>
<td>X-linked</td>
<td>No</td>
</tr>
<tr>
<td>Galactosylceramide lipidosis (Krabbe)</td>
<td>Galactocerebroside β-galactosidase</td>
<td>Early months</td>
<td>No</td>
<td>Clear</td>
<td>Optic atrophy</td>
<td>Normal</td>
<td>Profound loss of function</td>
<td>No</td>
<td>Normal</td>
<td>Storage not lysosomal</td>
<td>Yes</td>
</tr>
<tr>
<td>Wolman disease</td>
<td>Acid lipase</td>
<td>Neonatal</td>
<td>No</td>
<td>Clear</td>
<td>Normal</td>
<td>Both enlarged</td>
<td>Profound loss of function</td>
<td>No</td>
<td>Inclusion in WBC</td>
<td>—</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Table 56-1 | Lysosomal Storage Diseases—cont’d

<table>
<thead>
<tr>
<th>DISEASE (EPONYM)</th>
<th>ENZYME DEFICIENCY</th>
<th>CLINICAL ONSET</th>
<th>DYOSOSTOSIS MULTIPLEX</th>
<th>CORNEA</th>
<th>RETINA</th>
<th>LIVER, SPLEEN</th>
<th>CNS FINDINGS</th>
<th>STORED MATERIAL IN URINE</th>
<th>WBC/BONE MARROW</th>
<th>COMMENT</th>
<th>MULTIPLE FORMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farber lipogranulomatosis</td>
<td>Acid ceramidase</td>
<td>1st 4 mo</td>
<td>No</td>
<td>Usually clear</td>
<td>Cherry-red spots (12%)</td>
<td>May be enlarged</td>
<td>Normal or impaired</td>
<td>Usually not</td>
<td>—</td>
<td>Arthritis, nodules</td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### MUCOLIPIDOSES (ML) AND CLINICALLY RELATED DISEASE

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ENZYME DEFICIENCY</th>
<th>CLINICAL ONSET</th>
<th>DYOSOSTOSIS MULTIPLEX</th>
<th>CORNEA</th>
<th>RETINA</th>
<th>LIVER, SPLEEN</th>
<th>CNS FINDINGS</th>
<th>STORED MATERIAL IN URINE</th>
<th>WBC/BONE MARROW</th>
<th>COMMENT</th>
<th>MULTIPLE FORMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sialidosis II (formerly ML I)</td>
<td>Neuraminidase</td>
<td>Neonatal</td>
<td>Yes</td>
<td>Cloudy</td>
<td>Cherry-red spot</td>
<td>Both enlarged</td>
<td>Yes</td>
<td>Oligosaccharides</td>
<td>Vacularated lymphocytes</td>
<td>—</td>
<td>Yes (also see galactosialidosis)</td>
</tr>
<tr>
<td>Sialidosis I (formerly ML I)</td>
<td>Neuraminidase</td>
<td>Usually second decade</td>
<td>No</td>
<td>Fine opacities</td>
<td>Cherry-red spot</td>
<td>Normal</td>
<td>Myoclonus, seizures</td>
<td>Oligosaccharides</td>
<td>Usually none</td>
<td>Cherry-red spot/myoclonus syndrome</td>
<td>Severity varies</td>
</tr>
<tr>
<td>Galactosialidosis</td>
<td>Absence of PP/CathA and β-galactosidase</td>
<td>Usually second decade</td>
<td>Frequent</td>
<td>Clouding</td>
<td>Cherry-red spot</td>
<td>Occasionally enlarged</td>
<td>Myoclonus, seizures</td>
<td>Mental retardation</td>
<td>Oligosaccharides</td>
<td>Foamy lymphocytes</td>
<td>Onset from 1 to 40 yr</td>
</tr>
<tr>
<td>ML II (I-cell disease)</td>
<td>Mannosyl phosphotransferase</td>
<td>Neonatal</td>
<td>Yes</td>
<td>Clouding</td>
<td>—</td>
<td>Liver often enlarged</td>
<td>Profound loss of function</td>
<td>Oligosaccharides</td>
<td>No</td>
<td>Gingival hyperplasia</td>
<td>No</td>
</tr>
<tr>
<td>ML III (pseudo-Hurler polydystrophy)</td>
<td>Mannosyl phosphotransferase</td>
<td>2–4 yr</td>
<td>Yes</td>
<td>Late clouding</td>
<td>Normal</td>
<td>Normal in size?</td>
<td>Modest loss of function</td>
<td>Oligosaccharides</td>
<td>No</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>Multiple sulfatase deficiency</td>
<td>Many sulfatases</td>
<td>1–2 yr</td>
<td>Yes</td>
<td>Usually clear</td>
<td>Usually normal</td>
<td>Both enlarged</td>
<td>Profound loss of function</td>
<td>Acid mucopoly-saccharide</td>
<td>Alder-Reilly bodies (WBC)</td>
<td>Ichthyosis</td>
<td>Yes</td>
</tr>
<tr>
<td>Aspartylglycosaminuria</td>
<td>Aspartylglucosaminidase</td>
<td>6 mo</td>
<td>Mild</td>
<td>Clear</td>
<td>Normal</td>
<td>Early, not late</td>
<td>Profound loss of function</td>
<td>Aspartylgluco-samin</td>
<td>Inclusions in lymphocytes</td>
<td>Develop cataracts</td>
<td>No</td>
</tr>
<tr>
<td>Mannosidosis</td>
<td>α-Mannosidase</td>
<td>1st mo</td>
<td>Yes</td>
<td>Cloudy</td>
<td>—</td>
<td>Liver enlarged</td>
<td>Profound loss of function</td>
<td>Generally no</td>
<td>Inclusions in lymphocytes</td>
<td>Cataracts</td>
<td>Yes</td>
</tr>
<tr>
<td>Fucosidosis</td>
<td>α-L-Fucosidase</td>
<td>1st mo</td>
<td>Yes</td>
<td>Clear</td>
<td>May be pigmented</td>
<td>Both enlarged commonly</td>
<td>Profound loss of function</td>
<td>Oligosaccharides</td>
<td>Inclusions in lymphocytes</td>
<td>—</td>
<td>Yes</td>
</tr>
</tbody>
</table>

#### STORAGE DISEASES CAUSED BY DEFECTS INLYSOSOMAL PROTEOLYSIS

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ENZYME DEFICIENCY</th>
<th>CLINICAL ONSET</th>
<th>DYOSOSTOSIS MULTIPLEX</th>
<th>CORNEA</th>
<th>RETINA</th>
<th>LIVER, SPLEEN</th>
<th>CNS FINDINGS</th>
<th>STORED MATERIAL IN URINE</th>
<th>WBC/BONE MARROW</th>
<th>COMMENT</th>
<th>MULTIPLE FORMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuronal ceroid lipofuscinosis (NCL), Batten disease</td>
<td>Impaired lysosomal proteolysis</td>
<td>6 mo–10 yr, adult form</td>
<td>Various specific etiologies</td>
<td>No</td>
<td>Normal</td>
<td>May have brown pigment</td>
<td>Normal, distinct</td>
<td>Optic atrophy, seizures, dementia</td>
<td>Clinical picture consistent, time course variable</td>
<td>Etiologies for age-related forms</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy, myopathy, mental retardation, Danon disease</td>
<td>Lamp-2, a structural protein of lysosomes, is deficient</td>
<td>Usually 5–6 yr</td>
<td>No</td>
<td>Normal</td>
<td>Normal</td>
<td>Hepatomegaly</td>
<td>Delayed development, seizures</td>
<td>X-linked pediatric disease in males only</td>
<td>Variability in time course of signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephropathic cystinosis</td>
<td>Defect in cystine transport from lysosome to cytoplasm</td>
<td>6 mo–1 yr</td>
<td>No</td>
<td>Cystine crystals</td>
<td>Pigmentary retinopathy</td>
<td>Hepatomegaly</td>
<td>Normal CNS function</td>
<td>Generalized aminoaciduria</td>
<td>Elevated cystine in WBCs</td>
<td>Treatment with cysteamine is effective</td>
<td>Yes</td>
</tr>
<tr>
<td>Salla disease</td>
<td>Defect in sialic acid transport from lysosome to cytoplasm</td>
<td>6–9 mo</td>
<td>No</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Delayed development, ataxia, nystagmus, exotropia</td>
<td>Sialic aciduria</td>
<td>Vacuolated lymphocytes may be found</td>
<td>Growth retarded in some</td>
<td>Lethal infantile form</td>
</tr>
</tbody>
</table>

CNS, Central nervous system; WBC, white blood cell.
immune hydrops fetalis occurs in several lysosomal disorders. and lower airways may result in respiratory compromise. Non-mobility are common features. Storage in tissues of the upper developmental delay, corneal clouding, and limitation of joint Some are apparent only during adult life. Storage in solid 56-1). Some disorders affect many tissues but spare the brain. transplanted can restore lysosomal function. For other be catabolized. For some disorders, bone marrow (stem cell) in reducing the accumulation of the metabolite that cannot 

LYSOSOMAL STORAGE DISORDERS

Lysosomes are subcellular organelles that contain degradative enzymes for complex glycosaminoglycans, also called mucopolysaccharides. Glycosaminoglycans are macromolecules that play a number of roles within cells. Genetic disorders result from abnormal formation of the lysosome itself or from deficiency in specific hydrolytic enzymes, in the mechanisms that protect intralysosomal enzymes from hydrolytic destruction, or in the transport of materials into the lysosome and of metabolites out of the lysosome. These materials are stored in cells and ultimately result in their destruction, especially in the nervous system. The clinical disorders are diverse, reflecting tissue specificity of lysosomal function and the intrinsic turnover rates of the compounds whose cycling is affected (Table 56-1). Some disorders affect many tissues but spare the brain. Some are apparent only during adult life. Storage in solid organs results in organomegaly. In many of these disorders, developmental delay, corneal clouding, and limitation of joint mobility are common features. Storage in tissues of the upper and lower airways may result in respiratory compromise. Non-immune hydros fetalis occurs in several lysosomal disorders.

DIAGNOSTIC TESTING

Diagnostic testing includes measurement of glycosaminoglycans in urine and specific assays for lysosomal enzyme activity in white blood cells. If the urine test is positive, it helps direct specific enzyme measurement. If it is negative, it does not exclude a lysosomal storage disorder, and other testing modalities are needed if clinical signs are convincing. In disorders in which specific mutations are known, molecular testing refines the diagnosis. Specific diagnosis, carrier testing, and evaluation of at-risk family members require one of these approaches. Making a specific diagnosis is assuming increasing importance because specific treatment for some lysosomal disorders is very effective.

TREATMENT STRATEGIES

Specific treatment directed at the metabolic abnormality is available for some lysosomal disorders. In specific disorders (Gaucher disease) oral medication may be successful in reducing the accumulation of the metabolite that cannot be catabolized. For some disorders, bone marrow (stem cell) transplantation can restore lysosomal function. For others, replacement of the missing hydrolytic enzyme by systemic administration of the enzyme allows degradation of stored material. The disorders caused by deficient α-L-iduronidase (Hurler syndrome, Scheie syndrome, and their variants) respond to treatment with intravenous human recombinant α-L-iduronidase (laronidase). Other disorders for which enzyme therapy is available include MPS VI (Maroteaux-Lamy syndrome), Gaucher disease, Fabry disease, and MPS II (Hunter syndrome). Stem cell transplantation has been helpful or is under investigation in the following disorders: MPS type IH (Hurler syndrome), MPS type VI (Maroteaux-Lamy syndrome), MPS type VII (Sly syndrome), Krabbe disease, metachromatic leukodystrophy, alpha-fucosidosis, alpha-mannosidosis, Gaucher disease, and Niemann-Pick disease type B. However, treatment for many of these conditions is supportive, with careful attention to respiratory status and physical therapy. As a result of the rapidly changing therapeutic options, geneticists with a special interest in these disorders should be consulted when a diagnosis is suspected. Treatment decisions should be made by the family in the light of the potential therapeutic benefits and burdens of therapy and typically should be resolved before the onset of central nervous system manifestations, which are typically not improved by these approaches.

Chapter 57  MITOCHONDRIAL DISORDERS

Mitochondria are very complex organelles located in virtually all cells of the body. They perform a variety of functions such as intracellular signaling of oxygen tension and key roles in programmed cell death. From a biochemical perspective, mitochondria are the key site of energy production in the cell. Indeed they are the site of beta oxidation (see Chapter 55), the Krebs cycle, and parts of the urea cycle (see Figure 53-4). This complexity requires more than 1000 proteins localized specifically to the mitochondrion. Only 13 of these are encoded by the mitochondrial DNA (mtDNA); the remainder are nuclear encoded (on the chromosomes) and require import into the mitochondrion. In addition, the mitochondrial DNA needs its own set of proteins to allow for its maintenance, transcription, and translation.

Mitochondrial disorders are typically defined as defects in the ability to generate energy from oxidative phosphorylation to produce ATP by transferring electrons formed by glycolysis and the Krebs cycle to a cascade that generates NADH and FADH₂ (Fig. 57-1) and are also known as phosphorylation disorders or respiratory chain disorders. The more dependent on energy production an organ is, the more profound the symptoms of deficiency of mitochondrial function in that organ. Certain proteins are only expressed in specific tissues, and defects in these will lead to differing patterns of disease. Taken together, mitochondrial disorders may affect as many as 1 in 2500 people.
**Figure 57-1** The mammalian mitochondrial genome and its protein-coding gene repertoire involved in the oxidative phosphorylation pathway. (A) Schematic representation of genes within mammalian mitochondrial genome (~7000 bp). Genes on the outer circle are transcribed from the light strand. Location of the tRNAs (red boxes) conforms to the canonical placental mammalian arrangement. (B) Simplified view of the mitochondrial oxidative phosphorylation machinery. Complexes I (NADH dehydrogenase) and II (succinate dehydrogenase) receive electrons from either NADH or FADH2. Electrons are then carried between complexes by the carrier molecules coenzyme Q/ubiquinone (UQ) and cytochrome c (CYC). The potential energy of these electron transfer events is used to pump protons against the gradient, from the mitochondrial matrix into the intermembrane space [complexes I and III (cytochrome bc1) and IV (cytochrome c oxidase)]. ATP synthesis by complex V (ATP synthase) is driven by the proton gradient and occurs in the mitochondrial matrix. HSP, Putative heavy-strand promoter; IM, intermembrane space; MM, mitochondrial matrix; OHR, origin of heavy-strand replication; OLR, origin of light-strand replication. (From da Fonseca RR, Johnson WE, O’Brien SJ, et al: The adaptive evolution of the mammalian mitochondrial genome, BMC Genomics 9:119, 2008.)

**SIGNS AND SYMPTOMS OF GENETIC DISORDERS OF MITOCHONDRIAL FUNCTION**

The signs and symptoms of mitochondrial disorders are varied. Symptoms depend on how an organ is affected by energy deficiency. Muscle function that is compromised will result in muscle fatigue and weakness. Myopathy is common and may show **ragged red fibers** on a muscle biopsy. **Rhabdomyolysis** can occur. Brain dysfunction may be expressed as seizures, loss of intellectual function, headache, or signs consistent with stroke. Spastic paraplegia may occur. Ataxia and basal ganglia symptoms are features of some disorders. Vision and eye muscle movement may be compromised, with **progressive external ophthalmoplegia** being almost diagnostic of an oxidative phosphorylation defect. **Cardiomyopathy** is frequent, and cardiac rhythm disturbances occur. Liver dysfunction may be expressed as both synthetic deficiencies and liver failure. Diabetes may signal pancreatic involvement. Renal tubular abnormalities and renal failure both occur. Gastrointestinal symptoms include both diarrhea and constipation that are difficult to treat. **Alper disease** (cerebral degeneration and liver disease) and **Leigh disease** (subacute necrotizing encephalomyelopathy) show similar brain lesions but in distinctly different areas of the brain. Because the signs and symptoms may involve multiple organs and may seem nonspecific, physicians may not suspect a mitochondrial disorder until significant progression has occurred.

**BIOCHEMICAL ABNORMALITIES IN MITOCHONDRIAL FUNCTION**

Defects in the mitochondrial respiratory chain may produce **lactic acidosis**. Given the complexity of the respiratory chain, it is not surprising that the described defects are varied as to cause, intensity, and tissues affected. The metabolism of glucose to carbon dioxide and water, with pyruvate as an intermediate (Fig. 57-2), occurs as part of the energy cycle in many tissues. Interference with mitochondrial oxidative metabolism may result in the accumulation of pyruvate. Because lactate dehydrogenase is ubiquitous, and because the equilibrium catalyzed by this enzyme greatly favors lactate over pyruvate, the accumulation of pyruvate results in lactic acidosis. The most common cause of such lactic acidosis is oxygen deficiency caused by hypoxia or poor perfusion. Lactic acidosis also occurs when specific reactions of pyruvate are impaired. In the liver, pyruvate undergoes carboxylation to form oxaloacetate using the enzyme pyruvate carboxylase; deficiency in this enzyme causes severe lactic acidosis. In many tissues, lactate is catabolized to form acetyl coenzyme A (CoA) by the pyruvate dehydrogenase complex; deficiency in pyruvate dehydrogenase also can cause lactic acidosis. Because these reactions also play a role in gluconeogenesis, hypoglycemia can be a feature of these disorders. These disorders comprise forms of **primary lactic acidosis**. They frequently present as intractable, lethal acidosis in the first days or weeks of life and are difficult to treat. Some of the enzymes in this pathway can be measured
and specific diagnosis can be made. This may require white blood cells or tissue biopsy.

**GENETICS OF MITOCHONDRIAL DISORDERS**

Mitochondrial function is carried out by proteins that are coded for by both nuclear and mitochondrial genes. These enzymes are extremely complicated, and several are quite large. The mitochondrial genome encodes 13 subunits of the enzymes involved in mitochondrial oxidative phosphorylation. More than 85 autosomal genes code for the rest of the subunits of these enzymes. In children, only about 15% of cases of mitochondrial disease are caused by mutations in mitochondrial DNA (mtDNA); the rest are due to mutations in nuclear genes. The most frequent cases in several large series have been mutations that lead to a reduction in the ability of the mtDNA to maintain itself. Large population studies show carrier rates of about 2% of the population for mutations in polymerase (DNA directed), gamma (POLG), and deoxyguanosine kinase (DGUOK). Most disorders show autosomal recessive inheritance. A few are X linked or passed on by maternal mtDNA mutations, such as mitochondrial encephalopathy with lactic acidosis (MELAS) and mitochondrial encephalopathy with ragged red fibers (MERRF), or deletions such as maternally inherited diabetes and deafness (MIDD).

**TREATMENT OF MITOCHONDRIAL DISORDERS**

Repairing the basic energy deficit and getting the appropriate drugs and cofactors to the appropriate location within the mitochondrion are difficult. Nevertheless, a number of strategies are used, including judicious physical therapy and exercise with adequate rest, adequate nutrition, and cofactors for the deficient pathway. Specific treatment is limited for most mitochondrial defects. Vitamin cofactors for the respiratory chain, such as riboflavin and pharmaceutical forms of coenzyme Q, are often used. When a single organ bears most of the damage, organ transplant may be effective. Identification of family members at risk may allow earlier diagnosis and treatment.

The author would like to acknowledge Dr. Margretta R. Seashore for her superb work in the last edition. Hers was an excellent analysis of the topic and has informed much of the present discussion.

**Suggested Reading**


ASSESSMENT OF THE MOTHER, FETUS, AND NEWBORN

ASSESSMENT OF THE MOTHER

Pregnancies associated with perinatal morbidity or mortality are considered high risk. Identification of high-risk pregnancies is essential to the care of the infant because they may result in intrauterine fetal death, intrauterine growth restriction (IUGR), congenital anomalies, excessive fetal growth, birth asphyxia and trauma, prematurity (birth at <38 weeks) or postmaturity (birth at ≥42 weeks), neonatal disease, or long-term risks of cerebral palsy, mental retardation, and chronic sequelae of neonatal intensive care. Ten percent to 20% of women may be high risk at some time during their pregnancy. Although some obstetric complications are first seen during labor and delivery and cannot be predicted, more than 50% of perinatal mortality and morbidity results from problems identified before delivery as high risk. After a high-risk pregnancy is identified, measures can be instituted to prevent complications, provide intensive fetal surveillance, and initiate appropriate treatments of the mother and fetus.

A history of previous premature birth, intrauterine fetal death, multiple gestation, IUGR, congenital malformation, explained or unexplained neonatal death (e.g., group B streptococcal sepsis), birth trauma, preeclampsia, gestational diabetes, grand multipara status (five or more pregnancies), or cesarean section is associated with additional risk in subsequent pregnancies.

Pregnancy complications that increase the risk of a poor outcome can be secondary to maternal or fetal causes or both. Complications include placenta previa; abruptio placentae; preeclampsia; diabetes; oligohydramnios or polyhydramnios; multiple gestation; blood group sensitization; abnormal levels of unconjugated estriols, chorionic gonadotropin, or alpha-fetoprotein; abnormal fetal ultrasound; hydrops fetalis; maternal trauma or surgery; abnormal fetal presentation (breech); exposure to prescribed or illicit drugs; prolonged labor; cephalopelvic disproportion; prolapsed cord; fetal distress; prolonged or premature rupture of membranes; short cervical length (<25 mm) and the presence of fetal fibronectin in cervical secretions at less than 35 weeks’ gestation (a predictor of preterm labor); cervical infections and vaginosis; and congenital infections, including rubella, cytomegalovirus, herpes simplex, human immunodeficiency virus (HIV), toxoplasmosis, syphilis, and gonorrhea.

Maternal medical complications associated with increased risk of maternal and fetal morbidity and mortality include diabetes, chronic hypertension, congenital heart disease (especially with right-to-left shunting and Eisenmenger complex), glomerulonephritis, collagen vascular disease (especially systemic lupus erythematosus with or without antiphospholipid antibodies), lung disease (cystic fibrosis), severe anemia (sickle cell anemia), hyperthyroidism, myasthenia gravis, idiopathic thrombocytopenic purpura, inborn errors of metabolism (maternal phenylketonuria), and malignancy.

Obstetric complications often are associated with increased fetal or neonatal risk. Vaginal bleeding in the first trimester or early second trimester may be caused by a threatened or actual spontaneous abortion and is associated with increased risk of congenital malformations or chromosomal disorders. Painless vaginal bleeding that is not associated with labor and occurs in the late second or (more likely) third trimester often is the result of placenta previa. Bleeding develops when the placental mass overlies the internal cervical os; this may produce maternal hemorrhagic shock, necessitating transfusions. Bleeding also may result in premature delivery. Painful vaginal bleeding is often the result of retroplacental hemorrhage or placental abruption. Associated findings may be advanced maternal age and parity, maternal chronic hypertension, maternal cocaine use, preterm rupture of membranes, polyhydramnios, twin gestation, and preeclampsia. Fetal asphyxia ensues as the retroplacental hematoma causes placental separation that interferes with fetal oxygenation. Both types of bleeding are associated with fetal blood loss. Neonatal anemia may be more common with placenta previa.

Abnormalities in the volume of amniotic fluid, resulting in oligohydramnios or polyhydramnios, are associated with increased fetal and neonatal risk. Oligohydramnios (amniotic ultrasound fluid index ≤2 cm) is associated with IUGR and major congenital anomalies, particularly of the fetal kidneys, and with chromosomal syndromes. Bilateral renal agenesis results in diminished production of amniotic fluid and a specific deformation syndrome (Potter syndrome), which includes clubfeet, characteristic compressed facies, low-set ears, scaphoid abdomen, and diminished chest wall size accompanied by pulmonary hypoplasia and, often,
pneumothorax. Uterine compression in the absence of amniotic fluid retards lung growth, and patients with this condition die of respiratory failure rather than renal insufficiency. Twin-to-twin transfusion syndrome (donor) and complications from amniotic fluid leakage also are associated with oligohydramnios. Oligohydramnios increases the risk of fetal distress during labor (meconium-stained fluid and variable decelerations); the risk may be reduced by saline amnioinfusion during labor.

**Polyhydramnios** may be acute and associated with premature labor, maternal discomfort, and respiratory compromise. More often, polyhydramnios is chronic and is associated with diabetes, immune or nonimmune hydrops fetalis, multiple gestation, trisomy 18 or 21, and major congenital anomalies. Anencephaly, hydrocephaly, and meningomyelocele are associated with reduced fetal swallowing of amniotic fluid. Esophageal and duodenal atresia as well as cleft palate interfere with swallowing and gastrointestinal fluid dynamics. Additional causes of polyhydramnios include Werdnig-Hoffmann and Beckwith-Wiedemann syndromes, conjoined twins, chylothorax, cystic adenomatoid lung malformation, diaphragmatic hernia, gastroschisis, sacral teratoma, placental chorioamnionitis, and myotonic dystrophy. **Hydrops fetalis** may be a result of Rh or other blood group incompatibilities and anemia caused by intrauterine hemolysis of fetal erythrocytes by maternal IgG-sensitized antibodies crossing the placenta. Hydrops is characterized by fetal edema, ascites, hemoconcentration, and congestive heart failure. Causes of **nonimmune hydrops** include fetal arrhythmias (supraventricular tachycardia, congenital heart block), fetal anemia (bone marrow suppression, nonimmune hemolysis, or twin-to-twin transfusion), severe congenital malformedon, intrauterine infections, congenital neuroblastoma, inborn errors of metabolism (storage diseases), fetal hepatitis, nephrotic syndrome, and pulmonary lymphangiecistis. Twin-to-twin transfusion syndrome (recipient) also may be associated with polyhydramnios. Polyhydramnios is often the result of unknown causes. If severe, polyhydramnios may be managed with bed rest, indomethacin, or serial amnioinfusions.

**Premature rupture of the membranes**, which occurs in the absence of labor, and **prolonged rupture of the membranes** (>24 hours) are associated with an increased risk of maternal or fetal infection (chorioamnionitis) and preterm birth. In the immediate newborn period, group B streptococcus and *Escherichia coli* are the two most common pathogens associated with sepsis. *Listeria monocytogenes* is a less common cause. *Mycoplasma hominis, Ureaplasma urealyticum, Chlamydia trachomatis,* and anaerobic bacteria of the vaginal flora also have been implicated in infection of the amniotic fluid. Infection with community-acquired methicillin-resistant *Staphylococcus aureus* must be considered for infants with skin infections or with known exposures. The risk of serious fetal infection increases as the duration between rupture and labor (latent period) increases, especially if the period is greater than 24 hours. Intrapartum antibiotic therapy decreases the risk of neonatal sepsis.

**Multiple gestations** are associated with increased risk resulting from polyhydramnios, premature birth, IUGR, abnormal presentation (breech), congenital anomalies (intestinal atresia, porencephaly, and single umbilical artery), intrauterine fetal demise, birth asphyxia, and twin-to-twin transfusion syndrome. **Twin-to-twin transfusion syndrome** is associated with a high mortality and is seen only in monozygotic twins who share a common placenta and have an arterovenous connection between their circulations. The fetus on the arterial side of the shunt serves as the blood donor, resulting in fetal anemia, growth retardation, and oligohydramnios for this fetus. The recipient, or venous-side twin, is larger or discordant in size, is plethoric and polycythemic, and may show polyhydramnios. Weight differences of 20% and hemoglobin differences of 5 g/dL suggest the diagnosis. Ultrasonography in the second trimester reveals discordant amniotic fluid volume with oliguria/oligohydramnios and hypervolemia/polyuria/polyhydramnios with a distended bladder, with or without hydrops and heart failure. Treatment includes amniocentesis and attempts to ablate the arterovenous connection (using a laser). The birth order of twins also affects morbidity by increasing the risk of the second-born twin for breech position, birth asphyxia, birth trauma, and respiratory distress syndrome.

Overall, twinning is observed in 1 of 80 pregnancies; 80% of all twin gestations are dizygotic twins. The diagnosis of the type of twins can be determined by placenta, sex, fetal membrane structure, and, if necessary, tissue and blood group typing or DNA analysis.

Toxemia of pregnancy, or **preeclampsia/eclampsia,** is a disorder of unknown but probably vascular etiology that may lead to maternal hypertension, uteroplacental insufficiency, IUGR, intrauterine asphyxia, maternal seizures, and maternal death. Toxemia is more common in nulliparous women and in women with twin gestation, chronic hypertension, obesity, renal disease, positive family history of toxemia, or diabetes mellitus. A subcategory of preeclampsia, the **HELLP syndrome** (hemolysis, elevated liver enzyme levels, low platelets), is more severe and is often associated with a fetal inborn error of fatty acid oxidation (long-chain hydroxyacyl–coenzyme A dehydrogenase of the trifunctional protein complex).

**FETUS AND NEWBORN**

The late fetal–early neonatal period has the highest mortality rate of any age interval. **Perinatal mortality** refers to fetal deaths occurring from the 20th week of gestation until the 28th day after birth and is expressed as number of deaths per 1000 live births. Intrauterine fetal death accounts for 40% to 50% of the perinatal mortality rate. Such infants, defined as **stillborn,** are born without a heart rate and are apneic, limp, pale, and cyanotic. Many stillborn infants exhibit evidence of maceration; pale, peeling skin; corneal opacification; and soft cranial contents.

Mortality rates around the time of birth are expressed as number of deaths per 1000 live births. The **neonatal mortality rate** includes all infants dying during the period from after birth to the first 28 days of life. Modern neonatal intensive care allows many newborns with life-threatening diseases to survive the neonatal period, only to die of their original diseases or of complications of therapy after 28 days of life. This delayed mortality and mortality caused by acquired illnesses occur during the **postneonatal period,** which begins after 28 days of life and extends to the end of the first year of life.

The **infant mortality rate** encompasses the neonatal and the postneonatal periods. In the United States, it declined to 6.15:1000 in 2010. The rate for African American infants was approximately 11.6:1000. The most common causes of
perinatal and neonatal death are listed in Table 58-1. Overall, congenital anomalies and diseases of the premature infant are the most significant causes of neonatal mortality.

**Low birth weight** (LBW) infants, defined as infants having birth weights of less than 2500 g, represent a disproportionately large component of the neonatal and infant mortality rates. Although LBW infants make up only about 6% to 7% of all births, they account for more than 70% of neonatal deaths. IUGR is the most common cause of LBW in developing countries, whereas prematurity is the cause in developed countries.

**Very low birth weight** (VLBW) infants, weighing less than 1500 g at birth, represent about 1% of all births but account for 50% of neonatal deaths. Compared with infants weighing 2500 g or more, LBW infants are 40 times more likely to die in the neonatal period; VLBW infants have a 200-fold higher risk of neonatal death. The LBW rate has not improved in recent years and is one of the major reasons that the U.S. infant mortality rate is high compared with other large, modern, industrialized countries.

Maternal factors associated with a LBW caused by premature birth or IUGR include a previous LBW birth, low socioeconomic status, low level of maternal education, no antenatal care, maternal age younger than 16 years or older than 35 years, short interval between pregnancies, cigarette smoking, alcohol and illicit drug use, physical (excessive standing or walking) or psychological (poor social support) stresses, unmarried status, low pre-pregnancy weight (<45 kg), poor weight gain during pregnancy (<10 lb), and African American race. LBW and VLBW rates for African American women are twice the rates for white women. The neonatal and infant mortality rates are nearly twofold higher among African American infants. These racial differences are only partly explained by poverty.

### ASSESSMENT OF THE FETUS

**Fetal size** can be determined accurately by ultrasound techniques. **Fetal growth** can be assessed by determining the fundal height of the uterus through bimanual examination of the gravid abdomen. Ultrasound measurements of the fetal biretial diameter, femur length, and abdominal circumference are used to estimate fetal growth. A combination of these measurements predicts fetal weight. Deviations from the normal fetal growth curve are associated with high-risk conditions.

IUGR is present when fetal growth stops and, over time, declines to less than the 5th percentile of growth for gestational age or when growth proceeds slowly, but absolute size remains less than the 5th percentile. Growth restriction may result from fetal conditions that reduce the innate growth potential, such as fetal rubella infection, primordial dwarfing syndromes, chromosomal abnormalities, and congenital malformation syndromes. Reduced fetal production of insulin and insulin-like growth factor I is associated with fetal growth restriction. Placental causes of IUGR include villitis (congenital infections), placental tumors, chronic abruptio placentae, twin-to-twin transfusion syndrome, and placental insufficiency. Maternal causes include severe peripheral vascular diseases that reduce uterine blood flow (chronic hypertension, diabetic vasculopathy, and preeclampsia/eclampsia), reduced nutritional intake, alcohol or drug abuse, cigarette smoking, and uterine constraint (noted predominantly in mothers of small stature with a low prepregnancy weight) and reduced weight gain during pregnancy. The outcome of IUGR depends on the cause of the reduced fetal growth and the associated complications after birth (Table 58-2). Fetuses subjected to chronic intrauterine hypoxia as a result of uteroplacental insufficiency are at an increased risk for the comorbidities of birth asphyxia, polycythemia, and hypoglycemia. Fetuses with reduced tissue mass due to chromosomal, metabolic, or multiple congenital anomaly syndromes have poor outcomes based on the prognosis for the particular syndrome. Fetuses born to small mothers and fetuses with poor nutritional intake usually show catch-up growth after birth.

Fetal size does not always correlate with functional or structural maturity. Determining **fetal maturity** is crucial when making a decision to deliver a fetus because of fetal or maternal disease. Fetal gestational age may be determined accurately on the basis of a correct estimate of the last menstrual period. Clinically relevant landmark dates can be used to determine gestational age; the first audible heart tones by fetoscope are detected at 18 to 20 weeks (12 to 14 weeks by Doppler methods), and quickening of fetal movements usually is perceived at 18 to 20 weeks. However, it is not always

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**Table 58-1** Major Causes of Perinatal and Neonatal Mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FETUS</strong></td>
<td>Abruptio placentae, Chromosomal anomalies, Congenital malformations (heart, CNS, renal), Hydrops fetalis, Intrauterine asphyxia, Intrauterine infection, Maternal underlying disease (chronic hypertension, autoimmune disease, diabetes mellitus), Multiple gestation, Placental insufficiency, Umbilical cord accident</td>
</tr>
<tr>
<td><strong>PRETERM INFANT</strong></td>
<td>Respiratory distress syndrome/bronchopulmonary dysplasia (chronic lung disease), Severe immaturity, Congenital anomalies, Infection, Intraventricular hemorrhage, Necrotizing enterocolitis</td>
</tr>
<tr>
<td><strong>FULL-TERM INFANT</strong></td>
<td>Birth asphyxia, Birth trauma, Congenital anomalies, Infection, Macrosomia, Meconium aspiration pneumonia, Persistent pulmonary hypertension</td>
</tr>
</tbody>
</table>

CNS, Central nervous system. *Common.
possible to determine fetal maturity by such dating, especially in a high-risk situation, such as preterm labor or a diabetic pregnancy.

**Surfactant**, a combination of surface-active phospholipids and proteins, is produced by the maturing fetal lung and eventually is secreted into the amniotic fluid. The amount of surfactant in amniotic fluid is a direct reflection of surface-active material in the fetal lung and can be used to predict the presence or absence of **pulmonary maturity**. Because phosphatidylcholine, or lecithin, is a principal component of surfactant, the determination of lecithin in amniotic fluid is used to predict a mature fetus. Lecithin concentration increases with increasing gestational age, beginning at 32 to 34 weeks.

Methods used to assess **fetal well-being** before the onset of labor are focused on identifying a fetus at risk for asphyxia or a fetus already compromised by uteroplacental insufficiency. The **oxytocin challenge test** simulates uterine contractions through an infusion of oxytocin sufficient to produce three contractions in a 10-minute period. The development of periodic fetal bradycardia out of phase with uterine contractions (late deceleration) is a positive test result and predicts an at-risk fetus.

The **nonstress test** examines the heart rate response to fetal body movements. Heart rate increases of more than 15 beats/min lasting 15 seconds, are reassuring. If two such episodes occur in 30 minutes, the test result is considered reactive (versus nonreactive), and the fetus is not at risk. Additional signs of fetal well-being are fetal breathing movements, gross body movements, fetal tone, and the presence of amniotic fluid pockets more than 2 cm in size, detected by ultrasound. The **biophysical profile** combines the nonstress test with these four parameters and offers the most accurate fetal assessment.

**Doppler examination** of the fetal aorta or umbilical arteries permits identification of decreased or reversed diastolic blood flow associated with increased peripheral vascular resistance, fetal hypoxia with acidosis, and placental insufficiency. **Cordocentesis** (percutaneous umbilical blood sampling) can provide fetal blood for $P_{O_2}$, pH, lactate, and hemoglobin measurements to identify a hypoxic, acidicotic, or anemic fetus who is at risk for intrauterine fetal demise or birth asphyxia. Cordocentesis also can be used to determine fetal blood type, platelet count, microbial testing, antibody titer, and rapid karyotype.

In a high-risk pregnancy, the fetal heart rate should be monitored continuously during labor, as should uterine contractions. Fetal heart rate abnormalities may indicate baseline tachycardia (>160 beats/min as a result of anemia, β-sympathomimetic drugs, maternal fever, hyperthyroidism, arrhythmia, or fetal distress), baseline **bradycardia** (<120 beats/min as a result of fetal distress, complete heart block, or local anesthetics), or reduced beat-to-beat variability (flattened tracing resulting from fetal sleep, tachycardia, atropine, sedatives, prematurity, or fetal distress). Periodic changes of the heart rate relative to uterine pressure help determine the presence of hypoxia and acidosis caused by uteroplacental insufficiency or maternal hypotension (late or type II decelerations) or by umbilical cord compression (variable decelerations). In the presence of severe decelerations (late or repeated prolonged variable), a fetal scalp blood gas level should be obtained to assess **fetal acidosis**. A scalp pH of less than 7.20 indicates fetal hypoxic compromise. A pH between 7.20 and 7.25 is in a borderline zone and warrants repeat testing.

Fetal anomalies may be detected by ultrasonography. Emphasis should be placed on visualization of the genitourinary tract; the head (for anencephaly or hydrocephaly), neck (for thickened nuchal translucency), and back (for spina bifida); skeleton; gastrointestinal tract; and heart. Four-chamber and great artery views are required for detection of heart anomalies. **Chromosomal anomaly syndromes** are often associated with an abnormal “triple test” (low estriols, low maternal serum alpha-fetoprotein levels, and elevated placental chorionic gonadotropin levels). If a fetal abnormality is detected, fetal therapy or delivery with therapy in the neonatal intensive care unit may be lifesaving.

### ASSESSMENT OF THE NEWBORN

The approach to the birth of an infant requires a detailed history (Table 58-3). Knowing the mother’s risk factors enables the delivery room team to anticipate problems that may occur after birth. The history of a woman’s labor and delivery can reveal events that might lead to complications affecting either the mother or the neonate, even when the pregnancy was previously considered low risk. Anticipating the need to resuscitate a newborn as a result of fetal distress increases the likelihood of successful resuscitation.

The **transition from fetal to neonatal physiology** occurs at birth. Oxygen transport across the placenta results in a gradient between the maternal and fetal $P_{O_2}$. Although fetal oxygenated blood has a low $P_{O_2}$ level compared with that of adults and infants, the fetus is not anaerobic. Fetal oxygen uptake and consumption are similar to neonatal rates, even though the thermal environments and activity levels of fetuses and neonates differ. The oxygen content of fetal blood
is almost equal to the oxygen content in older infants and children because fetal blood has a much higher concentration of hemoglobin. Fetal hemoglobin (two alpha and two gamma chains) has a higher affinity for oxygen than adult hemoglobin, facilitating oxygen transfer across the placenta. The fetal hemoglobin-oxygen dissociation curve is shifted to the left of the adult curve (Fig. 58-1); at the same Pao2 level, fetal hemoglobin is more saturated than adult hemoglobin. Because fetal hemoglobin functions on the steep, lower end of the oxygen saturation curve (Pao2, 20 to 30 mm Hg), however, oxygen unloading to the tissue is not deficient. In contrast, at the higher oxygen concentrations present in the placenta, oxygen loading is enhanced. In the last trimester, fetal hemoglobin production begins to decrease as adult hemoglobin production begins to increase, becoming the only hemoglobin available to the infant by 3 to 6 months of life. At this time, the fetal hemoglobin dissociation curve has shifted to the adult position.

A portion of well-oxygenated umbilical venous blood returning to the heart from the placenta perfuses the liver. The remainder bypasses the liver through a shunt (the ductus venosus) and enters the inferior vena cava. This oxygenated blood in the vena cava constitutes 65% to 70% of venous return to the right atrium. The crista dividens in the right atrium directs one third of this blood across the patent foramen ovale to the left atrium, where it subsequently is pumped to the coronary, cerebral, and upper extremity circulations by the left ventricle. Venous return from the upper body combines with the remaining two thirds of the vena caval blood in the right atrium and is directed to the right ventricle. This mixture of venous low-oxygenated blood from the upper and lower body enters the pulmonary artery. Only 8% to 10% of it is pumped to the pulmonary circuit; the remaining 80% to 92% of the right ventricular output bypasses the lungs through a patent ductus arteriosus and enters the descending aorta. The amount of blood flowing to the pulmonary system is low because vasoconstriction produced by medial muscle

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Table 58-3 Components of the Perinatal History

<table>
<thead>
<tr>
<th>DEMOGRAPHIC SOCIAL INFORMATION</th>
<th>Fetal surveillance (OCT, NST, biophysical profile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Ultrasonography (anomalies, hydrops)</td>
</tr>
<tr>
<td>Race</td>
<td>Amniotic fluid analysis (L/S ratio)</td>
</tr>
<tr>
<td>Sexually transmitted infections, hepatitis, AIDS</td>
<td>Oligohydramnios-polyhydramnios</td>
</tr>
<tr>
<td>Illicit drugs, cigarettes, ethanol, cocaine</td>
<td>Vaginal bleeding</td>
</tr>
<tr>
<td>Immune status (syphilis, rubella, hepatitis B, HIV, blood group)</td>
<td>Preterm labor</td>
</tr>
<tr>
<td>Occupational exposure</td>
<td>Premature (prolonged) rupture of membranes (duration)</td>
</tr>
<tr>
<td>PAST MEDICAL DISEASES</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Colonization status (herpes simplex, group B streptococcus)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Medications/drugs</td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>Acute medical illness/exposure to infectious agents</td>
</tr>
<tr>
<td>Hematologic/malignancy</td>
<td>Fetal therapy</td>
</tr>
<tr>
<td>Collagen-vascular disease (SLE)</td>
<td>LABOR AND DELIVERY</td>
</tr>
<tr>
<td>Genetic history—inborn errors of metabolism, bleeding, jaundice</td>
<td>Duration of labor</td>
</tr>
<tr>
<td>Drug therapy</td>
<td>Presentation—vertex, breech</td>
</tr>
<tr>
<td>PRIOR PREGNANCY</td>
<td>Vaginal versus cesarean section</td>
</tr>
<tr>
<td>Abortion/stillbirths</td>
<td>Spontaneous labor versus augmented or induced with oxytocin (Pitocin)</td>
</tr>
<tr>
<td>Intrauterine fetal demise</td>
<td>Forceps delivery</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>Presence of meconium-stained fluid</td>
</tr>
<tr>
<td>Incompetent cervix</td>
<td>Maternal fever/amnionitis</td>
</tr>
<tr>
<td>Birth weight</td>
<td>Fetal heart rate patterns (distress)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>Scalp pH</td>
</tr>
<tr>
<td>Twins</td>
<td>Maternal analgesia, anesthesia</td>
</tr>
<tr>
<td>Blood group sensitization/neonatal jaundice</td>
<td>Nuchal cord</td>
</tr>
<tr>
<td>Hydrops</td>
<td>Apgar score/methods of resuscitation</td>
</tr>
<tr>
<td>Infertility</td>
<td>Gestational age assessment</td>
</tr>
<tr>
<td>PRESENT PREGNANCY</td>
<td>Growth status (AGA, LGA, SGA)</td>
</tr>
<tr>
<td>Current gestational age</td>
<td></td>
</tr>
<tr>
<td>Method of assessing gestational age</td>
<td></td>
</tr>
</tbody>
</table>

AGA, Average for gestational age; AIDS, acquired immunodeficiency syndrome; LGA, large for gestational age; L/S, lecithin-to-sphingomyelin ratio; NST, nonstress test; OCT, oxytocin challenge test; SGA, small for gestational age; SLE, systemic lupus erythematosus.
hypertrophy of the pulmonary arterioles and fluid in the fetal lung increases resistance to blood flow. Pulmonary artery tone also responds to hypoxia, hypercapnia, and acidosis with vasoconstriction, a response that may increase pulmonary vascular resistance further. The ductus arteriosus remains patent in the fetus because of low Pao2 levels and dilating prostaglandins. In utero, the right ventricle is the dominant ventricle, pumping 65% of the combined ventricular output, which is a high volume (450 mL/kg/min) compared with that pumped by an older infant's right ventricle (200 mL/kg/min).

The transition of the circulation, occurring between the fetal and neonatal periods, involves the removal of the low-resistance circulation of the placenta, the onset of breathing, reduction of pulmonary arterial resistance, and closure of in utero shunts. Clamping the umbilical cord eliminates the low-pressure system of the placenta and increases systemic blood pressure. Decreased venous return from the placenta decreases right atrial pressure. As breathing begins, air replaces lung fluid, maintaining the functional residual capacity. Fluid leaves the lung, in part, through the trachea; it is either swallowed or squeezed out during vaginal delivery. The pulmonary lymphatic and venous systems reabsorb the remaining fluid.

Most normal infants require little pressure to spontaneously open the lungs after birth (5 to 10 cm H2O). With the onset of breathing, pulmonary vascular resistance decreases, partly a result of the mechanics of breathing and partly a result of the elevated arterial oxygen tensions. The increased blood flow to the lungs increases the volume of pulmonary venous blood returning to the left atrium; left atrial pressure now exceeds right atrial pressure, and the foramen ovale closes. As the flow through the pulmonary circulation increases and arterial oxygen tensions rise, the ductus arteriosus begins to constrict. In a term infant, this constriction functionally closes the ductus arteriosus within 1 day after birth. A permanent closure requires thrombosis and fibrosis, a process that may take several weeks. In a premature infant, the ductus arteriosus is less sensitive to the effects of oxygen; if circulating levels of vasodilating prostaglandins are elevated, the ductus arteriosus may remain patent. This patency is a common problem in a premature infant with respiratory distress syndrome.

Ventilation, oxygenation, and normal pH and Pco2 levels immediately reduce pulmonary artery vasoconstriction by causing smooth muscle relaxation. Remodeling of the medial muscle hypertrophy begins at birth and continues for the next 3 months, resulting in a further reduction of pulmonary vascular resistance and a further increase of pulmonary blood flow. Persistence or aggravation of pulmonary vasoconstriction caused by acidosis, hypoxia, hypercapnia, hypothermia, polycythemia, asphyxia, shunting of blood from the lungs, or pulmonary parenchymal hypoplasia results in persistent pulmonary hypertension of the newborn (PPHN). Failure to replace pulmonary alveolar fluid completely with air can lead to respiratory distress (transient tachypnea of the newborn).

**Routine Delivery Room Care and Resuscitation**

Silver nitrate (1%) instilled into both eyes without being washed out is an indicated effective therapy for the prevention of neonatal gonococcal ophthalmia, which can result in severe panophthalmitis and subsequent blindness. Silver nitrate may produce a chemical conjunctivitis with a mucopurulent discharge and is not effective against C. trachomatis. Many hospitals use erythromycin drops to prevent neonatal gonococcal and chlamydial eye disease.

Bacterial colonization of a newborn may begin in utero if the fetal membranes have been ruptured. Most infants undergo colonization after birth and acquire the bacteria present in the mother’s genitourinary system, such as group B streptococci, staphylococci, E. coli, and clostridia. Antiseptic skin or cord care is routine in most nurseries to prevent the spread of pathologic bacteria from one infant to another and to prevent disease in the individual infant. Staphylococcal bullous impetigo, omphalitis, diarrhea, and systemic disease may result from colonization with virulent S. aureus. Triple antibiotic ointment (polymyxin B, neomycin, and bacitracin) or bacitracin may be applied to the umbilical cord to reduce its colonization with gram-positive bacteria. Epidemics of S. aureus nursery infections are managed with strict infectious disease control measures (cohorting, hand washing, and monitoring for colonization).

Vitamin K prophylaxis (intramuscular) should be given to all infants to prevent hemorrhagic disease of the newborn. Before discharge, infants should receive the hepatitis B vaccine and be screened for various diseases (Tables 58-4 and 58-5).

Fetal or neonatal hypoxia, hypercapnia, poor cardiac output, and a metabolic acidosis can result from numerous conditions affecting the fetus, the placenta, or the mother. Whether in utero or after birth, asphyxia-caused hypoxic-ischemic brain injury is the result of reduced gaseous exchange through the placenta or through the lungs. Asphyxia associated with severe bradycardia or cardiac insufficiency reduces or eliminates tissue blood flow, resulting in ischemia. The fetal and neonatal circulatory systems respond to reduced oxygen availability by shunting the blood preferentially to the brain, heart, and adrenal glands and away from the intestine, kidneys, lungs, and skin.
### Table 58-4  Core Disorders Recommended for Screening by American College of Medical Genetics

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>ACRONYM</th>
<th>PRIMARY MARKER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METABOLIC DISORDERS DETECTED USING TANDEM MASS SPECTROMETRY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Organic Acid Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-ketothiolase deficiency (mitochondrial acetoacetyl CoA thiolase deficiency)</td>
<td>BKT</td>
<td>C5:1/C5OH</td>
</tr>
<tr>
<td>Cobalamin defects A, B</td>
<td>CBL (A,B)</td>
<td>C3</td>
</tr>
<tr>
<td>Isovaleric acidemia*</td>
<td>IVA</td>
<td>C5</td>
</tr>
<tr>
<td>Glutaric aciduria I</td>
<td>GA-I</td>
<td>C5DC</td>
</tr>
<tr>
<td>3-Hydroxy 3-methylglutaryl-CoA lyase deficiency*</td>
<td>HMG</td>
<td>C5OH/C5-3M-DC</td>
</tr>
<tr>
<td>Multiple carboxylase deficiency*</td>
<td>MCD</td>
<td>C3/C5OH</td>
</tr>
<tr>
<td>3-Methylcrotonyl-CoA carboxylase deficiency</td>
<td>3MCC</td>
<td>C5OH</td>
</tr>
<tr>
<td>Methylmalonic aciduria (mutase)*</td>
<td>MMA</td>
<td>C3</td>
</tr>
<tr>
<td>Propionic acidemia*</td>
<td>PA</td>
<td>C3</td>
</tr>
<tr>
<td><strong>Fatty Acid Oxidation Defects</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carnitine uptake defect (carnitine transporter defect)</td>
<td>CUD</td>
<td>C0</td>
</tr>
<tr>
<td>Long-chain hydroxyacyl-CoA dehydrogenase deficiency*</td>
<td>LCHAD/D</td>
<td>C16OH/C18:1OH</td>
</tr>
<tr>
<td>Medium-chain acyl-CoA dehydrogenase deficiency</td>
<td>MCAD/D</td>
<td>C8</td>
</tr>
<tr>
<td>Trifunctional protein deficiency*</td>
<td>TFP</td>
<td>C16OH/C18:1OH</td>
</tr>
<tr>
<td>Very long chain acyl-CoA dehydrogenase deficiency</td>
<td>VLCAD/D</td>
<td>C14:1/C14</td>
</tr>
<tr>
<td><strong>Amino Acid Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argininosuccinic aciduria (argininosuccinate lyase deficiency)*</td>
<td>ASA</td>
<td>ASA</td>
</tr>
<tr>
<td>Citrullinemia I (argininosuccinate synthase deficiency)*</td>
<td>CIT-I</td>
<td>Citrulline</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>PKU</td>
<td>Phenylalanine</td>
</tr>
<tr>
<td>Maple syrup urine disease*</td>
<td>MSUD</td>
<td>Leucine</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>HCY</td>
<td>Methionine</td>
</tr>
<tr>
<td>Tyrosinemia type I</td>
<td>TYR-I</td>
<td>Tyrosine</td>
</tr>
<tr>
<td><strong>OTHER METABOLIC DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>BIOT</td>
<td>Biotinidase activity</td>
</tr>
<tr>
<td>Galactosemia*</td>
<td>GALT</td>
<td>Total galactose, GALT activity</td>
</tr>
<tr>
<td><strong>ENDOCRINE DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia*</td>
<td>CAH</td>
<td>17-Hydroxyprogesterone</td>
</tr>
<tr>
<td>Congenital hypothyroidism</td>
<td>CH</td>
<td>T₄, TSH</td>
</tr>
<tr>
<td><strong>HEMOGLOBIN DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>HbSS</td>
<td>Hb variants</td>
</tr>
<tr>
<td>Sickle cell disorder</td>
<td>HbS/C</td>
<td>Hb variants</td>
</tr>
<tr>
<td>Hemoglobin S/β-thalassemia</td>
<td>HbS/betaTh</td>
<td>Hb variants</td>
</tr>
<tr>
<td><strong>OTHER DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>CF</td>
<td>Immunoreactive trypsinogen</td>
</tr>
<tr>
<td>Hearing</td>
<td>HEAR</td>
<td></td>
</tr>
</tbody>
</table>


*Can manifest acutely in the first week of life.

Metabolic acidosis during asphyxia is caused by the combined effects of poor cardiac output secondary to hypoxic depression of myocardial function, systemic hypoxia, and tissue anaerobic metabolism. With severe or prolonged intrauterine or neonatal asphyxia, multiple vital organs are affected (Table 58-6).

Many conditions that contribute to fetal or neonatal asphyxia are the same medical or obstetric problems associated with high-risk pregnancy (Table 58-7). Maternal diseases that interfere with uteroplacental perfusion (chronic hypertension, preeclampsia, and diabetes mellitus) place the fetus at risk for intrauterine asphyxia. Maternal epidural anesthesia and the development of the vena caval compression syndrome may produce maternal hypotension, which decreases uterine perfusion. Maternal medications given to relieve pain during labor may cross the placenta and depress the infant’s respiratory center, resulting in apnea at the time of birth.
Table 58-5  Abnormal Newborn Screening Results: Possible Implications and Initial Action to Be Taken

<table>
<thead>
<tr>
<th>NEWBORN SCREENING FINDING</th>
<th>DIFFERENTIAL DIAGNOSIS</th>
<th>INITIAL ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Phenylalanine</td>
<td>PKU, non-PKU hyperphenylalaninemia, pterin defect, galactosemia, transient hyperphenylalaninemia</td>
<td>Repeat blood specimen</td>
</tr>
<tr>
<td>1 T₄, 1 TSH</td>
<td>Congenital hypothyroidism, iodine exposure</td>
<td>Repeat blood specimen or thyroid function testing, begin thyroxine treatment</td>
</tr>
<tr>
<td>1 T₄, normal TSH</td>
<td>Maternal hyperthyroidism, thyroxine-binding globulin deficiency, secondary hypothyroidism, congenital hypothyroidism with delayed TSH elevation</td>
<td>Repeat blood specimen</td>
</tr>
<tr>
<td>1 Galactose (1-P) transferase</td>
<td>Galactosemia, liver disease, reducing substance, repeat deficiency variant (Duarte), transient</td>
<td>Clinical evaluation, urine for blood specimen. If reducing substance positive, begin lactose-free formula</td>
</tr>
<tr>
<td>1 Galactose-1-phosphate uridytransferase</td>
<td>Galactosemia, transferase deficiency variant (Duarte), transient</td>
<td>Clinical evaluation, urine for reducing substance, repeat blood specimen. If reducing substance positive, begin lactose-free formula</td>
</tr>
<tr>
<td>1 Methionine</td>
<td>Homocystinuria, isolated liver dysfunction, tyrosinemia type I, transient hypermethioninemia</td>
<td>Repeat blood and urine specimen</td>
</tr>
<tr>
<td>1 Leucine</td>
<td>Maple syrup urine disease, transient elevation</td>
<td>Clinical evaluation including urine for ketones, acid-base status, amino acid studies, immediate neonatal ICU care if urine ketones positive</td>
</tr>
<tr>
<td>1 Tyrosine</td>
<td>Tyrosinemia type I or type II, transient tyrosinemia, liver disease</td>
<td>Repeat blood specimen</td>
</tr>
<tr>
<td>1 17α-Hydroxyprogesterone</td>
<td>Congenital adrenal hyperplasia, prematurity, transient (residual fetal adrenal cortex), stress in neonatal period, early specimen collection</td>
<td>Clinical evaluation including genital examination, serum electrolytes, repeat blood specimen</td>
</tr>
<tr>
<td>S-hemoglobin</td>
<td>Sickle cell disease, sickle cell trait</td>
<td>Hemoglobin electrophoresis</td>
</tr>
<tr>
<td>1 Trypsinogen</td>
<td>Cystic fibrosis, transient, intestinal anomalies, perinatal stress, trisomies 13 and 18, renal failure</td>
<td>Repeat blood specimen, possible sweat test and DNA testing</td>
</tr>
<tr>
<td>1 Creatinine phosphokinase</td>
<td>Duchenne muscular dystrophy, other type of muscular dystrophy, birth trauma, invasive procedure</td>
<td>Repeat blood test</td>
</tr>
<tr>
<td>1 Biotinidase</td>
<td>Biotinidase deficiency</td>
<td>Serum biotinidase assay, biotin therapy</td>
</tr>
<tr>
<td>1 G6PD</td>
<td>G6PD deficiency</td>
<td>Complete blood count, bilirubin determination</td>
</tr>
<tr>
<td>1 α₁-Antitrypsin</td>
<td>α₁-Antitrypsin deficiency</td>
<td>Confirmatory test</td>
</tr>
<tr>
<td>Toxoplasma antibody (IgM)</td>
<td>Congenital toxoplasmosis</td>
<td>Infectious disease consultation</td>
</tr>
<tr>
<td>HIV antibody (IgG)</td>
<td>Maternally transmitted HIV, possible AIDS</td>
<td>Infectious disease consultation</td>
</tr>
<tr>
<td>1 Organic acids</td>
<td>Fatty acid oxidation defects (medium-chain acyl-CoA dehydrogenase deficiency)</td>
<td>Perform specific assay (tandem mass spectroscopy); frequent feeds</td>
</tr>
</tbody>
</table>

From Kim SZ, Levy HL: Newborn screening. In Taeusch HW, Ballard RA, editors: Avery's Diseases of the Newborn, ed 7, Philadelphia, 1998, Saunders. AIDS, Acquired immunodeficiency syndrome; G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus; ICU, intensive care unit; PKU, phenylketonuria; T₄, thyroxine; TSH, thyroid-stimulating hormone.

Table 58-6  Effects of Asphyxia

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Hypoxic-ischemic encephalopathy, IVH, PVL, cerebral edema, seizures, hyponatremia, hypertension</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Myocardial ischemia, poor contractility, tricuspid insufficiency, hypotension</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Persistent pulmonary hypertension, respiratory distress syndrome</td>
</tr>
<tr>
<td>Renal</td>
<td>Acute tubular or cortical necrosis</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Adrenal hemorrhage</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Perforation, ulceration, necrosis</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Inappropriate ADH, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria</td>
</tr>
<tr>
<td>Integument</td>
<td>Subcutaneous fat necrosis</td>
</tr>
<tr>
<td>Hematology</td>
<td>Disseminated intravascular coagulation</td>
</tr>
</tbody>
</table>

ADH, Antidiuretic hormone; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia.
Fetal conditions associated with asphyxia usually do not become manifested until delivery, when the infant must initiate and sustain ventilation. In addition, the upper and lower airways must be patent and unobstructed. Alveoli must be free from foreign material, such as meconium, amniotic fluid debris, and infectious exudates, which increases airway resistance, reduces lung compliance, and leads to respiratory distress and hypoxia. Some extremely immature infants weighing less than 1000 g at birth may be unable to expand their lungs, even in the absence of other pathology. Their compliant chest walls and surfactant deficiency may result in poor air exchange, retractions, hypoxia, and apnea.

The newborn (particularly a preterm infant) responds paradoxically to hypoxia with apnea rather than tachypnea as occurs in adults. Episodes of intrauterine asphyxia also may depress the neonatal central nervous system. If recovery of the fetal heart rate occurs as a result of improved uteroplacental perfusion, fetal hypoxia and acidosis may resolve. Nonetheless, if the effect on the respiratory center is more severe, a newborn may not initiate an adequate ventilatory response at birth and may undergo another episode of asphyxia.

The Apgar examination, a rapid scoring system based on physiologic responses to the birth process, is a good method for assessing the need to resuscitate a newborn (Table 58-8). At intervals of 1 minute and 5 minutes after birth, each of the five physiologic parameters is observed or elicited by a qualified examiner. Full-term infants with a normal cardiopulmonary adaptation should score 8 to 9 at 1 and 5 minutes. Apgar scores of 4 to 7 warrant close attention to determine whether the infant’s status will improve and to ascertain whether any pathologic condition is contributing to the low Apgar score.

By definition, an Apgar score of 0 to 3 represents either a cardiopulmonary arrest or a condition caused by severe bradycardia, hypoventilation, or central nervous system depression. Most low Apgar scores are caused by difficulty in establishing adequate ventilation and not by primary cardiac pathology. In addition to an Apgar score of 0 to 3, most infants with asphyxia severe enough to cause neurologic injury also manifest fetal acidosis (pH <7); seizures, coma, or hypotonia; and multiorgan dysfunction. Low Apgar scores may be caused by fetal hypoxia or other factors listed in Table 58-7. Most infants with low Apgar scores respond to assisted ventilation by face mask or by endotracheal intubation and usually do not need emergency medication.

Resuscitation of a newborn with a low Apgar score follows the same systematic sequence as that for resuscitation of older patients, but in the newborn period this simplified ABCD approach requires some qualification (Fig. 58-2). In the ABCD approach, A stands for securing a patent airway by clearing amniotic fluid or meconium by suctioning; A is also a reminder of anticipation and the need for knowing the events of pregnancy, labor, and delivery. Evidence of a diaphragmatic hernia and a low Apgar score indicate that immediate endotracheal intubation is required. If a mask and bag are used, gas enters the lung and the stomach, and the latter may act as an expanding mass in the chest that compromises respiration. If fetal hydrops has occurred with pleural effusions, bilateral thoracentesis to evacuate the pleural effusions may be needed to establish adequate ventilation.

B represents breathing. If the neonate is apneic or hypoventilating and remains cyanotic, artificial ventilation should be initiated. Ventilation should be performed with a well-fitted mask attached to an anesthesia bag and a manometer to prevent extremely high pressures from being given to the newborn; 100% oxygen should be administered through the mask.
If the infant does not revive, an endotracheal tube should be placed, attached to the anesthesia bag and manometer, and 100% oxygen should be administered. The pressure generated should begin at 20 to 25 cm H\(_2\)O, with a rate of 40 to 60 breaths/minute. An adequate response to ventilation includes good chest rise, return of breath sounds, well-oxygenated color, heart rate returning to the normal range (120 to 160 beats/minute), normal end-tidal carbon dioxide, and, later, increased muscle activity and wakefulness. The usual recovery after a cardiac arrest first involves a return to a normal heart rate, followed by disappearance of cyanosis and noticeably improved perfusion. An infant may remain limp and be apneic for a prolonged time after return of cardiac output and correction of acidosis.

Breathing initially should be briefly delayed if meconium-stained amniotic fluid is present to avoid dissemination of meconium into the lungs, producing severe aspiration pneumonia. If meconium is noted in the amniotic fluid, the oropharynx should be suctioned when the head is delivered. After the birth of a depressed infant, the oral cavity should be...
suctioned again; the vocal cords should be visualized and the infant intubated.

C represents circulation and external cardiac massage. If artificial ventilation does not improve bradycardia, if asystole is present, or if peripheral pulses cannot be palpated, external cardiac massage should be performed at a rate of 120 compressions/minute with compressions and breaths given at a ratio of 3:1. External cardiac massage usually is not needed because most infants in the delivery room respond to ventilation.

D represents the administration of drugs. If bradycardia is unresponsive to ventilation or if asystole is present, epinephrine (1:10,000), 0.1 to 0.3 mL/kg, should be given through an umbilical venous line or injected into the endotracheal tube. However, when epinephrine is administered through the endotracheal tube, the result is often unpredictable. Before medications are administered in the presence of electrical cardiac activity with poor pulses, it is important to determine whether there is a pneumothorax. Transillumination of the thorax, involving the use of a bright light through each side of the thorax and over the sternum, may suggest pneumothorax if one side transmits more light than the other. Breath sounds or endotracheal suctioning suggest pulmonary disease. Meconium staining from asphyxia, drugs, or birth trauma. The first newborn examination is an important way to detect congenital malformations or deformations (Table 58-9). Significant congenital malformations may be present in 1% to 3% of all births.

### Table 58-9 Life-Threatening Congenital Anomalies

<table>
<thead>
<tr>
<th>NAME</th>
<th>MANIFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choanal atresia (stenosis)</td>
<td>Respiratory distress in delivery room, apnea, unable to pass nasogastric tube through nares</td>
</tr>
<tr>
<td>Pierre Robin syndrome</td>
<td>Micrognathia, cleft palate, airway obstruction</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>Scaphoid abdomen, bowel sounds present in left chest, heart shifted to right, respiratory distress, polyhydramnios</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
<td>Polyhydramnios, aspiration pneumonia, excessive salivation, unable to place nasogastric tube in stomach</td>
</tr>
<tr>
<td>Intestinal obstruction: volvulus, duodenal atresia, ileal atresia</td>
<td>Polyhydramnios, bile-stained emesis, abdominal distention</td>
</tr>
<tr>
<td>Gastrochisis/omphalocele</td>
<td>Polyhydramnios; intestinal obstruction</td>
</tr>
<tr>
<td>Renal agenesis/Potter syndrome</td>
<td>Oligohydramnios, anuria, pulmonary hypoplasia, pneumothorax</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>Bilateral abdominal masses</td>
</tr>
<tr>
<td>Neural tube defects: anencephaly, meningomyelocele</td>
<td>Polyhydramnios, elevated α-fetoprotein; decreased fetal activity</td>
</tr>
<tr>
<td>Down syndrome (trisomy 21)</td>
<td>Hypotonia, congenital heart disease, duodenal atresia</td>
</tr>
<tr>
<td>Ductal-dependent congenital heart disease</td>
<td>Cyanosis, murmur, shock</td>
</tr>
</tbody>
</table>

If central nervous system depression in the infant may be due to a narcotic medication given to the mother, 0.1 mg/kg of naloxone (Narcan) can be given to the infant intravenously or endotracheally. Before this drug is administered, the ABCs should be followed carefully. Naloxone should not be given to a newborn of a mother who is suspected of being addicted to narcotics or is on methadone maintenance because the newborn may experience severe withdrawal seizures.

In babies of more than 35 weeks’ gestation suffering hypoxic ischemic injury at birth, induced therapeutic hypothermia (33.0°C to 34.0°C) for 72 hours has been shown in clinical studies to be efficacious in reducing the severity of brain injury. Brain hypothermia, whether induced by whole-body or selective head cooling, provides neuroprotection against encephalopathy presumably due to hypoxic ischemia.

### Physical Examination and Gestational Age Assessment

The first physical examination of a newborn may be a general physical examination of a well infant or an examination to confirm fetal diagnoses or to determine the cause of various manifestations of neonatal diseases. Problems in the transition from fetal to neonatal life may be detectable immediately in the delivery room or during the first day of life. Physical examination also may reveal effects of the labor and delivery resulting from asphyxia, drugs, or birth trauma. The first newborn examination is an important way to detect congenital malformations or deformations (Table 58-9). Significant congenital malformations may be present in 1% to 3% of all births.

#### Appearance

Signs such as cyanosis, nasal flaring, intercostal retractions, and grunting suggest pulmonary disease. Meconium staining of the umbilical cord, nails, and skin suggest fetal distress and the possibility of aspiration pneumonia. The level of spontaneous activity, passive muscle tone, quality of the cry, and apnea are useful screening signs to evaluate the state of the nervous system.

#### Vital Signs

The examination should proceed with an assessment of vital signs, particularly heart rate (normal rate, 120 to 160 beats/min); respiratory rate (normal rate, 30 to 60 breaths/min); temperature (usually done per rectum and later as an axillary measurement); and blood pressure (often reserved for sick infants). Length, weight, and head circumference should be measured and plotted on growth curves to determine whether growth is normal, accelerated, or retarded for the specific gestational age.
Gestational Age

Gestational age is determined by an assessment of various physical signs (Fig. 58-3) and neuromuscular characteristics (Fig. 58-4) that vary according to fetal age and maturity. **Physical criteria** mature with advancing fetal age, including increasing firmness of the pinna of the ear; increasing size of the breast tissue; decreasing fine, immature lanugo hair over the back; and decreasing opacity of the skin. **Neurologic criteria** mature with gestational age, including increasing flexion of the legs, hips, and arms; increasing tone of the flexor muscles of the neck; and decreasing laxity of the joints. These signs are determined during the first day of life and are assigned scores. The cumulative score is correlated with a gestational age, which is usually accurate to within 2 weeks (Fig. 58-5).

Gestational age assessment permits the detection of abnormal fetal growth patterns, aiding in predicting the neonatal complications of largeness or smallness for gestational age (Fig. 58-6). Infants born at a weight greater than the 90th percentile for age are considered large for gestational age. Among the risks associated with being large for gestational age are all the risks of the infant of a diabetic mother and risks associated with postmaturity. Infants born at a weight less than 10th percentile for age (some growth curves use <2 standard deviations or the 5th percentile) are small for gestational age and have IUGR. Problems associated with small for gestational age infants include congenital malformations, in addition to the problems listed in Table 58-2.

Skin

The skin should be evaluated for pallor, plethora, jaundice, cyanosis, meconium staining, petechiae, ecchymoses, congenital nevi, and neonatal rashes. Vasomotor instability with cutis marmorata, telangiectasia, phlebectasia (intermittent mottling with venous prominence), and acrocyanosis (feet and hands) is normal in a premature infant. Acrocyanosis also may be noted in a healthy term infant in the first days after birth.

The skin is covered with lanugo hair, which disappears by term gestation. **Hair tufts** over the lumbar and sacral spine suggest a spinal cord defect. **Vernix caseosa**, a soft, white, creamy layer covering the skin in preterm infants, disappears by term. Post-term infants often have peeling, parchment-like skin. **Mongolian spots** are transient, dark blue to black pigmented macules seen over the lower back and buttocks in 90% of African American, Indian, and Asian infants. **Nevus simplex** (salmon patch), or pink macular hemangioma, is common, usually transient, and noted on the back of the neck, eyelids, and forehead. **Nevus flammeus**, or port-wine stain, is seen on the face and should cause the examiner to consider Sturge-Weber syndrome (trigeminal angiomatosis, convulsions, and ipsilateral intracranial tram-line calcifications).
Congenital melanocytic nevi are pigmented lesions of varying size noted in 1% of neonates. Giant pigmented nevi are uncommon but have malignant potential. Capillary hemangiomas are raised, red lesions, whereas cavernous hemangiomas are deeper, blue masses. Both lesions increase in size after birth, then resolve when the child is 1 to 4 years of age. When enlarged, these hemangiomas may produce high-output heart failure or platelet trapping and hemorrhage. Erythema toxicum is an erythematous, papular-vesicular rash common in neonates that develops after birth and involves eosinophils in the vesicular fluid. Pustular melanosis, more common in African American infants, may be seen at birth and consists of a small, dry vesicle on a pigmented brown macular base. Erythema toxicum and pustular melanosis are benign lesions but may mimic more serious conditions, such as the vesicular rash of disseminated herpes simplex or the bullous eruption of S. aureus impetigo. Tzanck smear, Gram stain, Wright stain, direct fluorescent antibody stain, polymerase chain reaction for herpes DNA, and appropriate cultures may be needed to distinguish these rashes. Other common characteristic rashes are milia (yellow-white epidermal cysts of the pilosebaceous follicles that are noted on the nose) and miliaria (prickly heat), which is caused by obstructed sweat glands. Edema may be present in preterm infants, but also suggests hydrops fetalis, sepsis, hypoalbuminemia, or lymphatic disorders.

Skull

The skull may be elongated and molded after a prolonged labor; this resolves 2 to 3 days after birth. The sutures should be palpated to determine the width and the presence of premature fusion or cranial synostosis. The anterior and posterior
fontanelles should be soft and nonbulging, with the anterior larger than the posterior. A large fontanelle is associated with hydrocephalus, hypothyroidism, rickets, and other disorders. Soft areas away from the fontanelle are craniotabes; these lesions feel like a Ping-Pong ball when they are palpated. They may be a result of in utero compression. The skull should be examined carefully for signs of trauma or lacerations from internal fetal electrode sites or fetal scalp pH sampling; abscesses may develop in these areas.

Face, Eyes, and Mouth
The face should be inspected for dysmorphic features, such as epicanthal folds, hypertelorism, preauricular tags or sinuses, low-set ears, long philtrum, and cleft lip or palate. Facial asymmetry may be a result of seventh nerve palsy; head tilt may be caused by torticollis.

The eyes should open spontaneously, especially in an upright position. Before 28 weeks' gestational age, the eyelids may be fused. Coloboma, megalocornea, and microphthalmia suggest other malformations or intrauterine infections. A cloudy cornea greater than 1 cm in diameter also may be seen in congenital glaucoma, uveal tract dysgenesis, and storage diseases. Conjunctival and retinal hemorrhages are common and usually of no significance. The pupillary response to light is present at 28 weeks of gestation. The red reflex of the retina is shown easily. A white reflex, or leukokoria, is abnormal and may be the result of cataracts, ocular tumor, severe chorioretinitis, persistent hyperplastic primary vitreous, or retinopathy of prematurity.

The mouth should be inspected for the presence of natal teeth, clefts of the soft and hard palate and uvula, and micrognathia. A bifid uvula suggests a submucosal cleft. White, shiny, multiple transient epidermal inclusion cysts (Epstein pearls) on the hard palate are normal. Hard, marble-sized masses in the buccal mucosa are usually transient idiopathic fat necrosis. The tympanic membranes are dull, gray, opaque, and immobile in the first 1 to 4 weeks. These findings should not be confused with otitis media.

Neck and Chest
The neck appears short and symmetrical. Abnormalities include midline clefts or masses caused by thyroglossal duct cysts or by goiter and lateral neck masses (or sinuses), which are the result of branchial clefts. Cystic hygromas and hemangiomas may be present. Shortening of the sternocleidomastoid muscle with a fibrous tumor over the muscle produces head tilt and asymmetrical facies (neonatal torticollis). Arnold-Chiari malformation and cervical spine lesions also produce torticollis. Edema and webbing of the neck suggest Turner syndrome. Both clavicles should be palpated for fractures.

Examination of the chest includes inspection of the chest wall to identify asymmetry resulting from absence of the pectoralis muscle and inspection of the breast tissue to determine gestational age and detect a breast abscess. Boys and girls may have breast engorgement and produce milk; milk expression should not be attempted. Supernumerary nipples may be bilateral and may be associated with renal anomalies.

Lungs
Examination of the lungs includes observations of the rate, depth, and nature of intercostal or sternal retractions. Breath sounds should be equal on both sides of the chest, and rales should not be heard after the first 1 to 2 hours of life. Diminished or absent breath sounds on one side suggest

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**Figure 58-6** Birth weight–specific and estimated gestational age–specific mortality rates. The dashed lines of the figure represent the 10th and 90th percentile weights. The grid lines are plotted by each gestational age and in 250-g weight increments. Each number in the box is the percent mortality rate for the grid defined by gestational age and birth weight range. (From Thomas P, Peabody J, Turnier V, et al: A new look at intrauterine growth and impact of race, attitude, and gender, Pediatrics 106:E21, 2000.)
pneumothorax, collapsed lung, pleural effusion, or diaphragmatic hernia. Shift of the cardiac impulse away from a tension pneumothorax and diaphragmatic hernia and toward the collapsed lung is a helpful physical finding for differentiating these disorders. Subcutaneous emphysema of the neck or chest also suggests a pneumothorax or pneumomediastinum, whereas bowel sounds auscultated in the chest in the presence of a scaphoid abdomen suggest a diaphragmatic hernia.

Heart
The position of the heart in infants is more midline than in older children. The first heart sound is normal, whereas the second heart sound may not be split in the first day of life. Decreased splitting of the second heart sound is noted in PPHN, transposition of the great vessels, and pulmonary atresia. Heart murmurs in newborns are common in the delivery room and during the first day of life. Most of these murmurs are transient and are due to closure of the ductus arteriosus, peripheral pulmonary artery stenosis, or a small ventral septal defect. Pulses should be palpated in the upper and lower extremities (over the brachial and femoral arteries). Blood pressure in the upper and lower extremities should be measured in all patients with a murmur or heart failure. An upper-to-lower extremity gradient of more than 10 to 20 mm Hg suggests coarctation of the aorta.

Abdomen
The liver may be palpable 2 cm below the right costal margin. The spleen tip is less likely to be palpable. A left-sided liver suggests situs inversus and asplenia syndrome. Both kidneys should be palpable in the first day of life with gentle, deep palpation. The first urination occurs during the first day of life in more than 95% of normal term infants.

Abdominal masses usually represent hydronephrosis or dysplastic-multicystic kidney disease. Less often, masses indicate ovarian cysts, intestinal duplication, neuroblastoma, or mesoblastic nephroma. Masses should be evaluated immediately with ultrasound. Abdominal distention may be caused by intestinal obstructions, such as ileal atresia, meconium ileus, midgut volvulus, imperforate anus, or Hirschsprung disease. Meconium stool is passed normally within 48 hours of birth in 99% of term infants. The anus should be patent. An imperforate anus is not always visible; the first temperature taken with a rectal thermometer should be taken carefully. The abdominal wall musculature may be absent, as in prune-belly syndrome, or weak, resulting in diastasis recti. Umbilical hernias are common in African American infants. The umbilical cord should be inspected to determine the presence of two arteries and one vein and the absence of an urachus or a herniation of abdominal contents, as occurs with an omphalocele. The latter is associated with extraintestinal problems, such as genetic trisomies and hypoglycemia (Beckwith-Wiedemann syndrome). Bleeding from the cord suggests a coagulation disorder, and a chronic discharge may be a granuloma of the umbilical stump or, less frequently, a draining omphalomesenteric cyst or urachus. Erythema around the umbilicus is omphalitis and may cause portal vein thrombophlebitis and subsequent extrahepatic portal hypertension. The herniation of bowel through the abdominal wall 2 to 3 cm lateral to the umbilicus is a gastroschisis.

Genitalia
At term, the testes should be descended into a well-formed pigmented and rugged scrotum. The testes occasionally are in the inguinal canal; this is more common among preterm infants, as is cryptorchidism. Scrotal swelling may represent a hernia, transient hydrocele, in utero torsion of the testes, or, rarely, dissected meconium from meconium ileus and peritonitis. Hydroceles are clear and readily seen by transillumination, whereas testicular torsion in the newborn may present as a painless, dark swelling. The urethral opening should be at the end of the penis. Epispadias or hypospadias alone should not raise concern about pseudohermaphroditism. However, if no testes are present in the scrotum and hypospadias is present, problems of sexual development should be suspected. Circumcision should be deferred with hypospadias because the foreskin is often needed for the repair. The normal prepuce is often too tight to retract in the neonatal period.

The female genitalia normally may reveal a milky white or blood-streaked vaginal discharge as a result of maternal hormone withdrawal. Mucosal tags of the labia majora are common. Distention of an imperforate hymen may produce hydrometrocolpos and a lower midline abdominal mass as a result of an enlarged uterus. Clitoral enlargement with fusion of the labial-scrotal folds (labia majora) suggests adrenogenital syndrome or exposure to masculinizing maternal hormones.

Extremities
Examination of the extremities should involve assessment of length, symmetry, and presence of hemihypertrrophy, atrophy, polydactyly, sydactyly, simian creases, absent fingers, overlapping fingers, rocker-bottom feet, clubfoot, congenital bands, fractures, and amputations.

Spine
The spine should be examined for evidence of sacral hair tufts, a dermal sinus tract above the gluteal folds, congenital scoliosis (a result of hemivertebra), and soft tissue masses such as lipomas or meningomyeloceles.

Hips
The hips should be examined for congenital dysplasia (dislocation). Gluteal fold asymmetry or leg length discrepancy is suggestive of dysplasia, but the examiner should perform the Barlow test and the Ortolani maneuver to evaluate the stability of the hip joint. These tests determine whether the femoral head can be displaced from the acetabulum (Barlow test) and then replaced (Ortolani maneuver).

NEUROLOGIC ASSESSMENT
The neurologic examination should include assessment of active and passive tone, level of alertness, primary neonatal
(primitive) reflexes, deep tendon reflexes, spontaneous motor activity, and cranial nerves (involving retinal examination, extraocular muscle movement, masseter power as in sucking, facial motility, hearing, and tongue function). The Moro reflex, present at birth and gone in 3 to 6 months, is one of the primary newborn reflexes. It is elicited by sudden, slight dropping of the supported head from a slightly raised supine position, which should elicit opening of the hands and extension and abduction of the arms, followed by upper extremity flexion and a cry. The palmar grasp is present by 28 weeks’ gestation and gone by 4 months of age. Deep tendon reflexes may be brisk in a normal newborn; 5 to 10 beats of ankle clonus are normal. The Babinski sign is extensor (upgoing). The sensory examination can be evaluated by withdrawal of an extremity, grimace, and cry in response to painful stimuli. The rooting reflex (turning of the head toward light tactile stimulation of the perioral area) is present by 32 weeks’ gestation.

### Table 58-10 Differential Diagnosis of Neonatal Cyanosis

<table>
<thead>
<tr>
<th>SYSTEM/DISEASE</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PULMONARY</strong></td>
<td>Surfactant deficiency</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>Surfactant deficiency</td>
</tr>
<tr>
<td>Sepsis, pneumonia</td>
<td>Inflammation, pulmonary hypertension, ARDS</td>
</tr>
<tr>
<td>Meconium aspiration pneumonia</td>
<td>Mechanical obstruction, inflammation, pulmonary hypertension</td>
</tr>
<tr>
<td>Persistent pulmonary hypertension of the newborn</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>Pulmonary hypoplasia, pulmonary hypertension</td>
</tr>
<tr>
<td>Transient tachypnea</td>
<td>Retained lung fluid</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR</strong></td>
<td>Right-to-left shunt as in pulmonary atresia, tetralogy of Fallot</td>
</tr>
<tr>
<td>Cyanotic heart disease with decreased pulmonary blood flow</td>
<td>Mixing lesion as in single ventricle or truncus arteriosus</td>
</tr>
<tr>
<td>Cyanotic heart disease with increased pulmonary blood flow</td>
<td>Pulmonary edema and poor cardiac output as in hypoplastic left heart and coarctation of aorta</td>
</tr>
<tr>
<td>Cyanotic heart disease with congestive heart failure</td>
<td>Pulmonary edema and poor cardiac contractility as in sepsis, myocarditis, supraventricular tachycardia, or complete heart block; high-output failure as in PDA or vein of Galen or other arteriovenous malformations</td>
</tr>
<tr>
<td>Heart failure alone</td>
<td>Pulmonary edema and poor cardiac contractility as in sepsis, myocarditis, supraventricular tachycardia, or complete heart block; high-output failure as in PDA or vein of Galen or other arteriovenous malformations</td>
</tr>
<tr>
<td><strong>CENTRAL NERVOUS SYSTEM (CNS)</strong></td>
<td>Hypoventilation, apnea</td>
</tr>
<tr>
<td>Maternal sedative drugs</td>
<td>CNS depression</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>CNS depression, seizure</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>Hypoventilation, pulmonary hypoplasia</td>
</tr>
<tr>
<td>Neuromuscular disease</td>
<td>Hypotonia, hypovolemia, pulmonary hypoplasia</td>
</tr>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
<td>Shock</td>
</tr>
<tr>
<td>Acute blood loss</td>
<td>Shock</td>
</tr>
<tr>
<td>Chronic blood loss</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Methemoglobinemia</td>
<td>Low-affinity hemoglobin or red blood cell enzyme defect</td>
</tr>
<tr>
<td><strong>METABOLIC</strong></td>
<td>Shock (salt-losing)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>CNS depression, congestive heart failure</td>
</tr>
<tr>
<td>Adrenogenital syndrome</td>
<td>Shock (salt-losing)</td>
</tr>
</tbody>
</table>

ARDS, Acute respiratory distress syndrome; CNS, central nervous system; PDA, patent ductus arteriosus.

### Special Conditions Requiring Resuscitation in the Delivery Room: Cyanosis

Cyanosis (blue color of the hands and feet with pink color of the rest of the body) is common in the delivery room and is usually normal. Central cyanosis of the trunk, mucosal membranes, and tongue can occur at any time after birth and is always a manifestation of a serious underlying condition. Cyanosis is noted with 4 to 5 g/dL of deoxygenated hemoglobin. Central cyanosis can be caused by problems in many different organ systems, although cardiopulmonary diseases are the most common (Table 58-10). Respiratory distress
syndrome, sepsis, and cyanotic heart disease are the three most common causes of cyanosis in infants admitted to a neonatal intensive care unit. A systematic evaluation of these and other causes of cyanosis is required for every cyanotic infant after prompt administration of oxygen, with or without assisted ventilation.

Life-Threatening Congenital Malformations
Various congenital anomalies can interfere with vital organ function after birth (see Table 58-9). Some malformations, such as choanal atresia and other lesions obstructing the airway, may complicate ventilation. Intrathoracic lesions, such as cysts or diaphragmatic hernia, interfere with respiration. Other malformations that obstruct the gastrointestinal system at the level of the esophagus, duodenum, ileum, or colon may lead to aspiration pneumonia, intestinal perforation, or gangrene. Gastrochisis and omphalocle are associated with exposed bowel on the abdominal wall. Omphalocle is often associated with other malformations, whereas intestinal necrosis is more common in gastrochisis.

Shock
Shock in the delivery room is manifested by pallor, poor capillary refill time, lack of palpable pulses, hypotonia, cyanosis, and eventually cardiopulmonary arrest. Blood loss before or during labor and delivery is a common cause of shock in the delivery room. Blood loss may be caused by fetal-maternal hemorrhage, placenta previa, vasa previa, twin-to-twin transfusion syndrome, or displacement of blood from the fetus to the placenta as during asphyxia (asphyxia pallida). Hemorrhage into a viscus, such as the liver or spleen, may be noted in macromesic infants, and hemorrhage into the cerebral ventricles may produce shock and apnea in preterm infants. Anemia, hypoalbuminemia, hypovolemia, and shock at birth are common manifestations of Rh immune hydrops.

Severe intrauterine bacterial sepsis may present with shock in the delivery room or immediately after the infant is transferred to the nursery. Typically these infants are mottled, hypotonic, and cyanotic and have diminished peripheral pulses. They have a normal hemoglobin concentration but may manifest neuropaenia, thrombocytopenia, and disseminated intravascular coagulation. Peripheral symmetrical gangrene (purpuric rash) often is a sign of hypotensive shock in infants with severe congenital bacterial infections. Congenital left ventricular cardiac obstruction (critical aortic stenosis or hypoplastic left heart syndrome) also produces shock, although not usually in the delivery room.

Treatment of newborn infants with shock should involve the management approaches used for the sick infant. Problems may be anticipated through knowledge of the infant's immune status, evidence of hydrops, or suspicion of intrauterine infection or anomalies. Stabilization of the airway and institution of respiratory support are essential. Hypovolemic shock should be managed with repeated boluses of 10 to 15 mL/kg of normal saline or lactated Ringer solution. If severe immune hemolysis is predicted, blood typed against the mother's blood should be available in the delivery room and should be given to the newborn if signs of anemia and shock are present. Thereafter, all blood should be crossmatched with the infant's and mother's blood before transfusion. Drugs such as dopamine, epinephrine, or cortisol may improve cardiac output and tissue perfusion.

Birth Injury
Birth injury refers to avoidable and unavoidable injury to the fetus during the birth process. Caput succedaneum is a diffuse, edematous, often dark swelling of the soft tissue of the scalp that extends across the midline and suture lines. In infants delivered from a face presentation, soft tissue edema of the eyelids and face is an equivalent phenomenon. Caput succedaneum may be seen after prolonged labor in full-term and preterm infants. Molding of the head often is associated with caput succedaneum and is the result of pressure that is induced from overriding the parietal and frontal bones against their respective sutures.

A cephalhematoma is a subperistial hemorrhage that does not cross the suture lines surrounding the respective bones. A linear skull fracture rarely may be seen underlying a cephalhematoma. With time, the cephalhematoma may organize, calcify, and form a central depression.

Infants with cephalhematoma and caput succedaneum require no specific treatment. Occasionally a premature infant may develop a massive scalp hemorrhage. This subgaleal bleeding and the bleeding noted from a cephalhematoma may cause indirect hyperbilirubinemia requiring phototherapy. Retinal and subconjunctival hemorrhages are common but usually are small and insignificant. No treatment is necessary.

Spinal cord or spine injuries may occur in the fetus as a result of the hyperextended star gazing posture. Injuries also may occur in infants after excessive rotational (at C3–4) or longitudinal (at C7–T1) force is transmitted to the neck during vertex or breech delivery. Fractures of vertebrae are rare; trauma may cause direct damage to the spinal cord, leading to transection and permanent sequelae, hemorrhage, edema, and neurologic signs. Rarely, a snapping sound indicating cord transection rather than vertebral displacement is heard at the time of delivery. Neurologic dysfunction usually involves complete flaccid paralysis, absence of deep tendon reflexes, and absence of responses to painful stimuli below the lesion. Painful stimuli may elicit reflex flexion of the legs. Infants with spinal cord injury often are flaccid, apneic, and asphyxiated, all of which may mask the underlying spinal cord transection.

Injury to the nerves of the brachial plexus may result from excessive traction on the neck, producing paresis or complete paralysis. The mildest injury (neurapraxia) is edema; axonotmesis is more severe and consists of disrupted nerve fibers with an intact myelin sheath; neurotmesis, or complete nerve disruption or root avulsion, is most severe. Erb-Duchenne paralysis involves the fifth and sixth cervical nerves and is the most common and usually mildest injury. The infant cannot abduct the arm at the shoulder, externally rotate the arm, or supinate the forearm. The usual picture is one of painless adduction, internal rotation of the arm, and pronation of the forearm. The Moro reflex is absent on the involved side, and the hand grasp is intact. Phrenic nerve palsy (C3, C4, and C5) may lead to diaphragmatic paralysis and respiratory distress. Elevation of the diaphragm caused by nerve injury must be differentiated from elevation caused by evagination resulting from congenital weakness or absence of diaphragm muscle. Klumpke paralysis is caused by injury to the seventh and eighth cervical nerves and the first thoracic nerve, resulting
in a paralyzed hand and, if the sympathetic nerves are injured, an ipsilateral Horner syndrome (ptosis, miosis). Complete arm and hand paralysis is noted with the most severe form of damage to C5, C6, C7, C8, and T1. Treatment of brachial plexus injury is supportive and includes positioning to avoid contractures. Active and passive range of motion exercises also may be beneficial. If the deficit persists, nerve grafting may be beneficial.

Facial nerve injury may be the result of compression of the seventh nerve between the facial bone and the mother’s pelvic bones or the physician’s forceps. This peripheral nerve injury is characterized by an asymmetric crying face whose normal side, including the forehead, moves in a regular manner. The affected side is flaccid, the eye does not close, the nasolabial fold is absent, and the side of the mouth droops at rest. If there is a central injury to the facial nerve, only the lower two thirds of the face (not the forehead) are involved. Complete agenesis of the facial nucleus results in a central facial paralysis; when this is bilateral, as in Möbius syndrome, the face appears expressionless.

Skull fractures are rare, are usually linear, and require no treatment other than observation for very rare, delayed (1 to 3 months) complications (e.g., leptomeningeal cyst). Depressed skull fractures are unusual, but may be seen with complicated forceps delivery and may need surgical elevation. Fractures of the clavicle usually are unilateral and are noted in neonates after shoulder dystocia. Often a snap is heard after a difficult delivery, and the infant exhibits an asymmetrical Moro response and decreased movement of the affected side. The prognosis is excellent; many infants require no treatment or a simple figure of eight bandage to immobilize the bone.

Extremity fractures are less common than fractures of the clavicle and involve the humerus more often than the femur. Treatment involves immobilization and a triangular splint bandage for the humerus and traction suspension of the legs for femoral fractures. The prognosis is excellent.

Fractures of the facial bones are rare, but dislocation of the cartilaginous part of the nasal septum out of the vomeral groove and columella is common. Clinical manifestations include feeding difficulty, respiratory distress, asymmetrical nares, and a flattened, laterally displaced nose. Treatment reduces the dislocation by elevating the cartilage back into the vomeral groove.

Visceral trauma to the liver, spleen, or adrenal gland occurs in macrosomic infants and in extremely premature infants, with or without breech or vaginal delivery. Rupture of the liver with subcapsular hematoma formation may lead to anemia, hypovolemia, shock, hemoperitoneum, and disseminated intravascular coagulation. Infants with anemia and shock who are suspected to have an intraventricular hemorrhage but with a normal head ultrasound examination should be evaluated for hepatic or splenic rupture. Adrenal hemorrhage may be asymptomatic, detected only by finding calcified adrenal glands in normal infants. Infants with severe adrenal hemorrhage may exhibit a flank mass, jaundice, and hematuria, with or without shock.

Temperature Regulation

After birth, a newborn remains covered by amniotic fluid and situated in a cold environment (20°C to 25°C). An infant’s skin temperature may decrease 0.3°C/min, and the core temperature may decrease 0.1°C/min in the delivery room. In the absence of an external heat source, the infant must increase metabolism substantially to maintain body temperature.

Heat loss occurs through four basic mechanisms. In the cold delivery room, the wet infant loses heat predominantly by evaporation (cutaneous and respiratory loss when wet or in low humidity), radiation (loss to nearby cold, solid surfaces), and convection (loss to air current). When the infant is dry, radiation, convection, and conduction (loss to object in direct contact with infant) are important causes of heat loss. After birth, all high-risk infants should be dried immediately to eliminate evaporative heat losses. A radiant or convective heat source should be provided for these high-risk infants. Normal term infants should be dried and wrapped in a blanket.

The ideal environmental temperature is the neutral thermal environment, the ambient temperature that results in the lowest rate of heat being produced by the infant and maintains normal body temperature. The neutral thermal environmental temperature decreases with increasing gestational and postnatal age. Ambient temperatures less than the neutral thermal environment result in increasing rates of oxygen consumption for heat production, which is designed to maintain normal body temperature. If the ambient temperature decreases further or if oxygen consumption cannot increase sufficiently (due to hypoxia, hypoglycemia, or drugs), the core body temperature decreases.

Heat production by a newborn is created predominantly by nonshivering thermogenesis in specialized areas of tissue containing brown adipose tissue. Brown fat is highly vascular, contains many mitochondria per cell, and is situated around large blood vessels, resulting in rapid heat transfer to the circulation. The vessels of the neck, thorax, and interscapular region are common locations of brown fat. These tissues also are innervated by the sympathetic nervous system, which serves as a primary stimulus for heat production by brown adipose cells. Shivering does not occur in newborns.

Severe cold injury in an infant is manifested by acidosis, hypoxia, hypoglycemia, apnea, bradycardia, pulmonary hemorrhage, and a pink skin color. The color is caused by trapping of oxygenated hemoglobin in the cutaneous capillaries. Many of these infants appear dead, but most respond to treatment and recover. Milder degrees of cold injury in the delivery room may contribute to metabolic acidosis and hypoxia after birth. Conversely, hypoxia delays heat generation in cold-stressed infants.

Treatment of severe hypothermia should involve resuscitation and rapid warming of core (e.g., lung and stomach) and external surfaces. Fluid resuscitation also is needed to treat hypovolemia seen in many of these infants. Reduced core temperature (32°C to 35°C) in the immediate newborn period often requires only external warming with a radiant warmer, incubator, or both.

Elevated Temperature

Exposure to ambient temperatures above the neutral thermal environment results in heat stress and an elevated core temperature. Sweating is uncommon in newborns and may be noted only on the forehead. In response to moderate heat stress, infants may increase their respiratory rate to dissipate heat. Excessive environmental temperatures may result in heatstroke or in hemorrhagic shock encephalopathy syndrome.
Hypocalcemia is common in sick and premature newborns. Calcium levels are higher in cord blood than in maternal blood because of active placental transfer of calcium to the fetus. Fetal calcium accretion in the third trimester approaches 150 mg/kg/24 hr; fetal bone mineral content doubles between 30 and 40 weeks of gestation. All infants show a slight decline of serum calcium levels after birth, reaching a trough level at 24 to 48 hours, the point at which hypocalcemia usually occurs. Total serum calcium levels of less than 7 mg/dL and ionized calcium levels of less than 3 to 3.5 mg/dL are considered hypocalcemia.

The etiology of hypocalcemia varies with the time of onset and the associated illnesses of the child. Early neonatal hypocalcemia occurs in the first 3 days of life and is often asymptomatic. Transient hypoparathyroidism and a reduced parathyroid response to the usual postnatal decline of serum calcium levels may be responsible for hypocalcemia in premature infants and infants of diabetic mothers. Congenital absence of the parathyroid gland with DiGeorge syndrome is a cause of hypocalcemia. Hypomagnesemia (<1.5 mg/dL) may be seen simultaneously with hypocalcemia, especially in infants of diabetic mothers. Treatment with calcium alone does not relieve symptoms or increase serum calcium levels until hypomagnesemia is also treated. Sodium bicarbonate therapy, phosphate release from cell necrosis, transient hypoparathyroidism, and hypercalcitoninemia may be responsible for early neonatal hypocalcemia associated with asphyxia. Early-onset hypocalcemia associated with asphyxia often occurs with seizures as a result of hypoxic-ischemic encephalopathy.

Late neonatal hypocalcemia, or neonatal tetany, often is the result of ingestion of high-phosphate-containing milk or the inability to excrete the usual phosphorus in commercial infant formula. Hyperphosphatemia (>8 mg/dL) usually occurs in infants with hypocalcemia after the first week of life. Vitamin D deficiency states and malabsorption also have been associated with late-onset hypocalcemia.

The clinical manifestations of hypocalcemia and hypomagnesemia include apnea, muscle twitching, seizures, laryngospasm, Chvostek sign (facial muscle spasm when the side of the face over the seventh nerve is tapped), and Trousseau sign (carpopedal spasm induced by partial inflation of a blood pressure cuff). The latter two signs are rare in the immediate newborn period.

Neonatal hypocalcemia may be prevented in high-risk neonates by administration of IV or oral calcium supplementation at a rate of 25 to 75 mg/kg/24 hr. Early asymptomatic hypocalcemia of preterm infants and infants of diabetic mothers often resolves spontaneously. Symptomatic hypocalcemia should be treated with 2 to 4 mL/kg of 10% calcium gluconate given intravenously and slowly over 10 to 15 minutes, followed by a continuous infusion of 75 mg/kg/24 hr of elemental calcium. If hypomagnesemia is associated with hypocalcemia, 50% magnesium sulfate, 0.1 mL/kg, should be given by intramuscular injection and repeated every 8 to 12 hours.

The treatment of late hypocalcemia includes immediate management, as in early hypocalcemia, plus the initiation of feedings with low-phosphate formula. Subcutaneous infiltration of IV calcium salts can cause tissue necrosis; oral supplements are hypertonic and may irritate the intestinal mucosa.

**Neonatal Drug Addiction and Withdrawal**

Infants may become passively and physiologically addicted to medications or to drugs of abuse (heroin, methadone, barbiturates, tranquilizers, amphetamines) taken chronically by the mother during pregnancy; these infants subsequently may have signs and symptoms of drug withdrawal. Many of these pregnancies are at high risk for other complications related to IV drug abuse, such as hepatitis, acquired immunodeficiency syndrome (AIDS), and syphilis. In addition, the LBW rate and the long-term risk for sudden infant death syndrome are higher in the infants of these high-risk women.

**Opiates**

Neonatal withdrawal signs and symptoms usually begin at 1 to 5 days of life with maternal heroin use and at 1 to 4 weeks with maternal methadone addiction. Clinical manifestations of withdrawal include sneezing, yawning, ravenous appetite, emesis, diarrhea, fever, diaphoresis, tachypnea, high-pitched cry, tremors, jitteriness, poor sleep, poor feeding, and seizures. The illness tends to be more severe during methadone withdrawal. The initial treatment includes swaddling in blankets in a quiet, dark room. When hyperactivity is constant, and irritability interferes with sleeping and feeding, or when diarrhea or seizures are present, pharmacologic treatment is indicated. Seizures usually are treated with phenobarbital. The other symptoms may be managed with replacement doses of a narcotic (usually tincture of opium) to calm the infant; weaning from narcotics may be prolonged over 1 to 2 months.

**Cocaine**

Cocaine use during pregnancy is associated with preterm labor, abruptio placenta, neonatal irritability, and decreased attentiveness. Infants may be small for gestational age and have small head circumferences. Usually no treatment is needed.

**MATERNAL DISEASES AFFECTING THE NEWBORN**

Maternal diseases during pregnancy can affect the fetus directly or indirectly (Table 59-1). Autoantibody-mediated diseases can have direct consequences on the fetus and neonate because the antibodies are usually of the IgG type and can cross the placenta to the fetal circulation.
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**ANTIPHOSPHOLIPID SYNDROME**

Antiphospholipid syndrome is associated with thrombophilia and recurrent pregnancy loss. Antiphospholipid antibodies are found in 2% to 5% of the general healthy population, but they also may be associated with systemic lupus erythematosus and other rheumatic diseases. Obstetric complications arise from the prothrombotic effects of the antiphospholipid antibodies on placental function. Vasculopathy, infarction, and thrombosis have been identified in mothers with antiphospholipid syndrome. Antiphospholipid syndrome can include fetal growth impairment, placental insufficiency, maternal preeclampsia, and premature birth.

**IDIOPATHIC THROMBOCYTOPENIA**

Idiopathic thrombocytopenic purpura (ITP) is seen in approximately 1 to 2 per 1000 live births and is an immune process in which antibodies are directed against platelets. Platelet-associated IgG antibodies can cross the placenta and cause thrombocytopenia in the fetus and newborn. The severely thrombocytopenic fetus is at increased risk for intracranial hemorrhage. ITP during pregnancy requires close maternal and fetal management to reduce the risks of life-threatening maternal hemorrhage and trauma to the fetus at delivery. Postnatal management involves observation of the infant's platelet count. For infants who have evidence of hemorrhage, single-donor irradiated platelets may be administered to control the bleeding. The infant may benefit from an infusion of intravenous immunoglobulin. Neonatal thrombocytopenia usually resolves within 4 to 6 weeks.

**SYSTEMIC LUPUS ERYTHEMATOSUS**

Immune abnormalities in systemic lupus erythematosus (SLE) can lead to the production of anti-Ro (SS-A) and anti-La (SS-B) antibodies that can cross the placenta and injure fetal tissue. The most serious complication is damage to the cardiac conducting system, which results in **congenital heart block**. The heart block observed in association with maternal SLE tends to be complete (third degree), although less advanced blocks have been observed. The mortality rate is approximately 20%; most surviving infants require pacing. Neonatal lupus may occur and is characterized by skin lesions (sharply demarcated erythematous plaques or central atrophic macules with peripheral scaling with predilection for the eyes, face, and scalp), thrombocytopenia, autoimmune hemolysis, and hepatic involvement.

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**Table 59-1 Maternal Disease Affecting the Fetus or Neonate**

<table>
<thead>
<tr>
<th>MATERNAL DISORDER</th>
<th>FETAL EFFECTS</th>
<th>MECHANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanotic heart disease</td>
<td>Intrauterine growth restriction</td>
<td>Low fetal oxygen delivery</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Large for gestational age, hypoglycemia</td>
<td>Fetal hyperglycemia—produces hyperinsulinemia promoting growth</td>
</tr>
<tr>
<td>Severe</td>
<td>Growth retardation</td>
<td>Vascular disease, placental insufficiency</td>
</tr>
<tr>
<td>Drug addiction</td>
<td>Intrauterine growth restriction, neonatal withdrawal</td>
<td>Direct drug effect, plus poor diet</td>
</tr>
<tr>
<td>Endemic goiter</td>
<td>Hypothyroidism</td>
<td>Iodine deficiency</td>
</tr>
<tr>
<td>Graves disease</td>
<td>Transient thyrotoxicosis</td>
<td>Placental immunoglobulin passage of thyrotropin receptor antibody</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Hypocalcemia</td>
<td>Maternal calcium crosses to fetus and suppresses fetal parathyroid gland</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Intrauterine growth restriction, intrauterine fetal demise</td>
<td>Placental insufficiency, fetal hypoxia</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>Thrombocytopenia</td>
<td>Nonspecific platelet antibodies cross placenta</td>
</tr>
<tr>
<td>Infection</td>
<td>Neonatal sepsis (see Chapter 66)</td>
<td>Transplacental or ascending infection</td>
</tr>
<tr>
<td>Isoimmune neutropenia or thrombocytopenia</td>
<td>Neutropenia or thrombocytopenia</td>
<td>Specific antifetal neutrophil or platelet antibody crosses placenta after sensitization of mother</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>Placental or fetal tumor</td>
<td>Metastasis</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Transient neonatal myasthenia</td>
<td>Immunoglobulin to acetylcholine receptor crosses the placenta</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Neonatal myotonic dystrophy</td>
<td>Autosomal dominant with genetic anticipation</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Microcephaly, retardation, ventricular septal defect</td>
<td>Elevated fetal phenylalanine levels</td>
</tr>
<tr>
<td>Rh or other blood group sensitization</td>
<td>Fetal anemia, hypoalbuminemia, hydrops, neonatal jaundice</td>
<td>Antibody crosses placenta directed at fetal cells with antigen</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Congenital heart block, rash, anemia, thrombocytopenia, neutropenia, cardiomyopathy, stillbirth</td>
<td>Antibody directed at fetal heart, red and white blood cells, and platelets; lupus anticoagulant</td>
</tr>
</tbody>
</table>

NEONATAL HYPTERTHYROIDISM
Graves disease is associated with thyroid-stimulating antibodies. The prevalence of clinical hyperthyroidism in pregnancy has been reported to be about 0.1% to 0.4%; it is the second most common endocrine disorder during pregnancy (after diabetes). Neonatal hyperthyroidism is due to the transplacental passage of thyroid-stimulating antibodies; hyperthyroidism can appear rapidly within the first 12 to 48 hours. Symptoms may include intrauterine growth restriction, prematurity, goiter (may cause tracheal obstruction), exophthalmos, stare, craniosynostosis (usually coronal), flushing, heart failure, tachycardia, arrhythmias, hypertension, hypoglycemia, thrombocytopenia, and hepatosplenomegaly. Treatment includes propylthiouracil, iodine drops, and propranolol. Autoimmune induced neonatal hyperthyroidism usually resolves in 2 to 4 months.

DIABETES MELLITUS
Diabetes mellitus that develops during pregnancy (gestational diabetes is noted in about 5% of women) or diabetes that is present before pregnancy adversely influences fetal and neonatal well-being. The effect of diabetes on the fetus depends, in part, on the severity of the diabetic state: age of onset of diabetes, duration of treatment with insulin, and presence of vascular disease. Poorly controlled maternal diabetes leads to maternal and fetal hyperglycemia that stimulates the fetal pancreas, resulting in hyperplasia of the islets of Langerhans. Fetal hyperinsulinemia results in increased fat and protein synthesis, producing a fetus that is large for gestational age. After birth, hyperinsulinemia persists, resulting in fasting neonatal hypoglycemia. Strictly controlling maternal diabetes during pregnancy and preventing hyperglycemia during labor and delivery prevent macrosomic fetal growth and neonatal hypoglycemia. Additional problems of the diabetic mother and her fetus and newborn are summarized in Table 59-2.

OTHER CONDITIONS
Other maternal illnesses, such as severe pulmonary disease (cystic fibrosis), cyanotic heart disease, and sickle cell anemia, may reduce oxygen availability to the fetus. Severe hypertensive or diabetic vasculopathy can result in uteroplacental insufficiency. The fetus and the newborn may also be adversely affected by the medications used to treat maternal illnesses. These effects may appear as teratogenesis (Table 59-3) or as an adverse metabolic, neurologic, or cardiopulmonary adaptation to extraterine life (Table 59-4). Acquired infectious diseases of the mother also may affect the fetus or newborn adversely.
<table>
<thead>
<tr>
<th>AGENT</th>
<th>POTENTIAL CONDITION(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>IUGR, hypotension, bradycardia</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Adrenal corticosteroids</td>
<td>Adrenocortical failure (rare)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Bradycardia, hypothyroidism</td>
</tr>
<tr>
<td>Anesthetic agents (volatile)</td>
<td>CNS depression</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Neonatal bleeding, prolonged gestation</td>
</tr>
<tr>
<td>Atenolol</td>
<td>IUGR, hypoglycemia</td>
</tr>
<tr>
<td>Blue cohosh herbal tea</td>
<td>Neonatal heart failure</td>
</tr>
<tr>
<td>Bromides</td>
<td>CNS depression, IUGR</td>
</tr>
<tr>
<td>Captopril, enalapril</td>
<td>Transient anuric renal failure, oligohydramnios</td>
</tr>
<tr>
<td>Caudal-paracervical anesthesia with mepivacaine (accidental introduction of anesthetic into scalp of infant)</td>
<td>Bradypnea, apnea, bradycardia, convulsions</td>
</tr>
<tr>
<td>Cholinergic agents (edrophonium, pyridostigmine)</td>
<td>Transient muscle weakness</td>
</tr>
<tr>
<td>CNS depressants (narcotics, barbiturates, benzodiazepines) during labor</td>
<td>CNS depression, hypotonia</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>Positive direct Coombs test reaction</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Possible transient neonatal withdrawal, hypertonicity, minor anomalies</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Hexamethonium bromide</td>
<td>Paralytic ileus</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Oligohydramnios, PPHN</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Oliguria, oligohydramnios, intestinal perforation, PPHN</td>
</tr>
<tr>
<td>Intravenous fluids during labor (e.g., salt-free solutions)</td>
<td>Electrolyte disturbances, hyponatremia, hypoglycemia</td>
</tr>
<tr>
<td>Iodide (radioactive)</td>
<td>Goiter</td>
</tr>
<tr>
<td>Iodides</td>
<td>Neonatal goiter</td>
</tr>
<tr>
<td>Lead</td>
<td>Reduced intellectual function</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>Respiratory depression, meconium plug, hypotonia</td>
</tr>
<tr>
<td>Methimazole</td>
<td>Goiter, hypothyroidism</td>
</tr>
<tr>
<td>Morphine and its derivatives (addiction)</td>
<td>Withdrawal symptoms (poor feeding, vomiting, diarrhea, restlessness, yawning and stretching, dyspnea and cyanosis, fever and sweating, pallor, tremors, convulsions)</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Hemolytic anemia (in G6PD-deficient infants)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Hemolytic anemia (in G6PD-deficient infants)</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Hyperbilirubinemia, hyponatremia</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Bleeding diathesis (vitamin K deficiency), possible long-term reduction in IQ, sedation</td>
</tr>
<tr>
<td>Primaquine</td>
<td>Hemolytic anemia (in G6PD-deficient infants)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Hypoglycemia, bradycardia, apnea</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Goiter, hypothyroidism</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Drowsiness, nasal congestion, poor temperature stability</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Interfere with protein binding of bilirubin; kernicterus at low levels of serum bilirubin, hemolysis with G6PD deficiency</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Refractory hypoglycemia</td>
</tr>
<tr>
<td>Sympathomimetic (tocolytic-β agonist) agents</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Neonatal thrombocytopenia (rare)</td>
</tr>
</tbody>
</table>


CNS, Central nervous system; G6PD, glucose-6-phosphate dehydrogenase; IUGR, intrauterine growth restriction; PPHN, persistent pulmonary hypertension of the newborn.
Chapter 60

DISEASES OF THE FETUS

The principal determinants of fetal disease include the fetal genotype and the in utero environment. Variation in environmental factors rather than the fetal genetics plays a more significant role in determining overall fetal well-being, although a genetically abnormal fetus may not thrive as well or survive. The ability to assess a fetus genetically, biochemically, and physically is greatly enhanced through the development of amniocentesis, fetoscopy, chorionic villus sampling, fetal blood sampling, genetic testing of circulating fetal DNA in the mother’s blood, and real-time ultrasonography.

INTRAUTERINE GROWTH RESTRICTION AND SMALL FOR GESTATIONAL AGE

Fetuses subjected to abnormal maternal, placental, or fetal conditions that restrain growth are a high-risk group and traditionally classified as having intrauterine growth restriction (IUGR). The terms IUGR and SGA (small for gestational age) are not synonymous. IUGR represents a deviation from expected growth patterns. The decreased fetal growth associated with IUGR is an adaptation to unfavorable intrauterine conditions that result in permanent alterations in metabolism, growth, and development. IUGR most frequently occurs with a variety of maternal conditions that are associated with preterm delivery. SGA describes an infant whose birth weight is statistically less than the 10th percentile or two standard deviations below the mean birth weight for gestational age. The cause of SGA may be pathologic, as in an infant with IUGR, or nonpathologic, as in an infant who is small but otherwise healthy (Table 60-1).

Only about 50% of IUGR infants are identified before delivery. Measurement and recording of maternal fundal height in conjunction with serial ultrasound assessment of the fetus (growth rate, amniotic fluid volume, malformations, anomalies, and Doppler velocimetry of uterine, placental, and fetal blood flow) can aid detection. When suspected and identified, IUGR and SGA fetuses must be monitored for fetal well-being, and appropriate maternal care needs to be instituted (see Chapter 58).

At birth, infants who are mildly to moderately SGA appear smaller than normal with decreased subcutaneous fat. More severely affected infants may present with a wasted appearance with asymmetrical findings, including larger heads for the size of the body (central nervous system sparing), widened anterior fontanelles, small abdomen, thin arms and legs, decreased subcutaneous fat, dry and redundant skin, decreased muscle mass, and thin (often meconium-stained) umbilical cord. Gestational age is often difficult to assess when based on physical appearance and perceived advanced neurologic maturity. Physical examination should detail the presence of dysmorphic features, abnormal extremities, or gross anomalies that might suggest underlying congenital malformations, chromosomal defects, or exposure to teratogens. Hepatosplenomegaly, jaundice, and skin rashes in addition to ocular disorders, such as chorioretinitis, cataracts, glaucoma, and cloudy cornea, suggest the presence of a congenital infection or inborn error of metabolism. Infants with severe IUGR or SGA, particularly in conjunction with fetal distress, may have problems at birth that include respiratory acidosis, metabolic acidosis, asphyxia, hypoxemia, hypoten, hypoglycemia, polycythemia, meconium aspiration syndrome, and persistent pulmonary hypertension of the newborn.

Management of IUGR and SGA infants is usually symptomatic and supportive. The diagnostic evaluation at birth

<table>
<thead>
<tr>
<th>Table 60-1</th>
<th>Etiologies for Intrauterine Growth Restriction and Small for Gestational Age at Birth</th>
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</thead>
<tbody>
<tr>
<td><strong>MATERNAL FACTORS</strong></td>
<td></td>
</tr>
<tr>
<td>Age (young and advanced)</td>
<td></td>
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<tr>
<td>Cigarette smoking</td>
<td></td>
</tr>
<tr>
<td>Genetics (short stature, weight)</td>
<td></td>
</tr>
<tr>
<td>Illnesses during pregnancy (preeclampsia, severe diabetes, chronic hypertension, connective tissue disease)</td>
<td></td>
</tr>
<tr>
<td>Infections (intrauterine)</td>
<td></td>
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<tr>
<td>Lack of good prenatal care</td>
<td></td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td></td>
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<tr>
<td>Poor nutrition</td>
<td></td>
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<tr>
<td>Race (African American)</td>
<td></td>
</tr>
<tr>
<td><strong>FETAL FACTORS</strong></td>
<td></td>
</tr>
<tr>
<td>Chromosomal abnormality and nonchromosomal syndromes</td>
<td></td>
</tr>
<tr>
<td>Congenital infections</td>
<td></td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td></td>
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<tr>
<td>Multiple gestations</td>
<td></td>
</tr>
<tr>
<td>Insulin resistance or reduced insulin or insulin-like growth factor-1 production</td>
<td></td>
</tr>
<tr>
<td><strong>MATERNAL MEDICATIONS</strong></td>
<td></td>
</tr>
<tr>
<td>Antimetabolites (methotrexate)</td>
<td></td>
</tr>
<tr>
<td>Heavy metals (mercury, lead)</td>
<td></td>
</tr>
<tr>
<td>Hydantoin</td>
<td></td>
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<tr>
<td>Narcotics (morphine, methadone)</td>
<td></td>
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<tr>
<td>Steroids (prednisone)</td>
<td></td>
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<tr>
<td>Substance and illicit drug use (alcohol, cocaine)</td>
<td></td>
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<tr>
<td>Warfarin</td>
<td></td>
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<tr>
<td><strong>PLACENTAL AND UTERINE ABNORMALITIES</strong></td>
<td></td>
</tr>
<tr>
<td>Abruptio placenta</td>
<td></td>
</tr>
<tr>
<td>Abnormal implantation</td>
<td></td>
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<tr>
<td>Abnormal placental vessels</td>
<td></td>
</tr>
<tr>
<td>Chorioangioma</td>
<td></td>
</tr>
<tr>
<td>Circumvallate placenta</td>
<td></td>
</tr>
<tr>
<td>Fetal vessel thrombosis</td>
<td></td>
</tr>
<tr>
<td>Ischemic villus necrosis</td>
<td></td>
</tr>
<tr>
<td>Multiple gestations</td>
<td></td>
</tr>
<tr>
<td>True knots in umbilical cord</td>
<td></td>
</tr>
<tr>
<td>Villitis (congenital infection)</td>
<td></td>
</tr>
</tbody>
</table>
should be directed at identifying the cause of the IUGR and SGA, if possible. The consequences of IUGR and SGA depend on the etiology, severity, and duration of growth retardation. The mortality rates of infants who are severely affected are 5 to 20 times those of infants who are appropriate for gestational age. Postnatal growth and development depend in part on the etiology, the postnatal nutritional intake, and the social environment. Infants who have IUGR and SGA secondary to congenital infection, chromosomal abnormalities, or constitutional syndromes remain small throughout life. Infants who have growth inhibited late in gestation because of uterine constraints, placental insufficiency, or poor nutrition have catch-up growth and, under optimal environmental conditions, approach their inherited growth and development potential.

### HYDROPS FETALIS

Hydrops fetalis is caused by immune and nonimmune conditions. Hydrops fetalis is a fetal clinical condition of excessive fluid accumulation in the skin and one or more other body compartments, including the pleural space, peritoneal cavity, pericardial sac, or placenta with resultant high morbidity and mortality. Hydrops initially was described in association with Rh immune hemolytic disease (RHD). The use of Rho (D) immune globulin has reduced the incidence of isoimmune fetal hydrops. Concurrently the incidence of nonimmune hydrops has increased as a cause of this severe clinical condition.

Fetal hydrops results from an imbalance of interstitial fluid accumulation and decreased removal of fluid by the capillaries and lymphatic system. Fluid accumulation can be secondary to congestive heart failure, obstructed lymphatic flow, or decreased plasma oncotic pressure (hypoproteinemic states). Edema formation is the final common pathway for many disease processes that affect the fetus, including fetal cardiac, genetic, hematologic, metabolic, infection, or malformation syndromes.

The diagnostic workup of the hydropic fetus should focus on discovering the underlying cause. Maternal findings may include hypertension, anemia, multiple gestation, thickened placenta, and polyhydramnios, whereas fetal findings may include tachycardia, ascites, scalp and body wall edema, and pleural and pericardial effusion. Invasive fetal testing may be performed, including fetal cardiac, genetic, hematologic, metabolic, infection, or malformation syndromes.

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Management depends on the underlying cause and the gestational age of the fetus. Resuscitative efforts at delivery are often required. It is often necessary to remove ascitic fluid from the abdomen or pleural fluid to improve ventilation. Profound anemia necessitates immediate transfusion with packed red blood cells.

The overall mortality for infants with nonimmune hydrops is approximately 50%. If the diagnosis is made before 24 weeks of gestation with subsequent premature delivery, the survival rate is approximately 4% to 6%.

### RESPIRATORY DISEASES OF THE NEWBORN

Respiratory distress that becomes manifested by tachypnea, intercostal retractions, reduced air exchange, cyanosis, expiratory grunting, and nasal flaring is a nonspecific response to serious illness. The differential diagnosis of respiratory distress includes pulmonary, cardiac, hematologic, infectious, anatomic, and metabolic disorders that may involve the lungs directly or indirectly. Surfactant deficiency causes **respiratory distress syndrome (RDS)**, resulting in cyanosis and tachypnea; infection produces pneumonia, shown by interstitial or lobar infiltrates; meconium aspiration results in a chemical pneumonitis with hypoxia and pulmonary hypertension; hydrops fetalis causes anemia and hypoalbuminemia with high-output heart failure and pulmonary edema; and congenital or acquired pulmonary hypoplasia causes pulmonary hypertension and pulmonary insufficiency. It also is clinically useful to differentiate the common causes of respiratory distress according to gestational age (Table 61-1).

In addition to the specific therapy for the individual disorder, supportive care and evaluation of the infant with respiratory distress can be applied to all the problems mentioned earlier (Table 61-2). Blood gas monitoring and interpretation are key components of general respiratory care.

Treatment of hypoxemia requires knowledge of normal values. In term infants, the arterial PaO\textsubscript{2} level is 55 to 60 mm Hg at 30 minutes of life, 75 mm Hg at 4 hours, and 90 mm Hg at 24 hours. Preterm infants have lower values. Paco\textsubscript{2} levels should be 35 to 40 mm Hg, and the pH should be 7.35 to 7.40. It is imperative that arterial blood gas analysis be performed in all infants with significant respiratory distress, whether or not cyanosis is perceived. Cyanosis becomes evident when there is 5 g of unsaturated hemoglobin; anemia may interfere with the perception of cyanosis. Jaundice also may interfere with the appearance of cyanosis. Capillary blood gas determinations are useful in determining blood pH and the Paco\textsubscript{2} level but may result in falsely low blood PaO\textsubscript{2} readings. Serial blood gas levels may be monitored by an indwelling arterial catheter placed in a peripheral artery or through the umbilical artery. Another method for monitoring blood gas levels is to combine capillary blood gas techniques with noninvasive methods used.
**Table 61-1** Etiology of Respiratory Distress

<table>
<thead>
<tr>
<th>PRETERM INFANT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress syndrome (RDS)†</td>
<td></td>
</tr>
<tr>
<td>Erythroblastosis fetalis</td>
<td></td>
</tr>
<tr>
<td>Nonimmune hydrops</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td></td>
</tr>
<tr>
<td><strong>FULL-TERM INFANT</strong></td>
<td></td>
</tr>
<tr>
<td>Primary pulmonary hypertension of the neonate †</td>
<td></td>
</tr>
<tr>
<td>Meconium aspiration pneumonia†</td>
<td></td>
</tr>
<tr>
<td>Polycythemia</td>
<td></td>
</tr>
<tr>
<td>Amniotic fluid aspiration</td>
<td></td>
</tr>
<tr>
<td><strong>PRETERM AND FULL-TERM INFANT</strong></td>
<td></td>
</tr>
<tr>
<td>Bacterial sepsis (GBS)†</td>
<td></td>
</tr>
<tr>
<td>Transient tachypnea</td>
<td></td>
</tr>
<tr>
<td>Spontaneous pneumothorax</td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies (e.g., congenital lobar emphysema, cystic adenomatoid malformation, diaphragmatic hernia)</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
<td></td>
</tr>
<tr>
<td>Viral infection (e.g., herpes simplex, CMV)</td>
<td></td>
</tr>
<tr>
<td>Inborn metabolic errors</td>
<td></td>
</tr>
</tbody>
</table>

CMV, Cytomegalovirus; GBS, group B streptococcus.  
*Common.

**Table 61-2** Initial Laboratory Evaluation of Respiratory Distress

<table>
<thead>
<tr>
<th>TEST</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiograph</td>
<td>To determine reticular granular pattern of RDS; to determine presence of pneumothorax, cardiomegaly, life-threatening congenital anomalies</td>
</tr>
<tr>
<td>Arterial blood gas</td>
<td>To determine severity of respiratory compromise, hypoxemia, and hypercapnia and type of acidosis; severity determines treatment strategy</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Hemoglobin/hematocrit to determine anemia and polycythemia; white blood cell count to determine neutropenia/sepsis; platelet count and smear to determine DIC</td>
</tr>
<tr>
<td>Blood culture</td>
<td>To recover potential pathogen To determine presence of hypoglycemia, which may produce or occur simultaneously with respiratory distress; to determine stress hyperglycemia</td>
</tr>
<tr>
<td>Blood culture, Blood glucose</td>
<td>To determine structural heart disease or PPHN</td>
</tr>
<tr>
<td>Echocardiogram, ECG</td>
<td>In the presence of a murmur, cardiomegaly, or refractory hypoxia; to determine structural heart disease or PPHN</td>
</tr>
</tbody>
</table>

DIC, Disseminated intravascular coagulation; ECG, electrocardiogram; PPHN, primary pulmonary hypertension of the newborn; RDS, respiratory distress syndrome.

The lining of the alveolus consists of 90% type I cells and 10% type II cells. After 20 weeks of gestation, the type II cells contain vacuolated, osmophilic, lamellar inclusion bodies, which are packages of surface-active material (Fig. 61-1). This lipoprotein surfactant is 90% lipid and is composed predominantly of saturated phosphatidylcholine (lecithin), but also contains phosphatidylglycerol, other phospholipids, and neutral lipids. The surfactant proteins, SP-A, SP-B, SP-C, and SP-D, are packaged into the lamellar body and contribute to surface-active properties and recycling of surfactant. Surfactant prevents atelectasis by reducing surface tension at low lung volumes when it is concentrated at end expiration as the alveolar radius decreases; surfactant contributes to lung recoil by increasing surface tension at larger lung volumes when it is diluted during inspiration as the alveolar radius increases. Without surfactant, surface tension forces are not reduced, and atelectasis develops during end expiration as the alveolus collapses.

The timing of surfactant production in quantities sufficient to prevent atelectasis depends on an increase in fetal cortisol levels that begins between 32 and 34 weeks of gestation. By 34 to 36 weeks, sufficient surface-active material is produced by the type II cells in the lung, is secreted into the alveolar lumen, and is excreted into the amniotic fluid. The concentration of

**RESPIRATORY DISTRESS SYNDROME (HYALINE MEMBRANE DISEASE)**

RDS occurs after the onset of breathing and is associated with an insufficiency of pulmonary surfactant.

**Lung Development**

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of surfactant synthesis. These factors also produce pulmonary hypothermia, acidosis, hypoxemia, and rare genetic disorders. Surfactant synthesis may also be reduced as a result of hypovolemia, arterial hypoxemia, and respiratory distress. Surfactant deficiency–induced atelectasis may not be mature.

A deficiency of pulmonary surfactant (most often due to prematurity) results in atelectasis, decreased functional residual capacity, arterial hypoxemia, and respiratory distress. Surfactant synthesis may also be reduced as a result of hypovolemia, hypothermia, acidosis, hypoxemia, and rare genetic disorders of surfactant synthesis. These factors also produce pulmonary hypertension, which may contribute to RDS in larger premature infants who have developed sufficient pulmonary arteriole smooth muscle to produce vasoconstriction. Surfactant deficiency–induced atelectasis causes alveoli to be perfused but not ventilated, which results in a pulmonary shunt and hypoxemia. As atelectasis increases, the lungs become increasingly difficult to expand, and lung compliance decreases. Because the chest wall of the premature infant is very compliant, the infant attempts to overcome decreased lung compliance with increasing inspiratory pressures, resulting in retractions of the chest wall. The sequence of decreased lung compliance and chest wall retractions leads to poor air exchange, an increased physiologic dead space, alveolar hypoventilation, and hypercapnia. A cycle of hypoxia, hypercapnia, and acidosis acts on type II cells to reduce surfactant synthesis and, in some infants, on the pulmonary arterioles to produce pulmonary hypertension.

Infants at greatest risk for RDS are premature and have an immature L/S ratio. The incidence of RDS increases with decreasing gestational age. RDS develops in 30% to 60% of infants between 28 and 32 weeks of gestation. Other risk factors include delivery of a previous preterm infant with RDS, maternal diabetes, hypothermia, fetal distress, asphyxia, male sex, white race, being the second-born of twins, and delivery by cesarean section without labor.

RDS may develop immediately in the delivery room in extremely immature infants at 26 to 30 weeks of gestation. Some more mature infants (34 weeks’ gestation) may not show signs of RDS until 3 to 4 hours after birth, correlating with the initial release of stored surfactant at the onset of breathing accompanied by the ongoing inability to replace the surfactant owing to inadequate stores. Manifestations of RDS include cyanosis, tachypnea, nasal flaring, intercostal and sternal retractions, and grunting. Grunting is caused by closure of the glottis during expiration, the effect of which is to maintain lung volume (decreasing atelectasis) and gas exchange during exhalation. Atelectasis is well documented by radiographic examination of the chest, which shows a ground-glass haze in the lung surrounding air-filled bronchi (the air bronchogram) (Fig. 61-2). Severe RDS may show an airless lung field (whiteout) on a radiograph, even obliterating the distinction between the atelectatic lungs and the heart.

During the first 72 hours, infants with untreated RDS have increasing distress and hypoxemia. In infants with severe RDS, the development of edema, apnea, and respiratory failure necessitates assisted ventilation. Thereafter, uncomplicated cases show a spontaneous improvement that often is heralded by diuresis and a marked resolution of edema. Complications include the development of a pneumothorax, a patent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD). The differential diagnosis of RDS includes diseases associated with cyanosis and respiratory distress (see Table 58-10).

Clinical Manifestations

A deficiency of pulmonary surfactant (most often due to prematurity) results in atelectasis, decreased functional residual capacity, arterial hypoxemia, and respiratory distress. Surfactant synthesis may also be reduced as a result of hypovolemia, hypothermia, acidosis, hypoxemia, and rare genetic disorders of surfactant synthesis. These factors also produce pulmonary hypertension, which may contribute to RDS in larger premature infants who have developed sufficient pulmonary arteriole smooth muscle to produce vasoconstriction.
mother (and thus to the fetus) stimulates fetal lung production of surfactant; this approach requires multiple doses for at least 48 hours.

After birth, RDS may be prevented or its severity reduced by intratracheal administration of exogenous surfactant immediately after birth in the delivery room or within a few hours of birth. A mammalian-derived surfactant is currently preferred. Exogenous surfactant can be administered repeatedly during the course of RDS in patients receiving endotracheal intubation, mechanical ventilation, and oxygen therapy. Additional management includes the general supportive and ventilation care presented in Table 61-3.

The Pao₂ level should be maintained between 60 and 70 mm Hg (oxygen saturation 90%), and the pH should be maintained above 7.25. An increased concentration of warm and humidified inspired oxygen administered by a nasal cannula or an oxygen hood may be all that is needed for larger premature infants. If hypoxemia (Pao₂ <50 mm Hg) is present, and the needed inspired oxygen concentration is 70% to 100%, nasal continuous positive airway pressure should be added at a distending pressure of 8 to 10 cm H₂O. If respiratory failure ensues (Paco₂ >60 mm Hg, pH <7.20, and Pao₂ <50 mm Hg with 100% oxygen), assisted ventilation using a ventilator is indicated. Conventional rate (25 to 60 breaths/min), high-frequency jet (150 to 600 breaths/min), and oscillatory (900 to 3000 breaths/min) ventilators all have been successful in managing respiratory failure caused by severe RDS. Suggested starting settings on a conventional ventilator are fraction of inspired oxygen, 0.60 to 1.0; peak inspiratory pressure, 20 to 25 cm H²O; positive end-expiratory pressure, 5 cm H²O; and respiratory rate, 30 to 50 breaths/min.

In response to persistent hypercapnia, alveolar ventilation (tidal volume − dead space × rate) must be increased. Ventilation can be increased by an increase in the ventilator's rate or an increase in the tidal volume (the gradient between peak inspiratory pressure and positive end-expiratory pressure using a pressure-controlled ventilator). In response to hypoxia, the inspired oxygen content may be increased. Alternatively, the degree of oxygenation depends on the mean airway pressure. Mean airway pressure is directly related to positive end-expiratory pressure, 5 cm H₂O; and respiratory rate, 30 to 50 breaths/min.

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### COMPLICATIONS OF RESPIRATORY DISTRESS SYNDROME
#### Patent Ductus Arteriosus

![Figure 61-2](image)

**Figure 61-2** Respiratory distress syndrome. The infant is intubated, and the lungs show a dense reticulonodular pattern with air bronchograms (A). To evaluate rotation on the frontal chest, the lengths of the posterior ribs are compared from left to right (arrows). Because the infant is supine, the side of the longer ribs indicates to which side the thorax is rotated. In this case, the left ribs are longer, and this radiograph is a left posterior oblique view. Surfactant was administered, resulting in significant improvement in the density of the lung (B). The right lung is slightly better aerated than the left. Uneven distribution of clearing is common. (From Hilton S, Edwards D: Practical Pediatric Radiology, ed 2, Philadelphia, 1994, Saunders.)

<table>
<thead>
<tr>
<th>Table 61-3</th>
<th>Potential Causes of Neonatal Apnea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central nervous system</strong></td>
<td>IVH, drugs, seizures, hypoxic injury</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td>Pneumonia, obstructive airway lesions, atelectasis, extreme prematurity (&lt;1000 g), laryngeal reflex, phrenic nerve paralysis, severe RDS, pneumothorax</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>Sepsis, necrotizing enterocolitis, meningitis (bacterial, fungal, viral)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Oral feeding, bowel movement, gastroesophageal reflux, esophagitis, intestinal perforation</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>↓ Glucose, ↓ calcium, ↓ P₉₀, ↓ sodium, ↑ ammonia, ↑ organic acids, ↑ ambient temperature, hypothermia</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Hypotension, hypertension, heart failure, anemia, hypovolemia, change in vagal tone</td>
</tr>
<tr>
<td><strong>Idiopathic</strong></td>
<td>Immaturity of respiratory center, sleep state, upper airway collapse</td>
</tr>
</tbody>
</table>

IVH, Intraventricular hemorrhage; RDS, respiratory distress syndrome.
Pulmonary Air Leaks

Assisted ventilation with high peak inspiratory pressures and positive end-expiratory pressures may cause overdistention of alveoli in localized areas of the lung. Rupture of the alveolar epithelial lining may produce pulmonary interstitial emphysema as gas dissects along the interstitial space and the perbronchial lymphatics. Extravasation of gas into the parenchyma reduces lung compliance and worsens respiratory failure. Gas dissection into the mediastinal space produces a pneumomediastinum, occasionally dissecting into the subcutaneous tissues around the neck, causing subcutaneous emphysema.

Alveolar rupture adjacent to the pleural space produces a pneumothorax (Fig. 61-3). If the gas is under tension, the pneumothorax shifts the mediastinum to the opposite side of the chest, producing hypotension, hypoxia, and hypercapnia.
The radiographic appearance of BPD is characterized initially by lung opacification and subsequently by development of cysts accompanied by areas of overdistention and atelectasis, giving the lung a spongolike appearance. The histopathology of BPD reveals interstitial edema, atelectasis, mucosal metaplasia, interstitial fibrosis, necrotizing obliterative bronchiolitis, and overdistended alveoli.

The clinical manifestations of BPD are oxygen dependence, hypercapnia with a compensatory metabolic alkalosis, pulmonary hypertension, poor growth, and development of rightsided heart failure. Increased airway resistance with reactive airway bronchoconstriction is also noted and is treated with bronchodilating agents. Severe chest retractions produce negative interstitial pressure that draws fluid into the interstitial space. Together with cor pulmonale, these chest retractions cause fluid retention, necessitating fluid restriction and the administration of diuretics.

Patients with severe BPD may need treatment with mechanical ventilation for many months. To reduce the risk of subglottic stenosis, a tracheotomy may be indicated. To reduce oxygen toxicity and barotrauma, ventilator settings are reduced to maintain blood gases with slightly lower PaO₂ (50 mm Hg) and higher Paco₂ (50 to 75 mm Hg) levels than for infants during the acute phase of RDS. Dexamethasone therapy may reduce inflammation, improve pulmonary function, and enhance weaning of patients from assisted ventilation. However, dexamethasone may increase the risk of cerebral palsy or abnormal neuromotor developmental outcome. Older survivors of BPD have hyperinflation, reactive airways, and developmental delay. They are at risk for severe respiratory syncytial virus pneumonia and as infants should receive prophylaxis against respiratory syncytial virus.

### Retinopathy of Prematurity (Retrolental Fibroplasia)

Retinopathy of prematurity (ROP) is caused by the acute and chronic effects of oxygen toxicity on the developing blood vessels of the premature infant’s retina. The completely vascularized retina of the term infant is not susceptible to ROP. ROP is a leading cause of blindness in very low birth weight infants (<1500 g). Excessive arterial oxygen tensions produce vasoconstriction of immature retinal vasculature in the first stage of this disease. Vaso-obliteration follows if the duration and extent of hyperoxia are prolonged beyond the time when vasoconstriction is reversible. Hypercarbia and hypoxia may contribute to ROP. The subsequent proliferative stages are characterized by extraretinal fibrovascular proliferation, forming a ridge between the vascular and avascular portions of the retina, and by the development of neovascular tufts. In mild cases, vasoproliferation is noted at the periphery of the retina. Severe cases may have neovascularization involving the entire retina, retinal detachment resulting from traction on vessels as they leave the optic disc, fibrous proliferation behind the lens producing leukokoria, and synechiae displacing the lens forward, leading to glaucoma. Both eyes usually are involved, but severity may be asymmetrical.

The incidence of ROP may be reduced by careful monitoring of arterial blood gas levels in all patients receiving oxygen. Although there is no absolutely safe PaO₂ level, it is wise to keep the arterial oxygen level between 50 and 70 mm Hg in premature infants. Infants who weigh less than 1500 g or who are born before 28 weeks’ gestational age (some authors say 32 weeks) should be screened when they are 4 weeks of age or more than 34 weeks’ corrected gestational age, whichever comes first. Laser therapy or (less often) cryotherapy may be used for vitreous hemorrhage or for severe, progressive vasoproliferation. Surgery is indicated for retinal detachment. Less severe stages of ROP resolve spontaneously and without visual impairment in most patients.

### Meconium Aspiration Syndrome

Meconium-stained amniotic fluid is seen in 15% of predominantly term and post-term deliveries. Although the passage of meconium into amniotic fluid is common in infants born in the breech presentation, meconium-stained fluid should be considered clinically as a sign of fetal distress in all infants. The presence of meconium in the amniotic fluid suggests in utero distress with asphyxia, hypoxia, and acidosis.

Aspiration of amniotic fluid contaminated with particulate meconium may occur in utero in a distressed, gasping fetus; more often, meconium is aspirated into the lung immediately after delivery. Affected infants have abnormal chest radiographs, showing a high incidence of pneumonia and pneumomediastinum.

### Meconium aspiration pneumonia

Meconium aspiration pneumonia is characterized by tachypnea, hypoxia, hypercapnia, and small airway obstruction causing a ball-valve effect, leading to air trapping, overdistention, and extra-alveolar air leaks. Complete small airway obstruction produces atelectasis. Within 24 to 48 hours, a chemical pneumonitis develops in addition to the mechanical effects of airway obstruction. Abnormal pulmonary function may be caused by the meconium, in part, through inactivation of surfactant. Primary pulmonary hypertension of the newborn (PPHN) frequently accompanies meconium aspiration.
with right-to-left shunting caused by increased pulmonary vascular resistance. The chest radiograph reveals patchy infiltrates, overdistention, flattening of the diaphragm, increased anteroposterior diameter, and a high incidence of pneumomediastinum and pneumothoraces. Comorbid diseases include those associated with in utero asphyxia that initiated the passage of meconium.

**Treatment** of meconium aspiration includes general supportive care and assisted ventilation. Infants with a PPHN-like presentation should be treated for PPHN. If severe hypoxia does not subside with conventional or high-frequency ventilation, surfactant therapy, and inhaled nitric oxide, extracorporeal membrane oxygenation (ECMO) may be beneficial.

Prevention of meconium aspiration syndrome involves careful in utero monitoring to prevent asphyxia. When meconium-stained fluid is observed, the obstetrician should suction the infant's oropharynx before delivering the rest of the infant's body. If the infant is depressed with poor tone, minimal respiratory effort, and cyanosis, the infant's oropharynx should be suctioned, the vocal cords visualized, and the area below the vocal cords suctioned to remove any meconium from the trachea. Saline intrauterine amniinfusion during labor may reduce the incidence of aspiration and pneumonia.

**PRIMARY PULMONARY HYPERTENSION OF THE NEWBORN**

PPHN occurs in post-term, term, or near-term infants. PPHN is characterized by severe hypoxemia, without evidence of parenchymal lung or structural heart disease. PPHN is often seen with asphyxia or meconium-stained fluid. The chest radiograph usually reveals normal lung fields rather than the expected infiltrates and hyperinflation that may accompany meconium aspiration. Additional problems that may lead to PPHN are congenital pneumonia, hyperviscosity-polycythemia, congenital diaphragmatic hernia, pulmonary hypoplasia, congenital cyanotic heart disease, hypoglycemia, and hypothermia. Total anomalous venous return associated with obstruction of blood flow may produce a clinical picture that involves severe hypoxia and that is initially indistinguishable from PPHN; however, a chest radiograph reveals severe pulmonary venous engorgement and a small heart. Echocardiography or cardiac catheterization confirms the diagnosis.

Significant right-to-left shunting through a patent foramen ovale, through a PDA, and through intrapulmonary channels is characteristic of PPHN. The pulmonary vasculature often shows hypertrophied arterial wall smooth muscle, suggesting that the process of or predisposition to PPHN began in utero as a result of previous periods of fetal hypoxia. After birth, hypoxia, hypercapnia, and acidosis exacerbate pulmonary artery vasoconstriction, leading to further hypoxia and acidosis. Some infants with PPHN have extrapulmonary manifestations as a result of asphyxia. Myocardial injuries include heart failure, transient mitral insufficiency, and papillary muscle or myocardial infarction. Thrombocytopenia, right atrial thrombi, and pulmonary embolism also may be noted.

The **diagnosis** is confirmed by echocardiographic examination, which shows elevated pulmonary artery pressures and sites of right-to-left shunting. Echocardiography also rules out structural congenital heart disease and transient myocardial dysfunction.

**APNEA OF PREMATURITY**

Although apnea typically is associated with immaturity of the respiratory control system, it also may be the presenting sign of other diseases or pathophysiologic states that affect preterm infants (see Table 61-3). A thorough consideration of possible causes is always warranted, especially with the onset or unexpected increase in the frequency of episodes of apnea (or bradycardia).

Apnea is defined as the cessation of pulmonary airflow for a specific time interval, usually longer than 10 to 20 seconds. Bradycardia often accompanies prolonged apnea. **Central apnea** refers to a complete cessation of airflow and respiratory efforts with no chest wall movement. **Obstructive apnea** refers to the absence of noticeable airflow but with the continuation of chest wall movements. **Mixed apnea**, a combination of these two events, is the most frequent type. It may begin as a brief episode of obstruction followed by a central apnea. Alternatively, central apnea may produce upper airway closure (passive pharyngeal hypotonia), resulting in mixed apnea.

A careful evaluation to determine the cause of apnea should be performed immediately in any infant with apnea. The incidence of apnea increases as gestational age decreases. Idiopathic apnea, a disease of premature infants, appears in the absence of any other identifiable disease states during the first week of life and usually resolves by 36 to 40 weeks of postconceptual age (gestational age at birth + postnatal age). The premature infant’s process of regulating respiration is especially vulnerable to apnea. Preterm infants respond paradoxically to hypoxia by developing apnea rather than by increasing respirations as in mature infants. Poor tone of the laryngeal muscles...
ANEMIA AND HYPERBILIRUBINEMIA

ANEMIA

Embryonic hematopoiesis begins by the 20th day of gestation and is evidenced as blood islands in the yolk sac. In midgestation, erythropoiesis occurs in the liver and spleen; the bone marrow becomes the predominant site in the last trimester. Hemoglobin concentration increases from 8 to 10 g/dL at 12 weeks to 16.5 to 18 g/dL at 40 weeks. Fetal red blood cell (RBC) production is responsive to erythropoietin; the concentration of this hormone increases with fetal hypoxia and anemia.

After birth, hemoglobin levels increase transiently at 6 to 12 hours, then decline to 11 to 12 g/dL at 3 to 6 months. A premature infant (<32 weeks’ gestational age) has a lower hemoglobin concentration and a more rapid postnatal decline of hemoglobin level, which achieves a nadir 1 to 2 months after birth. Fetal and neonatal RBCs have a shorter life span (70 to 90 days) and a higher mean corpuscular volume (110 to 120 fL) than adult cells. In the fetus, hemoglobin synthesis in the last two trimesters of pregnancy produces fetal hemoglobin (hemoglobin F), composed of two alpha chains and two gamma chains. Immediately before term, the infant begins to synthesize beta-hemoglobin chains; the term infant should have some adult hemoglobin (two alpha chains and two beta chains). Fetal hemoglobin represents 60% to 90% of hemoglobin at term birth. The levels decline to adult levels of less than 5% by 4 months of age.

For a term infant, blood volume is 72 to 93 mL/kg, and for a preterm infant, blood volume is 90 to 100 mL/kg. The placenta and umbilical vessels contain approximately 20 to 30 mL/kg of additional blood that can increase neonatal blood volume and hemoglobin levels transiently for the first 3 days of life if clamping or milking (stripping) of the umbilical cord is delayed at birth. Delayed clamping may increase the risk of polycythemia and jaundice, but it improves glomerular filtration. Early clamping may lead to anemia, a cardiac murmur, poor peripheral perfusion, and less tachypnea. Hydrostatic pressure affects blood transfer between the placenta and the infant at birth. An undesired fetal-to-placental transfusion occurs if the infant is situated above the level of the placenta.

The physiologic anemia noted at 2 to 3 months of age in term infants and at 1 to 2 months of age in preterm infants is a normal process that does not result in signs of illness and does not require any treatment. It is a physiologic condition believed to be related to several factors, including increased tissue oxygenation experienced at birth, shortened RBC life span, and low erythropoietin levels.

Etiology

Symptomatic anemia in the newborn period (Fig. 62-1) may be caused by decreased RBC production, increased RBC destruction, or blood loss.

Decreased Red Blood Cell Production

Anemia caused by decreased production of RBCs appears at birth with pallor, a low reticulocyte count, and absence of erythroid precursors in the bone marrow. Potential causes of neonatal decreased RBC production include bone marrow failure syndromes (congenital RBC aplasia [Diamond-Blackfan anemia]), infection (congenital viral infections [parvovirus, rubella], acquired bacterial or viral sepsis), nutritional deficiencies (protein, iron, folate, vitamin B₁₂), and congenital leukemia.

Increased Red Blood Cell Destruction

Immunologically mediated hemolysis in utero may lead to erythroblastosis fetalis, or the fetus may be spared and hematolytic disease may appear in the newborn. Hemolysis of fetal erythrocytes is a result of blood group differences between the sensitized mother and fetus, which causes production of maternal IgG antibodies directed against an antigen on fetal cells.

ABO blood group incompatibility with neonatal hemolysis develops only if the mother has IgG antibodies from a previous exposure to A or B antigens. These IgG antibodies cross the placenta by active transport and affect the fetus or newborn. Sensitization of the mother to fetal antigens may have occurred by previous transfusions or by conditions of pregnancy that result in transfer of fetal erythrocytes into the
maternal circulation, such as first-trimester abortion, ectopic pregnancy, amniocentesis, manual extraction of the placenta, version (external or internal) procedures, or normal pregnancy.

ABO incompatibility with sensitization usually does not cause fetal disease other than extremely mild anemia. It may produce hemolytic disease of the newborn, which is manifested as significant anemia and hyperbilirubinemia. Because many mothers who have blood group O have IgG antibodies to A and B before pregnancy, the firstborn infant of A or B blood type may be affected. In contrast to Rh disease, ABO hemolytic disease does not become more severe with subsequent pregnancies. Hemolysis with ABO incompatibility is less severe than hemolysis in Rh-sensitized pregnancy, either because the anti-A or anti-B antibody may bind to nonerythroidic cells that contain A or B antigen or because fetal erythrocytes have fewer A or B antigenic determinants than they have Rh sites. With the declining incidence of Rh hemolytic disease, ABO incompatibility has become the most common cause of neonatal hyperbilirubinemia requiring therapy—currently accounting for approximately 20% of clinically significant jaundice in the newborn.

Erythroblastosis fetalis classically is caused by Rh blood group incompatibility. Most Rh-negative women have no anti-Rh antibodies at the time of their first pregnancy. The Rh antigen system consists of five antigens: C, D, E, c, and e; the d type is not antigenic. In most Rh-sensitized cases, the D antigen of the fetus sensitizes the Rh-negative (d) mother, resulting in IgG antibody production during the first pregnancy. Because most mothers are not sensitized to Rh antigens at the start of pregnancy, Rh erythroblastosis fetalis is usually a disease of the second and subsequent pregnancies. The first affected pregnancy results in an antibody response in the mother, which may be detected during antenatal screening with the Coombs test and determined to be anti-D antibody. The first affected newborn may show no serious fetal disease and may manifest hemolytic disease of the newborn only by the development of anemia and hyperbilirubinemia. Subsequent pregnancies result in an increasing severity of response because of an earlier onset of hemolysis in utero. Fetal anemia, heart failure, elevated venous pressure, portal vein obstruction, and hypoalbuminemia result in fetal hydrops, which is characterized by ascites, pleural and pericardial effusions, and anasarca (see Chapter 60). The risk of fetal death is high.

The management of a pregnancy complicated by Rh sensitization depends on the severity of hemolysis, its effects on the fetus, and the maturity of the fetus at the time it becomes affected. The severity of the hemolysis can be assessed by the quantity of bilirubin transferred from the fetus to the amniotic fluid, quantified by spectrophotometric analysis of the optical density (at 450 nm) of amniotic fluid.
Three zones of optical densities with decreasing slopes toward term gestation have been developed to predict the severity of the illness. The high optical density zone 3 is associated with severe hemolysis. Fetuses in the lower zones probably are not affected. If a fetus's optical density measurement for bilirubin falls into zone 3, and the fetus has pulmonary maturity as determined by the lecithin-to-sphingomyelin ratio, the infant should be delivered and treated in the neonatal intensive care unit. If the lungs are immature and the fetus is between 22 and 33 weeks of gestational age, an ultrasound-guided intrauterine transfusion with O-negative blood into the umbilical vein is indicated and may have to be repeated until pulmonary maturity is reached or fetal distress is detected. Indications for fetal intravascular transfusion in sensitized fetuses between 22 and 32 weeks of gestational age include a fetal hematocrit of less than 25% to 30%, fetal hydrops, and fetal distress too early in gestation for delivery. Intravascular intraterine transfusion corrects fetal anemia, improves the outcome of severe hydrops, and reduces the need for postnatal exchange transfusion, but is associated with neonatal anemia as a result of continued hemolysis plus suppressed erythropoiesis.

Prevention of sensitization of the mother carrying an Rh-positive fetus is possible by treating the mother during gestation (>28 weeks' gestational age) and within 72 hours after birth with anti-Rh-positive immune globulin (RhoGAM). The dose of RhoGAM (300 μg) is based on the ability of this amount of anti-Rh-positive antibody to bind all the possible fetal Rh-positive erythrocytes entering the maternal circulation during the fetal-to-maternal transfusion at birth (approximately 30 mL). RhoGAM may bind Rh-positive fetal erythrocytes or interfere with maternal anti-Rh-positive antibody production by another, unknown mechanism. RhoGAM is effective only in preventing sensitization to the D antigen. Other blood group antigens that can cause immune hydrops and erythroblastosis include Rh C, E, Kell, and Duffy. Anti-Kell alloimmunity produces lower amniotic bilirubin levels and a lower reticulocyte count because, in addition to hemolysis, it inhibits erythropoiesis.

Nonimmune causes of hemolysis in the newborn include RBC enzyme deficiencies of the Embden-Meyerhof pathway, such as pyruvate kinase or glucose-6-phosphate dehydrogenase deficiency. RBC membrane disorders are another cause of nonimmune hemolysis. Hereditary spherocytosis is inherited as a severe autosomal recessive form or less severe autosomal dominant form and is the result of a deficiency of spectrin, a protein of the RBC membrane. Hemoglobinopathies, such as thalassemia, are another cause of nonimmunologically mediated hemolysis.

**Blood Loss**

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**Gastrointestinal Bleeding**

Bleeding

Anemia from blood loss at birth is manifested by two patterns of presentation, depending on the rapidity of blood loss. **Acute blood loss** after fetal-maternal hemorrhage, rupture of the umbilical cord, placenta previa, or internal hemorrhage (hepatic or splenic hematoma; retroperitoneal) is characterized by pallor, diminished peripheral pulses, and shock. There are no signs of extramedullary hematopoiesis and no hepatosplenomegaly. The hemoglobin content and serum iron levels initially are normal, but the hemoglobin levels decline during the subsequent 24 hours. Newborns with chronic blood loss caused by chronic fetal-maternal hemorrhage or a twin-to-twin transfusion present with marked pallor, heart failure, hepatosplenomegaly with or without hydrops, a low hemoglobin level at birth, a hypochromic microcytic blood smear, and decreased serum iron stores. Fetal-maternal bleeding occurs in 50% to 75% of all pregnancies, with fetal blood losses ranging from 1 to 50 mL; most blood losses are 1 mL or less, 1 in 400 are approximately 30 mL, and 1 in 2000 are approximately 100 mL.

The diagnosis of fetal-maternal hemorrhage is confirmed by the Kleihauer-Betke acid elution test. Pink fetal RBCs are observed and counted in the mother's peripheral blood smear because fetal hemoglobin is resistant to acid elution; adult hemoglobin is eluted, leaving discolored maternal cells (patients with sickle cell anemia or hereditary persistence of fetal hemoglobin may have a false-positive result, and ABO incompatibility may produce a false-negative result).

**Diagnosis and Management**

Hemolysis in utero resulting from any cause may produce a spectrum of clinical manifestations at birth. Severe hydrops with anasarca, heart failure, and pulmonary edema may prevent adequate ventilation at birth, resulting in asphyxia. Infants affected with hemolysis in utero have hepatosplenomegaly and pallor and become jaundiced within the first 24 hours after birth. Less severely affected infants manifest pallor and hepatosplenomegaly at birth and become jaundiced subsequently. Patients with ABO incompatibility often are asymptomatic and show no physical signs at birth; mild anemia with jaundice develops during the first 24 to 72 hours of life.

Because hydrops, anemia, or jaundice are secondary to many diverse causes of hemolysis, a laboratory evaluation is needed in all patients with suspected hemolysis. A complete blood count, blood smear, reticulocyte count, blood type, and direct Coombs test (to determine the presence of antibody-coated RBCs) should be performed in the initial evaluation of all infants with hemolysis. Reduced hemoglobin levels, reticulocytosis, and a blood smear characterized by polychromasia and anisocytosis are expected with isoimmune hemolysis. Spherocytes commonly are observed in ABO incompatibility. The determination of the blood type and the Coombs test identify the responsible antigen and antibody in immunologically mediated hemolysis.

In the absence of a positive Coombs test and blood group differences between the mother and fetus, other causes of nonimmune hemolysis must be considered. RBC enzyme assays, hemoglobin electrophoresis, or RBC membrane tests (osmotic fragility, spectrin assay) should be performed. Internal hemorrhage also may be associated with anemia, reticulocytosis, and jaundice when the hemorrhage reabsors; ultrasound evaluation of the brain, liver, spleen, or adrenal gland may be indicated when nonimmune hemolysis is suspected. Shock is more typical in patients with internal hemorrhage, whereas in hemolytic diseases, heart failure may be seen with severe anemia. Evaluation of a possible fetal-maternal hemorrhage should include the Kleihauer-Betke test.
The treatment of symptomatic neonatal anemia is transfusion of cross-matched packed RBCs. If immune hemolysis is present, the cells to be transfused must be cross-matched against maternal and neonatal plasma. Acute volume loss may necessitate resuscitation with nonblood products, such as saline if blood is not available; packed RBCs can be given subsequently. To correct anemia and any remaining blood volume deficit, 10 to 15 mL/kg of packed RBCs should be sufficient. Cytomegalovirus-seronegative blood should be given to cytomegalovirus-seronegative infants, and all blood products should be irradiated to reduce the risk of graft-versus-host disease; blood should be screened for HIV, hepatitis B and C, and syphilis. Recombinant erythropoietin may improve the hematocrit in infants with a hyporegenerative anemia after in utero transfusion.

HYPERBILIRUBINEMIA

Hemolytic disease of the newborn is a common cause of neonatal jaundice. Nonetheless, because of the immaturity of the pathways of bilirubin metabolism, many newborn infants without evidence of hemolysis become jaundiced.

Bilirubin is produced by the catabolism of hemoglobin in the reticuloendothelial system. The tetrapyrrole ring of heme is cleaved by heme oxygenase to form equivalent quantities of biliverdin and carbon monoxide. Because no other biologic source of carbon monoxide exists, the excretion of this gas is stoichiometrically identical to the production of bilirubin. Biliverdin is converted to bilirubin by biliverdin reductase. One gram of hemoglobin produces 35 mg of bilirubin. Sources of bilirubin other than circulating hemoglobin represent 20% of bilirubin production; these sources include inefficient (shunt) hemoglobin production and lysis of precursor cells in bone marrow. Compared with adults, newborns have a twofold to threefold greater rate of bilirubin production (6 to 10 mg/kg/24 hr versus 3 mg/kg/24 hr). This increased production is caused, in part, by an increased RBC mass (higher hematocrit) and a shortened erythrocyte life span of 70 to 90 days compared with the 120-day erythrocyte life span in adults.

Bilirubin produced after hemoglobin catabolism is lipid soluble and unconjugated and reacts as an indirect reagent in the van den Bergh test. Indirect-reacting, unconjugated bilirubin is toxic to the central nervous system and is insoluble in water, limiting its excretion. Unconjugated bilirubin binds to albumin on specific bilirubin binding sites; 1 g of albumin binds 8.5 mg of bilirubin in a newborn. If the binding sites become saturated or if a competitive compound binds at the site, displacing bound bilirubin, free bilirubin becomes available to enter the central nervous system. Organic acids such as free fatty acids and drugs such as sulfisoxazole can displace bilirubin from its binding site on albumin.

Bilirubin dissociates from albumin at the hepatocyte and becomes bound to a cytoplasmic liver protein Y (ligandin). Hepatic conjugation results in the production of bilirubin diglucuronide, which is water soluble and capable of biliary and renal excretion. The enzyme glucuronosyltransferase represents the rate-limiting step of bilirubin conjugation. The concentrations of ligandin and glucuronosyltransferase are lower in newborns, particularly in premature infants, than in older children.

Conjugated bilirubin gives a direct reaction in the van den Bergh test. Most conjugated bilirubin is excreted through the bile into the small intestine and eliminated in the stool. Some bilirubin may undergo hydrolysis back to the unconjugated fraction by intestinal glucuronidase, however, and may be reabsorbed (enterohepatic recirculation). In addition, bacteria in the neonatal intestine convert bilirubin to urobilinogen and stercobilinogen, which are excreted in urine and stool and usually limit bilirubin reabsorption. Delayed passage of meconium, which contains bilirubin, also may contribute to the enterohepatic recirculation of bilirubin.

Bilirubin is produced in utero by the normal fetus and by the fetus affected by erythroblastosis fetalis. Indirect, unconjugated, lipid-soluble fetal bilirubin is transferred across the placenta and becomes conjugated by maternal hepatic enzymes. The placenta is impermeable to conjugated water-soluble bilirubin. Fetal bilirubin levels become only mildly elevated in the presence of severe hemolysis, but may increase when hemolysis produces fetal hepatic inspissated bile stasis and conjugated hyperbilirubinemia. Maternal indirect (but not direct) hyperbilirubinemia also may increase fetal bilirubin levels.

Etiology of Indirect Unconjugated Hyperbilirubinemia

Physiologic jaundice is a common cause of hyperbilirubinemia among newborns. It is a diagnosis of exclusion, made after careful evaluation has ruled out more serious causes of jaundice, such as hemolysis, infection, and metabolic diseases. Physiologic jaundice is the result of many factors that are normal physiologic characteristics of newborns: increased bilirubin production resulting from an increased RBC mass, shortened RBC life span, and hepatic immaturity of ligandin and glucuronosyltransferase. Physiologic jaundice may be exaggerated among infants of Greek and Asian ancestry.

The clinical pattern of physiologic jaundice in term infants includes a peak indirect-reacting bilirubin level of no more than 12 mg/dL on day 3 of life. In premature infants, the peak is higher (15 mg/dL) and occurs later (fifth day). The peak level of indirect bilirubin during physiologic jaundice may be higher in breast milk–fed infants than in formula-fed infants (15 to 17 mg/dL versus 12 mg/dL). This higher level may be partly a result of the decreased fluid intake of infants fed breast milk. Jaundice is unphysiologic or pathologic if it is clinically evident on the first day of life, if the bilirubin level increases more than 0.5 mg/dL/hr, if the peak bilirubin is greater than 13 mg/dL in term infants, if the direct bilirubin fraction is greater than 1.5 mg/dL, or if hepatospplenomegaly and anemia are present.

Crigler-Najjar syndrome is a serious, rare, autosomal recessive, permanent deficiency of glucuronosyltransferase that results in severe indirect hyperbilirubinemia. Type II responds to enzyme induction by phenobarbital, producing an increase in enzyme activity and a reduction of bilirubin levels. Type I does not respond to phenobarbital and manifests as persistent indirect hyperbilirubinemia, often leading to kernicterus. Gilbert disease is caused by a mutation of the promoter region of glucuronosyltransferase and results in a mild indirect hyperbilirubinemia. In the presence of another icterogenic factor (hemolysis), more severe jaundice may develop.
Breast milk jaundice may be associated with unconjugated hyperbilirubinemia without evidence of hemolysis during the first to second week of life. Bilirubin levels rarely increase to more than 20 mg/dL. Interruption of breastfeeding for 1 to 2 days results in a rapid decline of bilirubin levels, which do not increase significantly after breastfeeding resumes. Breast milk may contain an inhibitor of bilirubin conjugation or may not increase significantly after breastfeeding resumes. Breast milk may contain an inhibitor of bilirubin conjugation or may increase enterohpatic recirculation of bilirubin because of breast milk glucuronidase.

Jaundice on the first day of life is always pathologic, and immediate attention is needed to establish the cause. Early onset often is a result of hemolysis, internal hemorrhage (cephalhematoma, hepatic or splenic hematoma), or infection (Table 62-1). Infection also is often associated with direct-reacting bilirubin resulting from perinatal congenital infections or from bacterial sepsis.

Physical evidence of jaundice is observed in infants when bilirubin levels reach 5 to 10 mg/dL (versus 2 to 3 mg/dL in adults). When jaundice is observed, the laboratory evaluation for hyperbilirubinemia should include a total bilirubin measurement to determine the magnitude of hyperbilirubinemia. Bilirubin levels greater than 5 mg/dL on the first day of life or greater than 13 mg/dL thereafter in term infants should be evaluated further with measurement of indirect and direct bilirubin levels, blood typing, Coombs test, complete blood count, blood smear, and reticulocyte count. These tests must be performed before treatment of hyperbilirubinemia with phototherapy or exchange transfusion. In the absence of hemolysis or evidence for either the common or the rare causes of nonhemolytic indirect hyperbilirubinemia, the diagnosis is either physiologic or breast milk jaundice. Jaundice present after 2 weeks of age is pathologic and suggests a direct-reacting hyperbilirubinemia.

Direct-reacting hyperbilirubinemia (defined as a direct bilirubin level >2 mg/dL or >20% of the total bilirubin) is never physiologic and should always be evaluated thoroughly according to the diagnostic categories (Table 62-2). Direct-reacting bilirubin (composed mostly of conjugated bilirubin) is not neurotoxic to the infant but signifies a serious underlying disorder involving cholestasis or hepatocellular injury. The diagnostic evaluation of patients with direct-reacting hyperbilirubinemia involves the determination of the levels of liver enzymes (aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, and γ-glutamyl transpeptidase), bacterial and viral cultures, metabolic screening tests, hepatic ultrasound, sweat chloride test, and occasionally liver biopsy. In addition, the presence of dark urine and gray-white (acholic) stools with jaundice after the second week of life strongly suggests biliary atresia. The treatment of disorders manifested by direct bilirubinemia is specific for the diseases that are listed in Table 62-2. These diseases do not respond to phototherapy or exchange transfusion.

Kernicterus (Bilirubin Encephalopathy)
Lipid-soluble, unconjugated, indirect bilirubin fraction is toxic to the developing central nervous system, especially when indirect bilirubin concentrations are high and exceed the binding capacity of albumin. Kernicterus results when indirect bilirubin is deposited in brain cells and disrupts neuronal metabolism and function, especially in the basal ganglia. Indirect bilirubin may cross the blood-brain barrier because of its lipid solubility. Other theories propose that a disruption of the blood-brain barrier permits entry of a bilirubin-albumin or free bilirubin–fatty acid complex.

Kernicterus usually is noted when the bilirubin level is excessively high for gestational age. It usually does not develop in term infants when bilirubin levels are less than 20 to

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### Table 62-1: Etiology of Unconjugated Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Hemolysis Present</th>
<th>Hemolysis Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Blood group incompatibility: ABO, Rh, Kell, Duffy infection</td>
<td>Physiologic jaundice, breast milk jaundice, internal hemorrhage, polycythemia, infant of diabetic mother</td>
</tr>
<tr>
<td>Rare</td>
<td>Red blood cell enzyme defects: glucose-6-phosphate dehydrogenase, pyruvate kinase</td>
<td>Mutations of glucuronyl transferase enzyme (Crigler-Najjar syndrome, Gilbert disease), pyloric stenosis, hypothyroidism, immune thrombocytopenia</td>
</tr>
</tbody>
</table>

### Table 62-2: Etiology of Conjugated Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Etiology</th>
<th>COMMON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperalimentation cholestasis</td>
<td></td>
</tr>
<tr>
<td>CMV infection</td>
<td></td>
</tr>
<tr>
<td>Other perinatal congenital infections (TORCH)</td>
<td></td>
</tr>
<tr>
<td>Inspissated bile from prolonged hemolysis</td>
<td></td>
</tr>
<tr>
<td>Neonatal hepatitis</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiology</th>
<th>UNCOMMON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic infarction</td>
<td></td>
</tr>
<tr>
<td>Inborn errors of metabolism (galactosemia, tyrosinemia)</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td>Biliary atresia</td>
<td></td>
</tr>
<tr>
<td>Choledochal cyst</td>
<td></td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td></td>
</tr>
<tr>
<td>Neonatal iron storage disease</td>
<td></td>
</tr>
<tr>
<td>Alagille syndrome (arteriohepatic dysplasia)</td>
<td></td>
</tr>
<tr>
<td>Byler disease</td>
<td></td>
</tr>
</tbody>
</table>

**CMV, Cytomegalovirus; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex.**
25 mg/dL, but the incidence increases as serum bilirubin levels exceed 25 mg/dL. Kernicterus may be noted at bilirubin levels less than 20 mg/dL in the presence of sepsis, meningitis, hemolysis, asphyxia, hypoxia, hypothermia, hypoglycemia, bilirubin-displacing drugs (sulfa drugs), and prematurity. Other risks for kernicterus in term infants are hemolysis, jaundice noted within 24 hours of birth, and delayed diagnosis of hyperbilirubinemia. Kernicterus has developed in extremely immature infants weighing less than 1000 g when bilirubin levels are less than 10 mg/dL, because of a more permeable blood-brain barrier associated with prematurity.

The earliest clinical manifestations of kernicterus are lethargy, hypotonia, irritability, poor Moro response, and poor feeding. A high-pitched cry and emesis also may be present. Early signs are noted after day 4 of life. Later signs include bulging fontanelle, opisthotonic posturing, pulmonary hemorrhage, fever, hypertonicity, paralysis of upward gaze, and seizures. Infants with severe cases of kernicterus die in the neonatal period. Spasticity resolves in surviving infants, who may manifest later nerve deafness, choreothetoid cerebral palsy, mental retardation, enameled dysplasia, and discoloration of teeth as permanent sequelae. Kernicterus may be prevented by avoiding excessively high indirect bilirubin levels and by avoiding conditions or drugs that may displace bilirubin from albumin. Early signs of kernicterus occasionally may be reversed by immediately instituting an exchange transfusion (see later).

**Therapy of Indirect Hyperbilirubinemia**

**Phototherapy** is an effective and safe method for reducing indirect bilirubin levels, particularly when initiated before serum bilirubin increases to levels associated with kernicterus. In term infants, phototherapy is begun when indirect bilirubin levels are between 16 and 18 mg/dL. Phototherapy is initiated in premature infants when bilirubin is at lower levels, to prevent bilirubin from reaching the high concentrations necessitating exchange transfusion. Blue lights and white lights are effective in reducing bilirubin levels.

Under the effects of phototherapy light with maximal irradiance in the 425- to 475-nm wavelength band, bilirubin is transformed into isomers that are water soluble and easily excreted. Unconjugated bilirubin (IX) is in the 4Z, 15Z configuration. Phototherapy causes a photosensitizing reaction producing the reversible, more water-soluble isomer 4Z, 15E bilirubin IX. This isomer can be excreted easily, bypassing the liver’s conjugation system. Another photochemical reaction results in the rapid production of lumirubin, a more water-soluble isomer than the aforementioned isomer, which does not spontaneously revert to unconjugated native bilirubin and can be excreted in urine.

Complications of phototherapy include an increased insensible water loss, diarrhea, and dehydration. Additional problems are macular-papular red skin rash, lethargy, masking of cyanosis, nasal obstruction by eye pads, and potential for retinal damage. Skin bronzing may be noted in infants with direct-reacting hyperbilirubinemia. Infants with mild hemolytic disease of the newborn occasionally may be managed successfully with phototherapy for hyperbilirubinemia, but care must be taken to follow these infants for the late occurrence of anemia from continued hemolysis.

**Exchange transfusion** usually is reserved for infants with dangerously high indirect bilirubin levels who are at risk for kernicterus. As a rule of thumb, a level of 20 mg/dL for indirect-reacting bilirubin is the exchange number for infants with hemolysis who weigh more than 2000 g. Asymptomatic infants with physiologic or breast milk jaundice may not require exchange transfusion, unless the indirect bilirubin level exceeds 25 mg/dL. The exchangeable level of indirect bilirubin for other infants may be estimated by calculating 10% of the birth weight in grams: the level in an infant weighing 1500 g would be 15 mg/dL. Infants weighing less than 1000 g usually do not require an exchange transfusion until the bilirubin level exceeds 10 mg/dL.

The exchange transfusion usually is performed through an umbilical venous catheter placed in the inferior vena cava or, if free flow is obtained, at the confluence of the umbilical vein and the portal system. The level of serum bilirubin immediately after the exchange transfusion declines to levels that are about half of those before the exchange; levels rebound 6 to 8 hours later as a result of continued hemolysis and redistribution of bilirubin from tissue stores.

**Complications** of exchange transfusion include problems related to the blood (transfusion reaction, metabolic instability, or infection), the catheter (vessel perforation or hemorrhage), or the procedure (hypotension or necrotizing enterocolitis [NEC]). Unusual complications include thrombocytopenia and graft-versus-host disease. Continuation of phototherapy may reduce the necessity for subsequent exchange transfusions.

**Polycythemia (Hyperviscosity Syndrome)**

Polycythemia is an excessively high hematocrit (265%), which may lead to hyperviscosity that produces symptoms related to vascular stasis, hypoperfusion, and ischemia. As the hematocrit increases from 40% to 60%, there is a small increase in blood viscosity. When the central hematocrit increases to greater than 65%, the blood viscosity begins to increase markedly, and symptoms may appear. Neonatal erythrocytes are less filterable or deformable than adult erythrocytes, which further contributes to hyperviscosity. A central venous hematocrit of 65% or greater is noted in 3% to 5% of infants. Infants at special risk for polycythemia are term and post-term small for gestational age infants, infants of diabetic mothers, infants with delayed cord clamping, and infants with neonatal hypothyroidism, adrenogenital syndrome, trisomy 13, trisomy 18, trisomy 21, twin-to-twin transfusion syndrome (recipient), or Beckwith-Wiedemann syndrome. In some infants, polycythemia may reflect a compensation for prolonged periods of fetal hypoxia caused by placental insufficiency; these infants have increased erythropoietin levels at birth.

Polycythemic patients appear pellorotic or ruddy and may develop acrocyanosis. Symptoms are a result of the increased RBC mass and of vascular compromise. Seizures, lethargy, and irritability reflect abnormalities of microcirculation of the brain, whereas hyperbilirubinemia may reflect the poor hepatic circulation or the increased amount of hemoglobin that is being broken down into bilirubin. Additional problems include respiratory distress and primary pulmonary hypertension of the newborn (PPHN) that result in part from elevated pulmonary vascular resistance. The chest radiograph often reveals cardiomegaly, increased vascular markings, pleural effusions, and interstitial edema. Other problems are NEC, hypoglycemia, thrombocytopenia, priapism, testicular
of glutamate on precursor proteins, converting them into the newborn period in the absence of maternal and vitamin K–dependent factors, the adult normal range.

Of factors V, VIII, and XIII; and platelet counts are within the newborns than in adults. Fibrinogen (factor I); plasma levels vitamin K–dependent factors II, VII, IX, and X. Contact factor V, and the fibrinolytic system.

Vitamin K–dependent protein that inhibits factors VIII and X), and the fibrinolytic system.

COAGULATION DISORDERS

Disorders of coagulation are common in the neonatal period. Hemorrhage during this time may be a result of trauma, inherited permanent deficiency of coagulation factors, transient deficiencies of vitamin K–dependent factors, disorders of platelets, and disseminated intravascular coagulation (DIC) seen in sick newborns with shock or hypoxia. Thrombosis also is a potential problem in the newborn because of developmentally lower circulating levels of antithrombin III, protein C (a vitamin K–dependent protein that inhibits factors VIII and V), and the fibrinolytic system.

Coagulation factors do not pass through the placenta to the fetus, and newborn infants have relatively low levels of the vitamin K–dependent factors II, VII, IX, and X. Contact factors XI and XII, prekallikrein, and kininogen also are lower in newborns than in adults. Fibrinogen (factor I); plasma levels of factors V, VIII, and XIII; and platelet counts are within the adult normal range.

Because of the transient, relative deficiencies of the contact and vitamin K–dependent factors, the partial thromboplastin time (PTT), which is dependent on factors XII, IX, VIII, X, V, II, and I, is prolonged in the newborn period. Preterm infants have the most marked prolongation of the PTT (50 to 80 seconds) compared with term infants (35 to 50 seconds) and older, more mature infants (25 to 35 seconds). The administration of heparin and the presence of DIC, hemophilia, and severe vitamin K deficiency prolong the PTT.

The prothrombin time (PT), which is dependent on factors X, VII, V, II, and I, is a more sensitive test for vitamin K deficiency. The PT is only slightly prolonged in term infants (13 to 20 seconds) compared with preterm infants (13 to 21 seconds) and more mature patients (12 to 14 seconds). Abnormal prolongations of the PT occur with vitamin K deficiency, hepatic injury, and DIC. Levels of fibrinogen and fibrin degradation products are similar in infants and adults. The bleeding time, which reflects platelet function and number, is normal during the newborn period in the absence of maternal salicylate therapy.

Vitamin K is a necessary cofactor for the carboxylation of glutamate on precursor proteins, converting them into the more active coagulation factors II, VII, IX, and X; γ-carboxyglutamic acid binds calcium, which is required for the immediate activation of factors during hemorrhage. There is no congenital deficiency of hepatic synthesis of these precursor proteins, but in the absence of vitamin K their conversion to the active factor is not possible. Levels of protein induced by vitamin K absence increase in vitamin K deficiency and are helpful diagnostic markers; vitamin K administration rapidly corrects the coagulation defects, reducing protein induced by vitamin K absence to undetectable levels.

Although most newborns are born with reduced levels of vitamin K–dependent factors, hemorrhagic complications develop only rarely. Infants at risk for hemorrhagic disease of the newborn have the most profound deficiency of vitamin K–dependent factors, and these factors decline further after birth. Because breast milk is a poor source of vitamin K, breastfed infants are at increased risk for hemorrhage that usually occurs between days 3 and 7 of life. Bleeding usually ensues from the umbilical cord, circumcision site, intestines, scalp, mucosa, and skin, but intracranial hemorrhage places the infant at risk for fatal complications, such as intracranial bleeding.

Hemorrhage on the first day of life resulting from a deficiency of the vitamin K–dependent factors often is associated with administration to the mother of drugs that affect vitamin K metabolism in the infant. This early pattern of hemorrhage has been seen with maternal warfarin or antibiotic (e.g., isoniazid or rifampin) therapy and in infants of mothers receiving phenobarbital and phenytoin. Bleeding also may occur 1 to 3 months after birth, particularly among breastfed infants. Vitamin K deficiency in breastfed infants also should raise suspicion about the possibility of vitamin K malabsorption resulting from cystic fibrosis, biliary atresia, hepatitis, or antibiotic suppression of the colonic bacteria that produce vitamin K.

Bleeding associated with vitamin K deficiency may be prevented by administration of vitamin K to all infants at birth. Before routine administration of vitamin K, 1% to 2% of all newborns had hemorrhagic disease of the newborn. One intramuscular dose (1 mg) of vitamin K prevents vitamin K–deficiency bleeding. Treatment of bleeding resulting from vitamin K deficiency involves intravenous administration of 1 mg of vitamin K. If severe, life-threatening hemorrhage is present, fresh frozen plasma also should be given. Unusually high doses of vitamin K may be needed for hepatic disease and for maternal warfarin or anticonvulsant therapy.

Clinical Manifestations and Differential Diagnoses of Bleeding Disorders

Bleeding disorders in a newborn may be associated with cutaneous bleeding, such as cephalhematoma, subgaleal hemorrhage, ecchymosis, and petechiae. Facial petechiae are common in infants born by vertex presentation, with or without a nuchal cord, and usually are insignificant. Mucosal bleeding may appear as hematemesis, melena, or epistaxis.
Internal hemorrhage results in organ-specific dysfunction, such as seizures associated with intracranial hemorrhage. Bleeding from venipuncture or heel-stick sites, circumcision sites, or the umbilical cord also is common.

The differential diagnosis depends on the clinical circumstances associated with the hemorrhage. In a sick newborn, the differential diagnosis should include DIC, hepatic failure, and thrombocytopenia. Thrombocytopenia in an ill neonate may be secondary to consumption by trapping of platelets in a hemangioma (Kasabach-Merritt syndrome) or may be associated with perinatal, congenital, or bacterial infections; NEC; thrombotic endocarditis; PPHN; organic acidemia; maternal preeclampsia; or asphyxia. Thrombocytopenia also may be due to peripheral washout of platelets after an exchange transfusion. Treatment of a sick infant with thrombocytopenia should be directed at the underlying disorder, supplemented by infusions of platelets, blood, or both.

The etiology of DIC in a newborn includes hypoxia, hypotension, asphyxia, bacterial or viral sepsis, NEC, death of a twin while in utero, cavernous hemangioma, nonimmune hydrops, neonatal cold injury, neonatal neoplasms, and hepatic disease. The treatment of DIC should be focused primarily on therapy for the initiating or underlying disorder. Supportive management of consumptive coagulopathy involves platelet transfusions and factor replacement with fresh frozen plasma. Heparin and factor C concentrate should be reserved for infants with DIC who also have thrombosis.

Disorders of hemostasis in a well child are not associated with systemic disease in a newborn but reflect coagulation factor or platelet deficiency. Hemophilia initially is associated with cutaneous or mucosal bleeding and no systemic illness. If bleeding continues, hypovolemic shock may develop. Bleeding into the brain, liver, or spleen may result in organ-specific signs and shock.

In a well child, thrombocytopenia may be part of a syndrome such as Fanconi anemia syndrome (involving hypoplasia and aplasia of the thumb), radial aplasia-thrombocytopenia syndrome (thumbs present), or Wiskott-Aldrich syndrome. Various maternal drugs also may reduce the neonatal platelet count without producing other adverse effects. These drugs include sulfonamides, quinidine, quinine, and thiazide diuretics.

The most common causes of thrombocytopenia in well newborns are transient isoimmune thrombocytopenia and transient neonatal thrombocytopenia. Isoimmune thrombocytopenia is caused by antiplatelet antibodies produced by the HPLA1-negative mother after her sensitization to specific paternal platelet antigen (HPA-1a and HPA-5b represent 85% and 10% of cases, respectively) expressed on the fetal platelet. The incidence is 1 in 1000 to 1 in 2000 births. This response to maternal-sensitized antibodies that produce isoimmune thrombocytopenia is analogous to the response that produces erythroblastosis fetalis. The maternal antiplatelet antibody does not produce maternal thrombocytopenia, but after crossing the placenta this IgG antibody binds to fetal platelets that are trapped by the reticuloendothelial tissue, resulting in thrombocytopenia. Infants with thrombocytopenia produced in this manner are at risk for development of petechiae, purpura, and intracranial hemorrhage (an incidence of 10% to 15%) before or after birth. Vaginal delivery may increase the risk of neonatal bleeding; cesarean section may be indicated.

Specific treatment for severe thrombocytopenia (<20,000 platelets/mm³) or significant bleeding is transfusion of ABO-compatible and RhD-compatible, HPA-1a-negative and HPA-5b-negative maternal platelets. Because the antibody in isooimmune thrombocytopenia is directed against the fetal rather than the maternal platelet, thrombocytapheresis of the mother yields sufficient platelets to treat the affected infant. After one platelet transfusion, the infant’s platelet count dramatically increases and usually remains in a safe range. Without treatment, thrombocytopenia resolves during the first month of life as the maternal antibody level declines. Treatment of the mother with intravenous immunoglobulin or the thrombocytopenic fetus with intravascular platelet transfusion (cordocentesis) is also effective. Cesarean section reduces the risk of intracranial hemorrhage.

Neonatal thrombocytopenia in infants born to women with idiopathic thrombocytopenic purpura (ITP) also is a result of placentation transfer of maternal IgG antibodies. In ITP, these auto-antibodies are directed against all platelet antigens; mother and newborn may have low platelet counts. The risks of hemorrhage in an infant born to a mother with ITP may be lessened by cesarean section and by treatment of the mother with corticosteroids. Treatment of an affected infant born to a mother with ITP may involve prednisone and intravenous immunoglobulin. In an emergency, random donor platelets may be used and may produce a transient increase in the infant’s platelet count. Thrombocytopenia resolves spontaneously during the first month of life as maternal-derived antibody levels decline. Elevated levels of platelet-associated antibodies also have been noted in thrombocytopenic infants with sepsis and thrombocytopenia of unknown cause who were born to mothers without demonstrable platelet antibodies.

The laboratory evaluation of an infant (well or sick) with bleeding must include a platelet count, blood smear, and evaluation of PTT and PT. Isolated thrombocytopenia in a well infant suggests immune thrombocytopenia. Laboratory evidence of DIC includes a markedly prolonged PTT and PT (minutes rather than seconds), thrombocytopenia, and a blood smear suggesting a microangiopathic hemolytic anemia (burr or fragmented blood cells). Further evaluation reveals low levels of fibrinogen (<100 mg/dL) and elevated levels of fibrin degradation products. Vitamin K deficiency prolongs the PT more than the PTT, whereas hemophilia resulting from factors VIII and IX deficiency prolongs only the PTT. Specific factor levels confirm the diagnosis of hemophilia.

**NECROZING ENTEROCOLITIS**

Necrotizing enterocolitis (NEC) is a syndrome of intestinal injury and is the most common intestinal emergency occurring in preterm infants admitted to the neonatal intensive care unit. NEC occurs in 1 to 3 per 1000 live births and 1% to 8%...
of admissions to the neonatal intensive care unit. Prematurity is the most consistent and significant factor associated with neonatal NEC. The disease occurs in 4% to 13% of infants who weigh less than 1500 g at birth. NEC is infrequent in term infants (<10% of affected infants).

Most cases of NEC occur in premature infants born before 34 weeks' gestation who have been fed enterally. Prematurity is associated with immaturity of the gastrointestinal tract, including decreased integrity of the intestinal mucosal barrier, depressed mucosal enzymes, suppressed gastrointestinal hormones, suppressed intestinal host defense system, decreased coordination of intestinal motility, and differences in blood flow autoregulation, which is thought to play a significant role in the pathogenesis of NEC. More than 90% of infants diagnosed with NEC have been fed enterally, but NEC has been reported in infants who have never been fed. Feeding with human milk has shown a beneficial role in reducing the incidence of NEC. In addition, probiotics may offer potential benefits for the preterm infant by increasing mucosal barrier function, improving nutrition, upregulating the immune system, and reducing mucosal colonization by potential pathogens. It also is theorized that compromised intestinal blood flow contributes to NEC.

Early clinical signs of NEC include abdominal distention, feeding intolerance/increased gastric residuals, emesis, rectal bleeding, and occasional diarrhea. As the disease progresses, patients may develop marked abdominal distention, bilious emesis, ascites, abdominal wall erythema, lethargy, temperature instability, increased episodes of apnea/bradycardia, disseminated intravascular coagulation, and shock. With abdominal perforation, the abdomen may develop a bluish discoloration.

The white blood cell count can be elevated, but often it is depressed. Thrombocytopenia is common. In addition, infants may develop coagulation abnormalities along with metabolic derangements, including metabolic acidosis, electrolyte imbalance, and hypoglycemia and hyperglycemia. No unique infectious agent has been associated with NEC; bacteriologic and fungal cultures may prove helpful but not conclusive.

Radiographic imaging is essential to the diagnosis of NEC. The earliest radiographic finding is intestinal ileus, often associated with thickening of the bowel loops and air-fluid levels. The pathognomonic radiographic finding is pneumatosis intestinalis caused by hydrogen gas production from pathogenic bacteria present between the subserosal and muscularis layers of the bowel wall. Radiographic findings also may include a fixed or persistent dilated loop of bowel, intrahepatic venous gas, and pneumoperitoneum seen with bowel perforation.

The differential diagnosis of NEC includes sepsis with intestinal ileus or a volvulus. Both conditions can present with systemic signs of sepsis and abdominal distention. The absence of pneumatosis on abdominal radiographs does not rule out the diagnosis of NEC; other causes of abdominal distention and perforation (gastric or ileal perforation) should be considered and investigated. Patients diagnosed with Hirschsprung enterocolitis or severe gastroenteritis may present with pneumatosis intestinalis.

The management of NEC includes the discontinuation of enteral feedings, gastrointestinal decompression with nasogastric suction, fluid and electrolyte replacement, total parenteral nutrition, and systemic broad-spectrum antibiotics. When the diagnosis of NEC is made, consultation with a pediatric surgeon should be obtained. Even with aggressive and appropriate medical management, 25% to 50% of infants with NEC require surgical intervention. The decision to perform surgery is obvious when the presence of a pneumoperitoneum is observed on abdominal radiograph. Other, not so obvious indications for surgical intervention include rapid clinical deterioration despite medical therapy, rapid onset and progression of pneumatosis, abdominal mass, and intestinal obstruction. The surgical procedure of choice is laparotomy with removal of the frankly necrotic and nonviable bowel. Many extremely small infants are managed initially with primary peritoneal drainage followed by surgical intervention as needed later, when the infant is stable and a laparotomy can be performed safely. The long-term outcome includes intestinal strictures requiring further surgical intervention, short bowel syndrome with poor absorption of enteral fluids and nutrients, associated cholestasis with resultant cirrhosis and liver failure from prolonged parenteral nutrition, and neurodevelopmental delay from prolonged hospitalization.
Seizures during the neonatal period may be the result of multiple causes, with characteristic historical and clinical manifestations. Seizures caused by hypoxic-ischemic encephalopathy (postasphyxial seizures), a common cause of seizures in the full-term infant, usually occur 12 to 24 hours after a history of birth asphyxia and often are refractory to conventional doses of anticonvulsant medications. Postasphyxial seizures also may be caused by metabolic disorders associated with neonatal asphyxia, such as hypoglycemia and hypocalcemia. Intraventricular hemorrhage (IVH) is a common cause of seizures in premature infants and often occurs between 1 and 3 days of age. Seizures with IVH are associated with a bulging fontanelle, hemorrhagic spinal fluid, anemia, lethargy, and coma. Seizures caused by hypoglycemia often occur when blood glucose levels decline to the lowest postnatal value (at 1 to 2 hours of age or after 24 to 48 hours of poor nutritional intake). Seizures caused by hypocalcemia and hypomagnesemia develop in high-risk infants and respond well to therapy with calcium, magnesium, or both.

Seizures noted in the delivery room often are caused by direct injection of local anesthetic agents into the fetal scalp (associated with transient bradycardia and fixed dilated pupils), severe anoxia, or congenital brain malformation. Seizures after the first 5 days of life may be the result of infection or drug withdrawal. Seizures associated with lethargy, acidosis, and a family history of infant deaths may be the result of an inborn error of metabolism. An infant whose parent has a history of a neonatal seizure also is at risk for benign familial seizures. In an infant who appears well, a sudden onset on day 1 to 3 of life of seizures that are of short duration and that do not recur may be the result of a subarachnoid hemorrhage. Focal seizures often are the result of local cerebral infarction.

Seizures may be difficult to differentiate from benign jitteriness or from tremulousness in infants of diabetic mothers, in infants with narcotic withdrawal syndrome, and in any infants after an episode of asphyxia. In contrast to seizures, jitteriness and tremors are sensory dependent, elicited by stimuli, and interrupted by holding the extremity. Seizure activity becomes manifested as coarse, fast and slow clonic activity, whereas jitteriness is characterized by fine, rapid movement. Seizures may be associated with abnormal eye movements, such as tonic deviation to one side. The electroencephalogram often shows seizure activity when the clinical diagnosis is uncertain. Identifying seizures in the newborn period is often difficult because the infant, especially the low birth weight infant, usually does not show the tonic-clonic major motor activity typical of the older child (Table 64-1). Subtle seizures are a common manifestation in newborns. The subtle signs of seizure activity include apnea, eye deviation, tongue thrusting, eye blinking, fluctuation of vital signs, and staring. Continuous bedside electroencephalographic monitoring can help identify subtle seizures.

The diagnostic evaluation of infants with seizures should involve an immediate determination of capillary blood glucose levels with a Chemstrip. In addition, blood concentrations of sodium, calcium, glucose, and bilirubin should be determined. When infection is suspected, cerebrospinal fluid and blood specimens should be obtained for culture. After the seizure has stopped, a careful examination should be done to identify signs of increased intracranial pressure, congenital malformations, and systemic illness. If signs of

<table>
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<tr>
<th>Table 64-1</th>
<th>Clinical Characteristics of Neonatal Seizures</th>
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<tbody>
<tr>
<td><strong>DESIGNATION</strong></td>
<td><strong>CHARACTERIZATION</strong></td>
</tr>
<tr>
<td>Focal clonic</td>
<td>Repetitive, rhythmic contractions of muscle groups of the limbs, face, or trunk May be unilateral or multifocal May appear synchronously or asynchronously in various body regions Cannot be suppressed by restraint</td>
</tr>
<tr>
<td>Focal tonic</td>
<td>Sustained posturing of single limbs Sustained asymmetric posturing of the trunk Sustained eye deviation Cannot be suppressed by stimulation or suppressed by restraint</td>
</tr>
<tr>
<td>Myoclonic</td>
<td>Arrhythmic contractions of muscle groups of the limbs, face, or trunk Typically not repetitive or may recur at a slow rate May be generalized, focal, or fragmentary May be provoked by stimulation</td>
</tr>
<tr>
<td>Generalized tonic</td>
<td>Sustained symmetric posturing of limbs, trunk, and neck May be flexor, extensor, or mixed extensor/flexor May be provoked by stimulation May be suppressed by restraint or repositioning</td>
</tr>
<tr>
<td>Ocular signs</td>
<td>Random and roving eye movements or nystagmus Distinct from tonic eye deviation</td>
</tr>
<tr>
<td>Orobuccolingual movements</td>
<td>Sucking, chewing, tongue protrusions May be provoked by stimulation</td>
</tr>
<tr>
<td>Progression movements</td>
<td>Rowing or swimming movements of the arms Pedaling or bicycling movements of the legs May be provoked by stimulation May be suppressed by restraint or repositioning</td>
</tr>
</tbody>
</table>

elevated intracranial pressure are absent, a lumbar puncture should be performed. If the diagnosis is not apparent at this point, further evaluation should involve magnetic resonance imaging, computed tomography, or cerebral ultrasound and tests to determine the presence of an inborn error of metabolism. Determinations of inborn errors of metabolism are especially important in infants with unexplained lethargy, coma, acidosis, ketonuria, or respiratory alkalosis.

The treatment of neonatal seizures may be specific, such as treatment of meningitis or the correction of hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, or vitamin B6 deficiency or dependency. In the absence of an identifiable cause, therapy should involve an anticonvulsant agent, such as 20 to 40 mg/kg of phenobarbital, 10 to 20 mg/kg of phenytoin, or 0.1 to 0.3 mg/kg of diazepam. Treatment of status epilepticus requires repeated doses of phenobarbital and may require diazepam or midazolam, titrated to clinical signs. The long-term outcome for neonatal seizures usually is related to the underlying cause and to the primary pathology, such as hypoxic-ischemic encephalopathy, meningitis, drug withdrawal, stroke, or hemorrhage.

INTRACRANIAL HEMORRHAGE
Intracranial hemorrhage may be confined to one anatomic area of the brain, such as the subdural, subarachnoid, periventricular, intraventricular, intraparenchymal, or cerebellar region. Subdural hemorrhages are seen in association with birth trauma, cephalopelvic disproportion, forceps delivery, large for gestational age infants, skull fractures, and postnatal head trauma. The subdural hematoma does not always cause symptoms immediately after birth; with time, however, the RBCs undergo hemolysis and water is drawn into the hemorrhage because of the high oncotic pressure of protein, resulting in an expanding symptomatic lesion. Anemia, vomiting, seizures, and macrocephaly may occur in an infant who is 1 to 2 months of age and has a subdural hematoma. Child abuse in this situation should be suspected and appropriate diagnostic evaluation undertaken to identify other possible signs of skeletal, ocular, or soft tissue injury. Occasionally, a massive subdural hemorrhage in the neonatal period is caused by rupture of the vein of Galen or by an inherited coagulation disorder, such as hemophilia. Infants with these conditions exhibit shock, seizures, and coma. The treatment of all symptomatic subdural hematomas is surgical evacuation.

Subarachnoid hemorrhages may be spontaneous, associated with hypoxia, or caused by bleeding from a cerebral arteriovenous malformation. Seizures are a common presenting manifestation, and the prognosis depends on the underlying injury. Treatment is directed at the seizure and the rare occurrence of posthemorrhagic hydrocephalus.

Periventricular hemorrhage and IVH are common in very low birth weight infants; the risk decreases with increasing gestational age. Fifty percent of infants weighing less than 1500 g have evidence of intracranial bleeding. The pathogenesis for these hemorrhages is unknown (they usually are not caused by coagulation disorders), but the initial site of bleeding may be the weak blood vessels in the periventricular germinal matrix. The vessels in this area have poor structural support. These vessels may rupture and hemorrhage because of passive changes in cerebral blood flow occurring with the variations of blood pressure that sick premature infants often exhibit (failure of autoregulation). In some sick infants, these blood pressure variations are the only identifiable etiologic factors. In others, the disorders that may cause the elevation or depression of blood pressure or that interfere with venous return from the head (venous stasis) increase the risk of IVH; these disorders include asphyxia, pneumothorax, mechanical ventilation, hypercapnia, hypoxemia, prolonged labor, breech delivery, patent ductus arteriosus, heart failure, and therapy with hypertonic solutions such as sodium bicarbonate.

Most periventricular hemorrhages and IVHs occur in the first 3 days of life. It is unusual for IVH to occur after day 5 of life. The clinical manifestations of IVH include seizures, apnea, bradycardia, lethargy, coma, hypotension, metabolic acidosis, anemia not corrected by blood transfusion, bulging fontanelle, and cutaneous mottling. Many infants with small hemorrhages (grade 1 or 2) are asymptomatic; infants with larger hemorrhages (grade 4) often have a catastrophic event that rapidly progresses to shock and coma.

The diagnosis of IVH is confirmed and the severity graded by ultrasound through the anterior fontanelle or computed tomography examination. Grade 1 IVH is confined to the germinal matrix; grade 2 is an extension of grade 1, with blood noted in the ventricle without ventricular enlargement; grade 3 is an extension of grade 2 with ventricular dilation; and grade 4 has blood in dilated ventricles and in the cerebral cortex, either contiguous with or distant from the ventricle. Grade 4 hemorrhage has a poor prognosis, as does the development of periventricular, small, echolucent cystic lesions, with or without porencephalic cysts and posthemorrhagic hydrocephalus. Periventricular cysts often are noted after the resolution of echodense areas in the periventricular white matter. The cysts may correspond to the development of periventricular leukomalacia, which may be a precursor to cerebral palsy. Extensive intraparenchymal echodensities represent hemorrhagic necrosis. They are associated with a high mortality rate and have a poor neurodevelopmental prognosis for survivors.

Treatment of an acute hemorrhage involves standard supportive care, including ventilation for apnea and blood transfusion for hemorrhagic shock. Posthemorrhagic hydrocephalus may be managed with serial daily lumbar punctures, an external ventriculostomy tube, or a permanent ventricular-peritoneal shunt. Implementation of the shunt often is delayed because of the high protein content of the hemorrhagic ventricular fluid.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY
Conditions known to reduce uteroplacental blood flow or to interfere with spontaneous respiration lead to perinatal hypoxia, lactic acidosis, and, if severe enough to reduce cardiac output or cause cardiac arrest, ischemia. The combination of the reduced availability of oxygen for the brain resulting from hypoxia and the diminished or absent blood flow to the brain resulting from ischemia leads to reduced glucose for metabolism and to an accumulation of lactate that produces local tissue acidosis. After reperfusion, hypoxic-ischemic injury also may be complicated by cell necrosis and vascular endothelial edema, reducing blood flow distal to the
involved vessel. Typically, hypoxic-ischemic encephalopathy in the term infant is characterized by cerebral edema, cortical necrosis, and involvement of the basal ganglia, whereas in the preterm infant it is characterized by periventricular leukomalacia. Both lesions may result in cortical atrophy, mental retardation, and spastic quadriplegia or diplegia.

The clinical manifestations and characteristic course of hypoxic-ischemic encephalopathy vary according to the severity of the injury (Table 64-2). Infants with severe stage 3 hypoxic-ischemic encephalopathy are usually hypotonic, although occasionally they initially appear hypertonic and hyperalert at birth. As cerebral edema develops, brain functions are affected in a descending order; cortical depression produces coma, and brainstem depression results in apnea. As cerebral edema progresses, refractory seizures begin 12 to 24 hours after birth. Concurrently the infant has no signs of spontaneous respirations, is hypotonic, and has diminished or absent deep tendon reflexes.

Survivors of stage 3 hypoxic-ischemic encephalopathy have a high incidence of seizures and serious neurodevelopmental handicaps. The prognosis of severe asphyxia also depends on other organ system injury (see Table 58-6). Another indicator of poor prognosis is time of onset of spontaneous respiration as estimated by Apgar score. Infants with Apgar scores of 0 to 3 at 10 minutes have a 20% mortality and a 5% incidence of cerebral palsy; if the score remains this low by 20 minutes, the mortality increases to 60%, and the incidence of cerebral palsy increases to 57%.

Survivors of stage 3 hypoxic-ischemic encephalopathy may have a high incidence of seizures and serious neurodevelopmental handicaps. The prognosis of severe asphyxia also depends on other organ system injury (see Table 58-6). Another indicator of poor prognosis is time of onset of spontaneous respiration as estimated by Apgar score. Infants with Apgar scores of 0 to 3 at 10 minutes have a 20% mortality and a 5% incidence of cerebral palsy; if the score remains this low by 20 minutes, the mortality increases to 60%, and the incidence of cerebral palsy increases to 57%.

Systemic and local infections (lung, cutaneous, ocular, umbilical, kidney, bone-joint, and meningeal) are common in the newborn period. Infection may be acquired in utero through the transplacental or transcervical routes and during or after birth. Ascending infection through the cervix, with or without rupture of the amniotic fluid membranes, may result in amnionitis, funisitis (infection of the umbilical cord), congenital pneumonia, and sepsis. The bacteria responsible for ascending infection of the fetus are common bacterial organisms of the maternal genitourinary tract, such as group B streptococci, *Escherichia coli*, *Haemophilus influenzae*, and *Klebsiella*. Herpes simplex virus (HSV)-1 or, more often, HSV-2 also causes ascending infection that at times may be indistinguishable from bacterial sepsis. Syphilis and *Listeria monocytogenes* are acquired by transplacental infection.

Maternal humoral immunity may protect the fetus against some neonatal pathogens, such as group B streptococci and HSV. Nonetheless, various deficiencies of the neonatal antimicrobial defense mechanism probably are more important than maternal immune status as a contributing factor for neonatal infection, especially in the low birth weight infant. The incidence of sepsis is approximately 1:1500 in full-term infants and 1:250 in preterm infants. The sixfold-higher rate of sepsis in preterm infants relates to the more immature immunologic systems of preterm infants and to their prolonged periods of hospitalization, which increase risk of nosocomially acquired infectious diseases.

Preterm infants before 32 weeks of gestational age have not received the full complement of maternal antibodies (IgG), which cross the placenta by active transport predominantly in the latter half of the third trimester. In addition, although low birth weight infants may generate IgM antibodies, their own IgG response to infection is reduced. These infants also have deficiencies of the alternate and, to a smaller degree, the classic complement activation pathways, which results in diminished complement-mediated opsonization. Newborn infants also show a deficit in phagocytic migration to the site of infection (to the lung) and in the bone marrow reserve pool of leukocytes. In addition, in the presence of suboptimal activation of complement, neonatal neutrophils ingest and kill bacteria less effectively than adult neutrophils do. Neutrophils from sick infants seem to have an even greater deficit in bacterial killing capacity compared with phagocytic cells from normal neonates.

Defense mechanisms against viral pathogens also may be deficient in a newborn. Neonatal antibody-dependent, cell-mediated immunity by the natural killer lymphocytes is deficient in the absence of maternal antibodies and in the presence of reduced interferon production; reduced antibody

<table>
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<tr>
<th>Table 64-2</th>
<th>Hypoxic-Ischemic Encephalopathy in Term Infants</th>
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<tbody>
<tr>
<td>SIGN</td>
<td>STAGE 1</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Hyperalert</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
</tr>
<tr>
<td>Tendon reflexes/clonus</td>
<td>Hyperactive</td>
</tr>
<tr>
<td>Moro reflex</td>
<td>Strong</td>
</tr>
<tr>
<td>Pupils</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Seizures</td>
<td>None</td>
</tr>
<tr>
<td>Electroencephalography</td>
<td>Normal</td>
</tr>
<tr>
<td>Duration</td>
<td>&gt;24 h if progresses, otherwise may remain normal</td>
</tr>
</tbody>
</table>

levels occur in premature infants and in infants born during a primary viral infection of the mother, such as with enteroviruses, HSV-2, or cytomegalovirus. In addition, antibody-independent cytotoxicity may be reduced in lymphocytes of newborns.

Bacterial sepsis and meningitis often are linked closely in neonates. Despite this association, the incidence of meningitis relative to neonatal sepsis has been on a steady decline. The incidence of meningitis is approximately 1 in 20 cases of sepsis. The causative organisms isolated most frequently are the same as for neonatal sepsis: group B streptococci, E. coli, and L. monocytogenes. Gram-negative organisms, such as Klebsiella, Salmonella, and Serratia marcescens, are more common in less developed countries, and coagulase-negative staphylococcus needs to be considered in very low birth weight infants. Male infants seem to be more susceptible to neonatal infection than female infants. Severely premature infants are at even greater risk secondary to less effective defense mechanisms and deficient transfer of antibodies from the mother to the fetus (which occurs mostly after 32 weeks' gestation). Neonates in the neonatal intensive care unit live in a hostile environment, with exposure to endotracheal tubes, central arterial and venous catheters, and blood draws, all predisposing to bacteremia and meningitis. Genetic factors have been implicated in the ability of bacteria to cross the blood-brain barrier. This penetration has been noted for group B streptococci, E. coli, Listeria, Citrobacter, and Streptococcus pneumoniae.

Neonatal sepsis presents during three periods. Early-onset sepsis often begins in utero and usually is a result of infection caused by the bacteria in the mother's genitourinary tract. Organisms related to this sepsis include group B streptococci, E. coli, Klebsiella, L. monocytogenes, and nontypeable H. influenzae. Most infected infants are premature and show nonspecific cardiorespiratory signs, such as grunting, tachypnea, and cyanosis at birth. Risk factors for early-onset sepsis include vaginal colonization with group B streptococci, prolonged rupture of the membranes (>24 hours), amnionitis, maternal fever or leukocytosis, fetal tachycardia, and preterm birth. African American race and male sex are unexplained additional risk factors for neonatal sepsis.

Early-onset sepsis (birth to 7 days) is an overwhelming multiorgan system disease frequently manifested as respiratory failure, shock, meningitis (in 30% of cases), disseminated intravascular coagulation, acute tubular necrosis, and symmetrical peripheral gangrene. Early manifestations—grunting, poor feeding, pallor, apnea, lethargy, hypothermia, or an abnormal cry—may be nonspecific. Profound neutropenia, hypoxia, and hypotension may be refractory to treatment with broad-spectrum antibiotics, mechanical ventilation, and vasopressors such as dopamine and dobutamine. In the initial stages of early-onset septicemia in a preterm infant, it is often difficult to differentiate sepsis from respiratory distress syndrome. Because of this difficulty, premature infants with respiratory distress syndrome receive broad-spectrum antibiotics.

The clinical manifestations of sepsis are difficult to separate from the manifestations of meningitis in the neonate. Infants with early-onset sepsis should be evaluated by blood and cerebrospinal fluid (CSF) cultures, CSF Gram stain, cell count, and protein and glucose levels. Normal newborns generally have an elevated CSF protein content (100 to 150 mg/dL) and may have 25 to 30/mm3 white blood cells (mean, 9/mm3), which are 75% lymphocytes in the absence of infection. Some infants with neonatal meningitis caused by group B streptococci do not have an elevated CSF leukocyte count but are seen to have microorganisms in the CSF on Gram stain. In addition to culture, other methods of identifying the pathogenic bacteria are the determination of bacterial antigen in samples of blood, urine, or CSF. In cases of neonatal meningitis, the ratio of CSF glucose to blood glucose usually is less than 50%. The polymerase chain reaction test primarily is used to identify viral infections. Serial complete blood counts should be performed to identify neutropenia, an increased number of immature neutrophils (bands), and thrombocytopenia. C-reactive protein levels are often elevated in neonatal patients with bacterial sepsis.

A chest radiograph also should be obtained to determine the presence of pneumonia. In addition to the traditional neonatal pathogens, pneumonia in very low birth weight infants may be the result of acquisition of maternal genital mycoplasmal agent (e.g., Ureaplasma urealyticum or Mycoplasma hominis). Arterial blood gases should be monitored to detect hypoxemia and metabolic acidosis that may be caused by hypoxia, shock, or both. Blood pressure, urine output, and peripheral perfusion should be monitored to determine the need to treat septic shock with fluids and vasopressor agents.

The mainstay of treatment for sepsis and meningitis is antibiotic therapy. Antibiotics are used to suppress bacterial growth, allowing the infant's defense mechanisms time to respond. In addition, support measures, such as assisted ventilation and cardiovascular support, are equally important to the management of the infant. A combination of ampicillin and an aminoglycoside (usually gentamicin) for 10 to 14 days is effective treatment against most organisms responsible for early-onset sepsis. The combination of ampicillin and cefotaxime also is proposed as an alternative method of treatment. If meningitis is present, the treatment should be extended to 21 days or 14 days after a negative result from a CSF culture. Persistently positive results from CSF cultures are common with neonatal meningitis caused by gram-negative organisms, even with appropriate antibiotic treatment, and may be present for 2 to 3 days after antibiotic therapy. If gram-negative meningitis is present, some authorities continue to treat with an effective penicillin derivative combined with an aminoglycoside, whereas most change to a third-generation cephalosporin. High-dose penicillin (250,000 to 450,000 U/kg/24 hr) is appropriate for group B streptococcal meningitis. Inhaled nitric oxide, extracorporeal membrane oxygenation (in term infants), or both may improve the outcome of sepsis-related pulmonary hypertension. Intratracheal surfactant may reverse respiratory failure. Intrapartum penicillin empirical prophylaxis for group B streptococcal colonized mothers or mothers with risk factors (fever, preterm labor, previous infant with group B streptococci, and amnionitis) has reduced the rate of early-onset infection.

Late-onset sepsis (8 to 28 days) usually occurs in a healthy full-term infant who was discharged in good health from the normal newborn nursery. Clinical manifestations may include lethargy, poor feeding, hypotonia, apathy, seizures, bulging fontanelle, fever, and direct-reacting hyperbilirubinemia. In addition to bacteremia, hematogenous seeding may result in focal infections, such as meningitis (in 75% of cases), osteomyelitis (group B streptococci, Staphylococcus aureus), arthritis (gonococcus, S. aureus, Candida albicans, gram-negative bacteria), and urinary tract infection (gram-negative bacteria).
The evaluation of infants with late-onset sepsis is similar to that for infants with early-onset sepsis, with special attention given to a careful physical examination of the bones (infants with osteomyelitis may exhibit pseudoparalysis) and to the laboratory examination and culture of urine obtained by sterile suprapubic aspiration or urethral catheterization. Late-onset sepsis may be caused by the same pathogens as early-onset sepsis, but infants exhibiting sepsis late in the neonatal period also may have infections caused by the pathogens usually found in older infants (H. influenzae, S. pneumoniae, and Neisseria meningitidis). In addition, viral agents (HSV, cytomegalovirus, or enteroviruses) may manifest with a late-onset, sepsis-like picture.

Because of the increased rate of resistance of H. influenzae and pneumococcus to ampicillin, some centers begin treatment with ampicillin and a third-generation cephalosporin (and vancomycin if meningitis is present) when sepsis occurs in the last week of the first month of life. The treatment of late-onset neonatal sepsis and meningitis is the same as that for early-onset sepsis.

**CONGENITAL INFECTIONS**

An infection acquired transplacentally during gestation is a congenital infection. Numerous pathogens that produce mild or subclinical disease in older infants and children can cause severe disease in neonates who acquire such infections perinatally or perinatally. Sepsis, meningitis, pneumonia, and other infections caused by perinatally or perinatally acquired pathogens are the cause of significant neonatal morbidity and mortality. Congenital infections include a well-known group of fungal, bacterial, and viral pathogens: toxoplasmosis, rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus, congenital syphilis, parvovirus, human immunodeficiency virus (HIV), hepatitis B, Neisseria gonorrhoeae, Chlamydia, and Mycobacterium tuberculosis.

Many of the clinical manifestations of congenital infections are similar, including intrauterine growth restriction, nonimmune hydrops, anemia, thrombocytopenia, jaundice, hepatosplenomegaly, chorioretinitis, and congenital malformations. Some unique manifestations and epidemiologic characteristics of these infections are listed in Table 66-1. Evaluation of patients thought to have a congenital infection should include attempts to isolate the organism by culture (for rubella, CMV, HSV, gonorrhea, and M. tuberculosis), to identify the antigen of the pathogen (for hepatitis B and Chlamydia trachomatis), to identify the pathogen's genome with polymerase chain reaction (PCR), and to identify specific fetal production of antibodies (IgM or increasing titer of IgG for Toxoplasma, syphilis, parvovirus, HIV, or Borrelia).

Treatment is not always available, specific, or effective. Nonetheless, some encouraging results have been reported for preventing the disease and for specifically treating the infant when the correct diagnosis is made (see Table 66-1).

**TOXOPLASMOSIS**

Vertical transmission of Toxoplasma gondii occurs by transplacental transfer of the organism from the mother to the fetus after an acute maternal infection. Fetal infection rarely can occur after reactivation of disease in an immunocompromised pregnant mother. Transmission from an acutely infected mother to her fetus occurs in about 30% to 40% of cases, but the rate varies directly with gestational age. Transmission rates and the timing of fetal infection correlate directly with placental blood flow; the risk of infection increases throughout gestation to 90% or greater near term, and the time interval between maternal and fetal infection decreases.

The severity of fetal disease varies inversely with the gestational age at which maternal infection occurs. Most infants have subclinical infection with no overt disease at birth; however, specific ophthalmologic and central nervous system (CNS) evaluations may reveal abnormalities. The classic findings of hydrocephalus, chorioretinitis, and intracerebral calcifications suggest the diagnosis of congenital toxoplasmosis. Affected infants tend to be small for gestational age, develop early-onset jaundice, have hepatosplenomegaly, and present with a generalized maculopapular rash. Seizures are common, and skull films may reveal diffuse cortical calcifications in contrast to the periventricular pattern observed with CMV. These infants are at increased risk for long-term neurologic and neurodevelopmental complications.

Serologic tests are the primary means of diagnosis. IgG-specific antibodies achieve a peak concentration 1 to 2 months after infection and remain positive indefinitely. For infants with seroconversion or a fourfold increase in IgG titers, specific IgM antibody determinations should be performed to confirm disease. Especially for congenital infections, measurement of IgA and IgE antibodies can be useful to confirm the disease. Thorough ophthalmologic, auditory, and neurologic evaluations (head computed tomography and cerebrospinal fluid [CSF] examination) are indicated.

For symptomatic and asymptomatic congenital infections, initial therapy should include pyrimethamine (supplemented with folic acid) combined with sulfadiazine. Duration of therapy is often prolonged, even up to 1 year. Optimal dosages of medications and duration of therapy should be determined in consultation with appropriate specialists.

**RUBELLA**

Vertical transmission of Rubella virus occurs by transplacental transfer of the virus from the mother to the fetus after an acute maternal infection. Fetal infection rarely can occur after reactivation of disease in an immunocompromised pregnant mother. Transmission from an acutely infected mother to her fetus occurs in about 30% to 40% of cases, but the rate varies directly with gestational age. Transmission rates and the timing of fetal infection correlate directly with placental blood flow; the risk of infection increases throughout gestation to 90% or greater near term, and the time interval between maternal and fetal infection decreases.

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Table 66-1 | Perinatal Congenital Infections (TORCH)

<table>
<thead>
<tr>
<th>AGENT</th>
<th>MATERNAL EPIDEMIOLOGY</th>
<th>NEONATAL FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasma gondii</td>
<td>Heterophil-negative mononucleosis Exposure to cats or raw meat or immunosuppression High-risk exposure at 10–24 wk gestation</td>
<td>Hydrocephalus, abnormal spinal fluid, intracranial calcifications, chorioretinitis, jaundice, hepatosplenomegaly, fever Many infants asymptomatic at birth Treatment: pyrimethamine plus sulfadiazine</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Unimmunized seronegative mother; fever ± rash Detectable defects with infection: by 8 wk, 85% 9–12 wk, 50% 13–20 wk, 16% Virus may be present in infant’s throat for 1 yr Prevention: vaccine</td>
<td>Intrauterine growth restriction, microcephaly, microphthalmia, cataracts, glaucoma, “salt and pepper” chorioretinitis, hepatosplenomegaly, jaundice, PDA, deafness, blueberry muffin rash, anemia, thrombocytopenia, leukopenia, metaphyseal luencies, B-cell and T-cell deficiency Infant may be asymptomatic at birth</td>
</tr>
<tr>
<td>CMV</td>
<td>Sexually transmitted disease: primary genital infection may be asymptomatic Heterophil-negative mononucleosis; infant may have viruria for 1–6 yr</td>
<td>Sepsis, intrauterine growth restriction, chorioretinitis, microcephaly, periventricular calcifications, blueberry muffin rash, anemia, thrombocytopenia, neutropenia, hepatosplenomegaly, jaundice, deafness, pneumonia Many asymptomatic at birth Prevention: CMV-negative blood products Possible treatment: ganciclovir</td>
</tr>
<tr>
<td>Herpes simplex type 2 or 1 virus</td>
<td>Sexually transmitted disease: primary genital infection may be asymptomatic, intrauterine infection rare, acquisition at time of birth more common</td>
<td>Intrauterine infection: chorioretinitis, skin lesions, microcephaly Postnatal: encephalitis, localized or disseminated disease, skin vesicles, keratoconjunctivitis Treatment: acyclovir</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Intrauterine infection with chickenpox Infant develops severe neonatal varicella with maternal illness 5 days before or 2 days after delivery</td>
<td>Microphthalmia, cataracts, chorioretinitis, cutaneous and bony aplasia/hypoplasia/atrophy, cutaneous scars Zoster as in older child Prevention of neonatal condition with VZIG Treatment of ill neonate: acyclovir</td>
</tr>
<tr>
<td>Treponema pallidum (syphilis)</td>
<td>Sexually transmitted disease Maternal primary asymptomatic: painless “hidden” chancre Penicillin, not erythromycin, prevents fetal infection</td>
<td>Presentation at birth as nonimmune hydrops, prematurity, anemia, neutropenia, thrombocytopenia, pneumonia, hepatosplenomegaly Late neonatal as snuffles (rhinitis), rash, hepatosplenomegaly, condylomata lata, metaphysitis, cerebrospinal fluid pleocytosis, keratitis, periosteal new bone, lymphocytosis, hepatitis Late onset: teeth, eye, bone, skin, central nervous system, ear Treatment: penicillin</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Etiology of fifth disease; fever, rash, arthralgia in adults</td>
<td>Nonimmune hydrops, fetal anemia Treatment: in utero transfusion</td>
</tr>
<tr>
<td>HIV</td>
<td>AIDS; most mothers are asymptomatic and HIV positive; high-risk history: prostitute, drug abuse, married to bisexual, or hemophiliac</td>
<td>AIDS symptoms develop between 3 and 6 mo of age in 10%–25%; failure to thrive, recurrent infection, hepatosplenomegaly, neurologic abnormalities Management: trimethoprim/sulfamethoxazole, AZT, other antiretroviral agents Prevention: prenatal, intrapartum, postpartum AZT, avoid breastfeeding</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Vertical transmission common; may result in cirrhosis, hepatocellular carcinoma</td>
<td>Acute neonatal hepatitis; many become asymptomatic carriers Prevention: HBIG, vaccine</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Sexually transmitted disease, infant acquires at birth Treatment: cefotaxime, ceftriaxone</td>
<td>Gonococcal ophthalmia, sepsis, meningitis Prevention: silver nitrate, erythromycin eye drops Treatment: ceftriaxone</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Sexually transmitted disease, infant acquires at birth Treatment: oral erythromycin</td>
<td>Conjunctivitis, pneumonia Prevention: erythromycin eye drops Treatment: oral erythromycin</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Positive PPD skin test, recent converter, positive chest radiograph, positive family member Treatment: INH and rifampin ± ethambutol</td>
<td>Congenital rare septic pneumonia; acquired primary pulmonary TB; asymptomatic, follow PPD Prevention: INH, BCG, separation Treatment: INH, rifampin, pyrazinamide</td>
</tr>
<tr>
<td>Trypanosoma cruzi (Chagas disease)</td>
<td>Central South American native, immigrant, travel Chronic disease in mother</td>
<td>Failure to thrive, heart failure, achalasia Treatment: nifurtimox</td>
</tr>
</tbody>
</table>

AZT, Zidovudine (azidothymidine); BCG, bacille Calmette-Guerin; CMV, cytomegalovirus; HBIG, hepatitis B immune globulin; INH, isoniazid; PDA, patent ductus arteriosus; PPD, purified protein derivative; TB, tuberculosis; VZIG, varicella-zoster immune globulin.
With the widespread use of vaccination, congenital rubella is rare in developed countries. Acquired in utero during early gestation, rubella can cause severe neonatal consequences. The occurrence of congenital defects approaches 85% if infection is acquired during the first 4 weeks of gestation; close to 40% spontaneously abort or are stillborn. If infection occurs during weeks 13 to 16, 35% of infants can have abnormalities. Infection after 4 months’ gestation does not seem to cause disease.

The most common characteristic abnormalities associated with congenital rubella include ophthalmologic (cataracts, retinopathy, and glaucoma), cardiac (patent ductus arteriosus and peripheral pulmonary artery stenosis), auditory (sensorineural hearing loss), and neurologic (behavioral disorders, meningoencephalitis, and mental retardation) conditions. In addition, infants can present with growth retardation, hepatosplenomegaly, early-onset jaundice, thrombocytopenia, radiolucent bone disease, and purpuric skin lesions (“blueberry muffin” appearance from dermal erythropoiesis).

Detection of rubella-specific IgM antibody usually indicates recent infection. Measurement of rubella-specific IgG over several months can be confirmatory. Rubella virus can be isolated from blood, urine, CSF, and throat swab specimens. Infants with congenital rubella are chronically and persistently infected and tend to shed live virus in urine, stools, and respiratory secretions for 1 year. Infants should be isolated while in the hospital and kept away from susceptible pregnant women when sent home.

**CYTOMEGALOVIRUS**

CMV is the most common congenital infection and the leading cause of sensorineural hearing loss, mental retardation, retinal disease, and cerebral palsy. Congenital CMV occurs in about 0.5% to 1.5% of births. When primary infection occurs in mothers during a pregnancy, the virus is transmitted to the fetus in approximately 35% of cases. Rates of CMV infection are three to seven times greater in infants born to adolescent mothers compared to others. The risk of transmission of CMV to the fetus is independent of gestational age at the time of maternal infection. The earlier in gestation that the primary maternal infection occurs, the more symptomatic the infant will be at birth. The most common sources of CMV for primary infections occurring in mothers during pregnancy are sexual contacts and contact with young children. It is well known that CMV can be transmitted to the fetus even when maternal infection occurred long before conception. This transmission can occur as the result of virus reactivation, chronic infection, or re-infection with a new strain.

More than 90% of infants who have congenital CMV infection exhibit no clinical evidence of disease at birth. Approximately 10% of infected infants are small for gestational age and have symptoms at birth. Findings include microcephaly, thrombocytopenia, hepatosplenomegaly, hepatitis, intracranial calcifications, chorioretinitis, and hearing abnormalities. Some infants can present with a blueberry muffin appearance as the result of dermal erythropoiesis. Skull films may reveal periventricular calcifications. An additional 10% of infected infants may not present until later in infancy or early childhood, when they are found to have sensorineural hearing loss and developmental delays. Mortality is 10% to 15% in symptomatic newborns. Perinatal CMV infection acquired during birth or from mother’s milk is not associated with newborn illness or CNS sequelae.

Congenital CMV infection is diagnosed by detection of virus in the urine or saliva. Detection is often accomplished by traditional virus culture methods but can take several weeks to obtain a result. Rapid culture methods using centrifugation to enhance infectivity and monoclonal antibody to detect early antigens in infected tissue culture can give results in 24 hours. PCR also can be used to detect small amounts of CMV DNA in the urine. Detection of CMV within the first 3 weeks after birth is considered proof of congenital CMV infection.

Trial studies in severely symptomatic newborns of the antiviral agent ganciclovir have shown a lack of progression of hearing loss.

**HERPES SIMPLEX VIRUS**

HSV-2 accounts for 90% of primary genital herpes. About 70% to 85% of neonatal herpes simplex infections are caused by HSV-2. Most commonly, neonatal infections are acquired from the mother shortly before (ascending infection) or during passage through the birth canal at delivery. The incidence of neonatal HSV is estimated to range from 1 in 3000 to 1 in 20,000 live births. Infants with HSV infections are more likely to be born prematurely (40% of affected infants are <36 weeks’ gestation). The risk of infection at delivery in an infant born vaginally to a mother with primary genital herpes is about 33% to 50%. The risk to an infant born to a mother with a reactivated infection is less than 5%. More than 75% of infants who acquire HSV infection are born to mothers who have no previous history or clinical findings consistent with HSV infection.

Most infants are normal at birth, and symptoms of infection develop at 5 to 10 days of life. Symptoms of neonatal HSV infection include disseminated disease involving multiple organ systems, most notably the liver and lungs; localized infection to the CNS; or localized infection to the skin, eyes, and mouth. Symptoms may overlap, and in many cases of disseminated disease, skin lesions are a late finding. Disseminated infection should be considered in any infant with symptoms of sepsis, liver dysfunction, and negative bacteriologic cultures. HSV infection also should be suspected in any neonate who presents with fever, irritability, abnormal CSF findings, and seizures. Initial symptoms can occur anytime between birth and 4 weeks of age, although disseminated disease usually occurs during the first week of life. HSV infections are often severe, and a delay in treatment can result in significant morbidity and mortality.

For the diagnosis of neonatal HSV infection, specimens for culture should be obtained from any skin vesicle, nasopharynx, eyes, urine, blood, CSF, stool, or rectum. Positive cultures obtained from these sites more than 48 hours after birth indicate intrapartum exposure. PCR is a sensitive method for detecting HSV DNA in blood, urine, and CSF.
Parenteral acyclovir is the treatment of choice for neonatal HSV infections. Acyclovir should be administered to all infants suspected to have infection or diagnosed with HSV. The most benign outcome with regard to morbidity and mortality is observed in infants with disease limited to the skin, eyes, and mouth.

## CONGENITAL SYPHILIS

### Decision-Making Algorithms

**Available @ StudentConsult.com**

- Rhinorrhea
- Abnormal Head Size, Shape, and Fontanels
- Red Eye
- Hoarseness
- Hepatomegaly
- Hearing Loss
- Lymphadenopathy

Congenital syphilis most commonly results from transplacental infection of the fetus, although the fetus can acquire infection by contact with a chancr at birth. In addition, hematogenous infection can occur throughout pregnancy. The longer the time elapsed between the mother's infection and pregnancy, the less likely she is to transmit the disease to the fetus.

Intrauterine infection can result in stillbirth, hydrops fetalis, or prematurity. Clinical symptoms vary but include hepatosplenomegaly, snuffles, lymphadenopathy, mucocutaneous lesions, osteochondritis, rash, hemolytic anemia, and thrombocytopenia. Untreated infants, regardless of whether they manifest symptoms at birth, may develop late symptoms, which usually appear after 2 years of age and involve the CNS, bones, joints, teeth, eyes, and skin. Some manifestations of disease may not become apparent until many years after birth, such as interstitial keratitis, eighth cranial nerve deafness, Hutchinson teeth, bowing of the shins, frontal bossing, mulberry molars, saddle nose, rhagades, and Clutton joints. The combination of interstitial keratitis, eighth cranial nerve deafness, and Hutchinson teeth is commonly referred to as the *Hutchinson triad* (see Table 66-1).

Many infants are asymptomatic at the time of diagnosis. If untreated, many infants develop symptoms within the first 5 weeks of life. The most striking lesions affect the mucocutaneous tissues and bones. Early signs of infection may be poor feeding and snuffles (syphilitic rhinitis). Snuffles are more severe and persistent than the common cold and are often bloody. A maculopapular desquamative rash develops over the palms and soles and around the mouth and anus. The rash may progress to become vesicular with bullae. Severely ill infants may be born with hydrops and have profound anemia. Severe consolidated pneumonia may be present at birth, and infants may be born with hydrops and have profound anemia. The most benign outcome with regard to morbidity and mortality is observed in infants with disease limited to the skin, eyes, and mouth.

### Feedback

Parenteral penicillin is the preferred drug of choice for treatment of syphilis. Penicillin G for 10 to 14 days is the only documented effective therapy for infants who have congenital syphilis and neurosyphilis. Infants should have repeat nontreponemal antibody titers repeated at 3, 6, and 12 months to document falling titers. Infants with neurosyphilis must be followed carefully with serologic testing and CSF determinations every 6 months for at least 3 years or until CSF findings are normal.

## HUMAN IMMUNODEFICIENCY VIRUS

*(SEE CHAPTER 125)*

## HEPATITIS B

*(SEE CHAPTER 113)*

## NEISSERIA GONORRHOEAE

N. *gonorrhoeae* infection in a newborn usually involves the eyes (ophthalmia neonatorum). Other sites of infection include scalp abscesses (often associated with fetal monitoring with scalp electrodes), vaginitis, and disseminated disease with bacteremia, arthritis, or meningitis. Transmission to the infant usually occurs during passage through the birth canal when mucous membranes come in contact with infected secretions. Infection usually is present within the first 5 days of life and is characterized initially by a clear, watery discharge, which rapidly becomes purulent. There is marked conjunctival hyperemia and chemosis. Infection tends to be bilateral; however, one eye may be clinically worse than the other. Untreated infections can spread to the cornea (keratitis) and anterior chamber of the eye. This extension can result in corneal perforation and blindness.
Recommended treatment for isolated infection, such as ophthalmia neonatorum, is one intramuscular dose of ceftriaxone. Infants with gonococcal ophthalmia should receive eye irrigations with saline solution at frequent intervals before discharge. Topical antibiotic therapy alone is inadequate and is unnecessary when recommended systemic antimicrobial therapy is given. Infants with gonococcal ophthalmia should be hospitalized and evaluated for disseminated disease (sepsis, arthritis, meningitis). Disseminated disease should be treated with antimicrobial therapy (ceftriaxone or cefotaxime) for 7 days. Cefotaxime can be used in infants with hyperbilirubinemia. If documented, infants with meningitis should be treated for 10 to 14 days.

Tests for concomitant infection with *C. trachomatis*, congenital syphilis, and HIV should be performed. Results of the maternal test for hepatitis B surface antigen should be confirmed. Topical prophylaxis with silver nitrate, erythromycin, or tetracycline is recommended for all newborns for the prevention of gonococcal ophthalmia.

**CHLAMYDIA**

*C. trachomatis* is the most common reportable sexually transmitted infection, with a high rate of infection among sexually active adolescents and young adults. Prevalence of the organism in pregnant women ranges from 6% to 12% and can be 40% in adolescents. *Chlamydia* can be transmitted from the genital tract of an infected mother to her newborn. Acquisition occurs in about 50% of infants born vaginally to infected mothers. Transmission also has been reported in some infants delivered by cesarean section with intact membranes. In infected infants, the risk of conjunctivitis is 25% to 50%, and the risk of pneumonia is 5% to 20%. The nasopharynx is the most commonly infected anatomic site.

Neonatal chlamydial conjunctivitis is characterized by ocular congestion, edema, and discharge developing 5 to 14 days to several weeks after birth and lasting for 1 to 2 weeks. Clinical manifestations vary from mild conjunctivitis to intense inflammation and swelling. Both eyes are almost always involved; however, one eye may appear to be more swollen and infected than the other. The cornea is rarely involved, and preauricular adenopathy is rare.

Pneumonia in a young infant can occur between 2 and 19 weeks of age and is characterized by an afebrile illness with a repetitive staccato cough, tachypnea, and rales. Wheezing is uncommon. Hyperinflation with diffuse infiltrates can be seen on chest radiograph. Nasal stuffiness and otitis media can occur.

Diagnosis can be made by scraping the conjunctiva and culturing the material. Giemsa staining of the conjunctival scrapings revealing the presence of blue-stained intracytoplasmic inclusions within the epithelial cells is diagnostic. PCR is also available. Infants with conjunctivitis and pneumonia are treated with oral erythromycin for 14 days. Topical treatment of conjunctivitis is ineffective and unnecessary. The recommended topical prophylaxis with silver nitrate, erythromycin, or tetracycline for all newborns for the prevention of gonococcal ophthalmia does not prevent neonatal chlamydial conjunctivitis.

**MYCOBACTERIUM TUBERCULOSIS**

(SEE CHAPTER 124)

**Suggested Reading**


OVERVIEW AND ASSESSMENT OF ADOLESCENTS

The leading causes of mortality (Table 67-1) and morbidity (Table 67-2) in adolescents in the United States are behaviorally mediated. Motor vehicle injuries and other injuries account for more than 75% of all deaths. Unhealthy dietary behaviors and inadequate physical activity result in adolescent obesity with associated health complications (e.g., diabetes, hypertension).

It is the physician’s responsibility to use every opportunity to inquire about risk-taking behaviors (Fig. 67-1), regardless of the presenting issue. Physical symptoms in adolescents are often related to psychosocial problems.

INTERVIEWING ADOLESCENTS

The adolescent interview shifts from information gathering from the parent to the adolescent. Interviewing an adolescent alone and discussing confidentiality are the cornerstones of obtaining information regarding risk-taking behaviors, anticipatory guidance, and protective factors (see Chapters 7 and 9).

The interview should take into account the developmental age of the adolescent (Table 67-3). Conversations about sports, friends, movies, and activities outside of school can be useful for all ages and help build rapport (Fig. 67-2).

Confidentiality is a key element when interviewing an adolescent (Table 67-4). The vital, open discussion about risk-taking behavior is more likely to happen when the adolescent is alone (Table 67-5). Some issues cannot be kept confidential, such as suicidal intent and disclosure of sexual or physical abuse. If there is an ambiguous situation, it is wise to obtain legal, ethical, or social work consultation. When caring for a young adolescent, the health care provider should encourage open discussions with a parent, guardian, or other adult.

The law confers certain rights on adolescents, depending on their health condition and personal characteristics, allowing them to receive health services without parental permission (Table 67-6). Usually adolescents can seek health care without parental consent for reproductive, mental, and emergency health services. Emancipated adolescents and mature minors may be treated without parental consent; such status should be documented in the record. The key characteristics of mature minors are their competence and capacity to understand, not their chronologic age. There must be a reasonable judgment that the health intervention is in the best interests of the minor.

### Table 67-1 Leading Causes of Death in Adolescents

<table>
<thead>
<tr>
<th>RANK</th>
<th>CAUSE</th>
<th>RATE (PER 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unintentional injuries</td>
<td>30.3</td>
</tr>
<tr>
<td>2</td>
<td>Assault (homicide)</td>
<td>10.4</td>
</tr>
<tr>
<td>3</td>
<td>Suicide</td>
<td>6.9</td>
</tr>
<tr>
<td>4</td>
<td>Malignant neoplasms (cancer)</td>
<td>3.2</td>
</tr>
<tr>
<td>5</td>
<td>Diseases of the heart</td>
<td>1.6</td>
</tr>
</tbody>
</table>


### Table 67-2 Prevalence of Common Chronic Illnesses of Children and Adolescents

<table>
<thead>
<tr>
<th>ILLNESS</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PULMONARY</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>8%–12%</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1:2500 white, 1:17,000 black</td>
</tr>
<tr>
<td>NEUROMUSCULAR</td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>2–3:1000</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>1%–2%</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>3.5:1000</td>
</tr>
<tr>
<td>Any seizure</td>
<td>3%–5%</td>
</tr>
<tr>
<td>Auditory-visual defects</td>
<td>2%–3%</td>
</tr>
<tr>
<td>Traumatic paralysis</td>
<td>2:1000</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>3% males, 5% females</td>
</tr>
<tr>
<td>Migraine</td>
<td>6%–27% (↑ with increasing age)</td>
</tr>
<tr>
<td>ENDOCRINE/NUTRITION</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.8:1000</td>
</tr>
<tr>
<td>Obesity</td>
<td>25%–30%</td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td>0.5%–1%</td>
</tr>
<tr>
<td>Bulimia</td>
<td>1% (young adolescence), 5%–10% (19–20 yr)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>20%</td>
</tr>
<tr>
<td>Acne</td>
<td>65%</td>
</tr>
</tbody>
</table>
### Structured Communication Adolescent Guide (SCAG)

**Instructions for scoring this form**

After your check-up, please score your doctor (or medical student) using this form.

**Examples:**

- **0 = Did Not**
  - Dr. didn’t ask at all.
- **1 = Did**
  - Dr. asked as if reading a list.
  - Dr. asked as if embarrassed.
  - I felt judged.
  - I felt a bit uncomfortable.
- **2 = Did Well**
  - Dr. established a relationship.
  - Dr. comfortable with questions.
  - Dr. did not judge.
  - I felt comfortable.

**General Rating:** Give a general impression of each section.

- A = Excellent, B = Good, C = Average, D = Poor, F = Fail

<table>
<thead>
<tr>
<th></th>
<th>Did Not</th>
<th>Did</th>
<th>Did Well</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. GETTING STARTED</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Greeted me.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. Introduced self.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. Discussed confidentiality.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>GENERAL RATING</strong></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Did Not</th>
<th>Did</th>
<th>Did Well</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B. GATHERING INFORMATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Good body language.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5. Encouraged me to speak by asking questions other than ones with a yes/no answer.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6. Encouraged parent to speak <em>(leave out if no parent present).</em></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7. Listened and did not judge me.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>8. Established relationship with me by appropriate choice of words.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>GENERAL RATING</strong></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
</tbody>
</table>

---

**Figure 67-1** The Structured Communication Adolescent Guide (SCAG). The SCAG is an interviewing tool developed for learners to use with real or standardized adolescent patients. It incorporates the four major interview components: confidentiality, separation of the adolescent from the adult, psychosocial data gathering (using the HEADDSS mnemonic), and a nonjudgmental approach. The SCAG is at a grade 5 reading level and has demonstrated reliability and validity. A printable version is available through MedEdPORTAL.
### C. TEEN ALONE

<table>
<thead>
<tr>
<th>Task</th>
<th>Did Not</th>
<th>Did 1</th>
<th>Did Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Separated me and parent. <em>(Leave out if no parent present.)</em></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10. Discussed confidentiality.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>11. Gave me a chance to talk about things other than what I came in to discuss.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>12. Reflected on my feelings or concerns <em>(example: You seem...)</em></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**LIFESTYLES:** Physician asks or talks about the following:

<table>
<thead>
<tr>
<th>Category</th>
<th>Did Not</th>
<th>Did 1</th>
<th>Did Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. Home: Family</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>14. Education: School</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>15. Friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16. Activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>17. Alcohol: Beer and hard liquor</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>18. Drugs: Cigarettes</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>19. Marijuana</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>20. Street drugs</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>21. Diet: Weight/diet/eating habits</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>22. Sex: Boyfriend/girlfriend</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>23. Sexual activity</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>24. Safe sex/contraception</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>25. Self: Body image, self-esteem</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>26. Moods/depression/suicide</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**GENERAL RATING**

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Did Not</td>
<td>Did 1</td>
<td>Did Well</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments: Please give examples of things that stood out in your interview.

**Example:** I wasn’t sure what the next step would be.

### D. WRAP UP

<table>
<thead>
<tr>
<th>Task</th>
<th>Did Not</th>
<th>Did 1</th>
<th>Did Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>27. Summary, recapped issues</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>28. Kept the confidentiality</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>29. Asked if there were any questions</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>30. Talked about what to do next <em>(plan and follow-up)</em></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**GENERAL RATING**

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Did Not</td>
<td>Did 1</td>
<td>Did Well</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Overview and Assessment of Adolescents

**Table 67-3**  
Adolescent Psychological Development

<table>
<thead>
<tr>
<th>STAGE</th>
<th>AGE</th>
<th>THINKING</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early teens</td>
<td>10–14</td>
<td>Concrete I</td>
<td>Appearance—“Am I normal?”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Invincible</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peer group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No tomorrow</td>
</tr>
<tr>
<td>Middle teens</td>
<td>15–17</td>
<td>Risk-taking increased</td>
<td>Limit testing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“Who am I?”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Experiment with ideas</td>
</tr>
<tr>
<td>Late teens</td>
<td>18–21</td>
<td>Formal operational</td>
<td>Future</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Planning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partner</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Separation</td>
</tr>
</tbody>
</table>

**Table 67-5**  
Interviewing the Adolescent Alone: Discussion of HEADDSS Topics

<table>
<thead>
<tr>
<th>SETTING – TOPICS – EXPLORE – PLAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explore topics “Get the story.”</td>
</tr>
<tr>
<td>HEADDSS</td>
</tr>
<tr>
<td>See Table 67-5</td>
</tr>
<tr>
<td>Relationships</td>
</tr>
<tr>
<td>Functioning</td>
</tr>
<tr>
<td>Attitudes</td>
</tr>
<tr>
<td>Behaviors</td>
</tr>
</tbody>
</table>

**Table 67-6**  
Legal Rights of Minors

<table>
<thead>
<tr>
<th>Age of majority (≥18 years of age in most states)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exceptions in which health care services can be provided to a minor:</td>
</tr>
<tr>
<td>Emergency care (e.g., life-threatening condition or condition in which a delay in treatment would increase significantly the likelihood of morbidity)</td>
</tr>
<tr>
<td>Diagnosis and treatment of sexuality-related health care</td>
</tr>
<tr>
<td>Diagnosis and treatment of drug-related health care</td>
</tr>
<tr>
<td>Emancipated minors (physically and financially independent of family; Armed Forces; married; childbirth)</td>
</tr>
<tr>
<td>Mature minors (able to comprehend the risks and benefits of evaluation and treatment)</td>
</tr>
<tr>
<td>All exceptions should be documented clearly in the patient’s health record.</td>
</tr>
</tbody>
</table>

*The acronym HEADDSS can represent other terms, that is, A = Activities, D = Depression. Also see Figure 67-1.

**Table 67-4**  
Guidelines for Confidentiality

| Prepare the preadolescent and parent for confidentiality and being interviewed alone. |
| Discuss confidentiality at the start of the interview. |
| Conversations with parents/guardians/adolescent are confidential (with exceptions). |
| Reaffirm confidentiality when alone with your adolescent patient. |

*Exceptions to confidentiality include major or impending harm to any person (i.e., abuse, suicide, homicide).

**PHYSICAL GROWTH AND DEVELOPMENT OF ADOLESCENTS**

**Girls**

Breast budding under the areola (thelarche) and fine straight pubic hair over the mons pubis (adrenarche or pubarche) are early pubertal changes occurring around 11 years of age (range, 8 to 13 years) (see Chapter 174). These changes mark the sexual maturity rating, or Tanner stage, II of pubertal development (Figs. 67-3 and 67-4). Completion of the Tanner stages should take 4 to 5 years. The peak growth spur usually
occurs approximately 1 year after thelarche at sexual maturity rating stage III to IV breast development and before the onset of menstruation (menarche). Menarche is a relatively late pubertal event. Females grow only 2 to 5 cm in height before menarche (see Chapter 174).

The mean ages of thelarche and adrenarche are approximately 9 and 10 years for African American and white girls, respectively. The mean ages of menarche are 12.2 and 12.9 years for African American and white girls, respectively. The interval from the initiation of thelarche to the onset of menses (menarche) is 2.3 ± 1 years. Pubertal changes before 6 years of age in African American and 7 years of age in white girls are considered precocious.

**Boys**

Testicular enlargement (≥2.5 cm) corresponds to sexual maturity rating, or Tanner, stages I to II (Figs. 67-5 and 67-6). Testicular enlargement is followed by pubic hair development at the base of the penis (adrenarche) and then axillary hair within the year. The growth spurt is a relatively late event; it can occur from 10½ years of age to 16 years of age. Deepening of the
Figure 67-4  Sequence of pubertal events in the average American female. More recent studies suggest that onset of breast development may be 9 years of age for African American girls and 10 years of age for white girls. (From Brookman RR, Rauh JL, Morrison JA, et al: The Princeton maturation study, 1976, unpublished data for adolescents in Cincinnati, Ohio. Reprinted from Assessment of Pubertal Development, Columbus, Ohio, 1986, Ross Laboratories.)

Figure 67-5  Typical progression of male pubertal development. A, Pubertal development in the size of male genitalia. B, Pubertal development of male pubic hair. Note that in stage 1 there is no pubic hair. (Courtesy of J.M. Tanner, MD, Institute of Child Health, Department of Growth and Development, University of London, London, England.)

Figure 67-6  Sequence of pubertal events in the average American male. Testicular volume less than 4 mL using an orchidometer (Prader Beads) represents prepubertal stage. (From Brookman RR, Rauh JL, Morrison JA, et al: The Princeton maturation study, 1976, unpublished data for adolescents in Cincinnati, Ohio. Reprinted from Assessment of Pubertal Development, Columbus, Ohio, 1986, Ross Laboratories.)
voice, facial hair, and acne indicate the early stages of puberty. See Chapter 174 for discussion of disorders of puberty.

Changes Associated with Physical Maturation
Tanner stages mark biologic maturation that can be related to specific laboratory value changes and certain physical conditions. The higher hematocrit values in adolescent boys than in adolescent girls are the result of greater androgenic stimulation of the bone marrow and not loss through menstruation. Alkaline phosphatase levels in boys and girls increase during puberty because of rapid bone turnover, especially during the growth spurt. Worsening of mild scoliosis is common in adolescents during their growth spurt.

PSYCHOLOGICAL GROWTH AND DEVELOPMENT OF ADOLESCENTS
SEE TABLE 67-3 AND CHAPTERS 7 AND 9.

Chapter 68
WELL-ADOLESCENT CARE

When interviewing an adolescent, use a nonjudgmental approach and find some common ground to get the adolescent talking about himself or herself. The HEADDSS (home, education, alcohol, drugs, diet, sex, suicide/depression) mnemonic addresses important risk-taking elements of the history (see Table 67-5). Adolescents who experiment in one area of risk-taking often have contemplated or tried multiple other risk-taking behaviors. When all of the risk-taking information has been gathered, the physician should choose one or two health care issues to discuss, making it clear that the information is confidential and that he or she is there to help the adolescent in a partnership way. Although the focus in adolescent care is on psychosocial issues, a general examination also needs to be performed (Table 68-1). Pediatric issues, such as immunization (see Chapter 94) and health screening, should be included (see Table 9-5).

EARLY ADOLESCENCE (AGES 10 TO 14 YEARS)
Rapid changes in physical appearance and behavior are the major characteristics of early adolescence, leading to a great deal of self-consciousness and need for privacy. The history focuses on the early adolescent’s physical and psychosocial health.

MIDDLE ADOLESCENCE (AGES 15 TO 17 YEARS)
Autonomy and a global sense of identity are the major characteristics of middle adolescence. The history focuses on the middle adolescent’s interactions with family, school, and peers. High-risk behaviors as a result of experimentation are common.

LATE ADOLESCENCE (AGES 18 TO 21 YEARS)
Individuality and planning for the future are the major characteristics of late adolescence. Greater emphasis is placed on the late adolescent’s responsibility for his or her health.

PELVIC EXAMINATION
A full pelvic examination is rarely required in a virginal adolescent girl. A bimanual rectal-abdominal examination (all midline internal genitalia are immediately anterior to the rectal wall) is as efficient as a vaginal-abdominal examination. In some girls, anesthesia may be required for a full pelvic examination.

Before a pelvic examination, the patient should be informed about the importance of the assessment and what maneuvers will take place; she should be encouraged to ask questions before, during, or after the examination. A chaperone should be offered when a family caregiver is not present. Assuring the patient that she has complete control over the examination and allowing participating by using a mirror or guiding the examiner is important. The examiner should maintain
eye contact during the examination. Before all maneuvers, the patient must be informed of what to expect and the sensations.

A padded examination table with the patient in a frog-leg position maximizes comfort of a pelvic examination. Stirrups can be used but are less comfortable. The examination room, lubricants, and instruments should be warm. The examination should be unhurried but efficient.

**Inspection** of the genitalia includes evaluation of the pubic hair, labia majora and minora, clitoris, urethra, and hymenal ring. When a **speculum examination** is required, it must be performed before bimanual palpation of internal genitalia because lubricants interfere with the evaluation of microscopic and microbiologic samples. The speculum allows visualization of the vaginal walls and cervical os for collection of appropriate specimens, such as cultures or Papanicolaou (Pap) smears. A Pap smear is not needed until the adolescent is sexually active, unless there is a history of sexual abuse or vulvar infection with human papillomavirus. In the rare circumstance that a vaginal examination is necessary in a virginal girl, a Huffman (0.5 in. × 4.5 in.) or Pederson (0.9 in. × 4.5 in.) speculum should be used. A non-virginal introitus frequently admits a small to medium-sized adult speculum.

**NORMAL VARIANTS OF PUBERTY**

**Breast Asymmetry and Masses**

It is not unusual for one breast to begin growth before (or to grow more rapidly than) the other, with resulting asymmetry. Reassurance that after full maturation the asymmetry will be less obvious and that all women have some degree of asymmetry is needed by some. The breast bud is a pea-sized mass below the nipple that is often tender. Occasionally young women present with a breast mass; usually these are **benign fibroadenomas** or cysts (Table 68-2). Breast cancer is extremely rare in this age group. An ultrasound evaluation is better for the evaluation of young, dense breasts and avoids the radiation exposure of mammography.

**Physiologic Leukorrhea**

Peripubertal girls (sexual maturity rating stage III) often complain of vaginal discharge. If the discharge is clear without symptoms of pruritus or odor, it is most likely physiologic leukorrhea, due to ovarian estrogen stimulation of the uterus and vagina. A physical examination should reveal evidence of an estrogenized vulva and hymen without erythema or excoriation. The physician should always be alert for signs of abuse. If there are symptoms, cultures should be obtained. In these circumstances, vaginal cultures can be obtained without a speculum because **sexually transmitted infections** are vaginal until menarche, when cervical infections are the rule. Inspection of physiologic leukorrhea shows few white blood cells, estrogen maturation of vaginal epithelial cells, and no pathogens on a culture.

**Irregular Menses**

Menarche typically occurs approximately 2 years after thelarche, at the average age of 12.6 years. The initial menses are anovulatory and tend to be irregular in duration. This irregularity may persist for 2 to 5 years, so reassurance may be required. During this phase, estrogen feedback on the hypothalamus decreases gonadotropin secretion, which reduces estrogen production and induces an estrogen withdrawal bleed that can be prolonged and heavy. Anovulatory bleeding is usually painless. As the hypothalamic-pituitary-gonadal axis matures, the cycle becomes ovulatory, and menses are secondary to progesterone withdrawal. When ovulation is established, the average cycle length is 21 to 45 days. Some adolescents ovulate with their first cycle, as indicated by pregnancy before menarche.


**Gynecomastia**

Breast enlargement in boys is usually a benign, self-limited condition. Gynecomastia is noted in 50% to 60% of boys during early adolescence. It is often idiopathic, but it may be noted in various conditions (Table 68-3). Typical findings include the appearance of a 1- to 3-cm, round, freely mobile, often tender, and firm mass immediately beneath the areola during sexual maturity rating stage III. Large, hard, or fixed enlargements and masses associated with any nipple discharge warrant further investigation. Reassurance is usually the only treatment required. If the condition worsens and is associated with psychological morbidity, it may be treated with bromocriptine. Surgical treatment with reduction mammoplasty can be helpful with massive hypertrophy.

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**Chapter 69**

**ADOLESCENT GYNECOLOGY**

**MENSTRUAL DISORDERS**

Irregular menses is the most common complaint of early adolescent girls. As regular, ovulatory cycles become established, pain with menstruation (dysmenorrhea) is a frequent complaint.

**Amenorrhea**

Primary amenorrhea is the complete absence of menstruation by 16 years of age in the presence of breast development or by 14 years of age in the absence of breast development. However 98% of adolescents have onset of menarche by age 15; therefore, investigations should begin at that age in young women without menses. Secondary amenorrhea refers to the cessation of menses for more than 3 consecutive months, any time after menarche.

Primary amenorrhea may be a result of functional or anatomic abnormalities of the hypothalamus, pituitary gland, ovaries, uterus, or vagina. Physiologic immaturity, stress, excessive exercise, and abnormal dietary patterns (anorexia/bulimia) are the most common causes of amenorrhea. Pregnancy should be considered in all cases of secondary amenorrhea, even if the patient denies sexual activity.

The history and physical examination should guide the investigation. An outflow tract obstruction should be ruled out in adolescents with primary amenorrhea, abdominal pain, and secondary sexual characteristics. An abdominal mass resulting from accumulated blood may be present. Low outflow tract obstructions, such as an imperforate hymen, are visible on examination. An endocrine evaluation is indicated for girls with primary amenorrhea without secondary sexual characteristics and an unremarkable history and physical examination. Elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) indicate primary ovarian insufficiency, which may reflect ovarian dysgenesis or ovarian agenesis and warrants a karyotype. Turner syndrome is a common cause, but other chromosomal anomalies, fragile X premutation carriers, and autoimmune etiologies should be ruled out. Low levels of FSH and LH suggest hypothalamic dysfunction, which may be due to physiologic immaturity (often familial), isolated gonadotropin deficiency, or hypogonadotropic hypogonadism (chronic illness, low body weight, stressful life events). Additional hormone evaluation includes thyroid-stimulating hormone and prolactin. Hypothyroidism is a common cause of menstrual dysfunction. A prolactinoma, although rare, must be ruled out.

Girls with secondary amenorrhea have secondary sexual characteristics. The most common causes are pregnancy, anorexia/stress (low LH, FSH, and estradiol), and polycystic ovary syndrome (PCOS). In PCOS there may be symptoms of androgen excess, such as acne and hirsutism, and weight gain and, with insulin resistance, acanthosis. If hirsutism or virilization is present, free and total testosterone, androstenedione, and dihydroepiandrosterone sulfate should be measured to rule out ovarian or adrenal tumors. A normal 17-hydroxyprogesterone level rules out late-onset congenital adrenal hyperplasia. PCOS is diagnosed with two of the following: infrequent menstrual bleeding or secondary amenorrhea, clinical or biochemical hyperandrogenism, and polycystic morphology of ovaries on ultrasound. Estradiol may be normal or low; and androgens, including dihydroepiandrosterone sulfate, may be elevated, although not to the extent that a tumor produces. Patients may have impaired glucose tolerance or hypercholesterolemia.

In a patient with amenorrhea (primary or secondary), normal secondary sex characteristics, negative pregnancy test, normal prolactin and thyroid-stimulating hormone, and no evidence of outflow tract obstruction, the total effect of estrogen on the uterus (rather than a single point estradiol level) can be determined by a progesterone withdrawal test. To achieve this, 5 to 10 mg of medroxyprogesterone (depending on body weight) is given daily for 5 days. If the uterus is normal and primed by estrogen (an intact hypothalamic-pituitary-gonadal axis) with no outflow tract obstruction, there should be bleeding within 1 week after the last progesterone tablet. If there is bleeding, the amenorrhea is secondary to anovulation. If there is no progesterone withdrawal bleeding, the uterus has been insufficiently exposed to estrogen, and there is systemic estrogen deficiency.

Therapy for the amenorrhea should be directed at the cause. Anovulation can be managed with either cyclic progesterone withdrawal or combined hormonal contraceptives (CHCs). In hypothalamic amenorrhea and ovarian failure, there is an associated hypoestrogenism; therapy is directed at replacing estrogen and progesterone, usually with a CHC. PCOS usually can be treated effectively with weight loss, exercise, progesterone withdrawal, or CHC. If there is evidence of androgen...
excess, CHCs reduce androgen production from the ovaries and increases sex hormone–binding globulin to reduce the amount of available androgen. Spironolactone helps treat hirsutism, and when there is evidence of insulin insensitivity, metformin can restore ovulatory cycles. Contraception should be prescribed, if applicable.

**Abnormal Uterine Bleeding**

Normal, ovulatory menses can occur 21 to 45 days apart, measuring from the first day of menstruation to the first day of the next menstruation. The average duration of flow is 3 to 7 days, with more than 7 days considered prolonged. More than 8 well-soaked pads or 12 tampons per day may be considered excessive, although classically blood loss is difficult to estimate. Table 69-1 defines menstrual disorders according to the new International Federation of Gynecology and Obstetrics nomenclature and classification of abnormal uterine bleeding (AUB). If the menstrual problem is unclear and nonacute, observation and charting on a menstrual calendar are warranted. Excessively heavy, prolonged, or infrequent bleeding in the first year after menarche is often physiologic but should be investigated, especially if there is associated iron deficiency anemia.

Approximately 20% of adolescents with heavy or prolonged menses, especially those presenting in early menarche, have a coagulation disorder and 10% have other pathology. If an underlying pathology is discovered, treatment should be directed at the primary disorder and the secondary menstrual dysfunction.

The differential diagnosis of AUB is found in Table 69-2. Anovulation is the most common etiology of AUB in adolescents. Without progesterone from the corpus luteum, unopposed estrogen causes endometrial hyperplasia and irregular endometrial shedding, which can be prolonged and heavy, sometimes life threatening. Progesterone induces a secretory endometrium. When progesterone is withdrawn, the endometrium sheds in a synchronous fashion with myometrial and vascular contractions (causing dysmenorrhea but limiting blood loss). For the first 1 to 2 years post-menarche, the majority of adolescent cycles are anovulatory. After 1 year of regular cycles, irregular bleeding usually indicates an organic abnormality.

A thorough history with a menstrual calendar indicating the amount of flow and associated symptoms is followed by physical examination, including a pelvic examination in a nonvirginal adolescent or an ultrasound in a virginal adolescent. Physical examination should also assess for signs of anemia, bruising or petechia, signs of hyperandrogenism or thyroid disease. A complete blood count, pregnancy test, thyroid function tests, and coagulation screen should be performed. In sexually active adolescents, sexually transmitted infections (STIs) should be ruled out.

Unpredictable, heavy, and prolonged menses may impair school attendance and social functioning; iron deficiency anemia is associated with lower academic scores. Treatment is indicated for heavy menses. Chronic and acute bleeding can be managed with CHCs; multiple daily doses may be required until blood loss is controlled. Occasionally uncontrollable bleeding requires hospitalization for intravenous fluids and high-dose estrogen. Uterine curettage is rarely indicated in adolescents. Iron therapy is also important. Use of CHCs to regulate menstruation and allow the hypothalamic–pituitary–gonadal axis to mature is appropriate; only 6 to 12 months of therapy may be required. CHCs are paramount in the management of heavy menstrual bleeding in individuals with bleeding disorders (von Willebrand disease), although adjuvant therapy with tranexamic acid may be needed for management of any scheduled withdrawal bleeds. Parents are often concerned that CHC use will cause their daughter to become sexually active, but literature and experience do not support this.

### Table 69-1 Definition of Menstrual Disorders

<table>
<thead>
<tr>
<th>CLINICAL DIMENSION</th>
<th>DESCRPTIVE TERM</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Frequent menstrual bleeding</td>
<td>&lt;21 days/cycle</td>
</tr>
<tr>
<td></td>
<td>Infrequent menstrual bleeding</td>
<td>&gt;35 days/cycle</td>
</tr>
<tr>
<td>Regularity</td>
<td>Amenorrhea</td>
<td>Absent for 6 months or more</td>
</tr>
<tr>
<td></td>
<td>Irregular menstrual bleeding</td>
<td>&gt;20 day variation in cycle length</td>
</tr>
<tr>
<td>Duration</td>
<td>Prolonged menstrual bleeding</td>
<td>&gt;8 days of flow</td>
</tr>
<tr>
<td></td>
<td>Shortened menstrual bleeding</td>
<td>&lt;2 days of flow</td>
</tr>
<tr>
<td>Flow</td>
<td>Heavy menstrual bleeding</td>
<td>&gt;80 cc loss</td>
</tr>
<tr>
<td></td>
<td>Light menstrual bleeding</td>
<td>&lt;5 cc loss</td>
</tr>
<tr>
<td>Intermenstrual bleeding</td>
<td>Bleeding between normally timed periods</td>
<td></td>
</tr>
</tbody>
</table>

### Table 69-2 Differential Diagnosis of Abnormal Vaginal Bleeding

- Pregnancy, including ectopic pregnancy
- Infection—usually sexually transmitted
- Endocrine disorder—thyroid disorder, PCOS, pituitary disorder
- Blood dyscrasia
- Systemic disease
- Trauma
- Medications
- Contraception
- Vaginal, cervical, or uterine disorders
- Ovarian tumor/cyst
- Foreign body

PCOS, Polycystic ovary syndrome

*When all excluded, the diagnosis of dysfunctional uterine bleeding can be made.*
Dysmenorrhea

Table 69-3 Treatment of Dysmenorrhea

<table>
<thead>
<tr>
<th>NSAIDs</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over-the-counter</td>
<td>Diclofenac 100 mg PO stat then 50 mg tid</td>
</tr>
<tr>
<td>Ibuprofen or naproxen sodium taken every 4 h</td>
<td>Mefenamic acid 500 mg PO stat then 250 mg qid or 500 mg PO tid</td>
</tr>
<tr>
<td>Ibuprofen 400 mg PO qid</td>
<td>Naproxen 500 mg PO stat then 250 PO to 500 mg PO bid</td>
</tr>
<tr>
<td>Naproxen 500 mg PO stat then 250 PO to 500 mg PO bid</td>
<td>Mefenamic acid 500 mg PO stat then 250 mg qid or 500 mg PO tid</td>
</tr>
<tr>
<td>Mefenamic acid 500 mg PO stat then 250 mg qid or 500 mg PO tid</td>
<td>Diclofenac 100 mg PO stat then 50 mg tid</td>
</tr>
<tr>
<td>Diclofenacin 100 mg PO stat then 50 mg tid</td>
<td>Combined hormonal contraceptives—cyclic or continuous</td>
</tr>
<tr>
<td>Combined hormonal contraceptives—cyclic or continuous</td>
<td>Progestogen-only pill</td>
</tr>
<tr>
<td>Progestogen-only pill</td>
<td>Depo-Provera—150 mg IM every 12–14 wk</td>
</tr>
<tr>
<td>LNG Intrauterine System</td>
<td>LNG, Levonorgestrel; NSAIDs, nonsteroidal anti-inflammatory drugs.</td>
</tr>
</tbody>
</table>

The most common gynecologic complaint of young women is painful menstruation, or dysmenorrhea, during the first 1 to 3 days of bleeding. **Primary dysmenorrhea** is defined as pelvic pain during menstruation in the absence of pelvic pathology and is a feature of ovulation, typically developing 1 to 3 years after menarche, with an increasing incidence to the age of 24, as ovulatory cycles are established. The release of prostaglandins and leukotrienes from the degenerating endometrium after progesterone levels decline causes increased uterine tone and increased frequency and dysrhythmia of uterine contractions. This creates excessive uterine pressures and ischemia that heightens the sensitivity of pain fibers to bradykinin and other physical stimuli.

**Secondary dysmenorrhea** is menstrual pain associated with pelvic pathology and is caused most frequently by endometriosis or pelvic inflammatory disease. Adolescents with endometriosis usually have mild to moderate disease, but girls with obstructed outflow tracts tend to have severe endometriosis soon after menarche. The types of dysmenorrhea usually can be distinguished by history and physical examination. Ultrasound is preferred as the initial screen for obstructing genital tract lesions. Magnetic resonance imaging may be useful in complex reproductive tract anomalies. Laparoscopy is required to diagnose endometriosis and pelvic inflammatory disease with certainty, although it usually is reserved for patients who fail medical therapy.

**Treatment** of primary dysmenorrhea should be considered with symptoms causing significant distress. First-line therapy is nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 69-3). To maximize pain relief, NSAIDs should be taken before or as soon as menstruation begins, and the dosing schedule should be followed closely. Typically NSAIDs are needed for 2 to 3 days. If NSAIDs fail to provide adequate relief, CHCs or long-acting reversible contraceptives (LARCs) may be added.

These contraceptives may be first-line therapy, depending on need for pregnancy prevention.

If dysmenorrhea persists despite an adequate trial of CHCs (>4 months), an alternative diagnosis, such as endometriosis, should be considered. When CHCs fail, a laparoscopy may be performed before advancing therapy to confirm the diagnosis and excise endometriotic lesions. Extended CHC therapy (84 days of active CHC followed by a 5- to 7-day hormone-free interval) may control symptoms. Alternatives are depot medroxyprogesterone acetate (150 mg) every 2 months until symptoms are controlled, then every 3 months of levonorgestrel-releasing intrauterine system. Endometriosis may be treated with gonadotropin-releasing hormone agonists (nafarelin or leuprolide) and hormonal therapy, in older adolescents (>16 years of age) when symptom relief is required.

**PREGNANCY**

The median age of first intercourse in the United States is 17 years for girls and 16 years for boys; this is similar to other developed countries. Although the age of coital initiation is similar among different socioeconomic groups, the prevalence of adolescent childbearing is greatest in the lower socioeconomic strata. Risk factors for adolescent pregnancy include lower socioeconomic status, lower education, low self-esteem, lack of access to contraception, alcohol and drug use, and adverse early life experiences in the adolescent home. Approximately 900,000 U.S. females 12 to 19 years of age become pregnant each year. In women younger than 20 years of age, there are 97 pregnancies, 54 births, and 29 abortions per 1000. Increased use of contraceptives has reduced adolescent pregnancy by up to 35% since the peak year of 1990. Adolescents who continue their pregnancy have an increased incidence of preterm and very preterm births, low birth weight infants, infant neonatal admission, postneonatal mortality, child abuse, subsequent maternal unemployment, and poor maternal educational achievement. These risks are influenced by behavior and socioeconomic status, as well as inherent biologic risks within adolescents. Good prenatal care, nutrition, and social support improve pregnancy outcomes.

**Diagnosis**

Pregnancy should be considered and ruled out in any adolescent presenting with secondary amenorrhea. Frequently pregnant adolescents delay seeking a diagnosis until several periods have been missed and initially may deny having intercourse. Early adolescents often present with other symptoms, such as vomiting, vague pains, or deteriorating behavior and may report normal periods. Because of the varied presentations of adolescent pregnancy, a thorough menstrual history should be obtained in all menstruating adolescents. Urine pregnancy tests are sensitive approximately 7 to 10 days after conception. Rape or incest should be ruled out in all cases of adolescent pregnancy.

When pregnancy is confirmed, immediate gestational dating is important to assist in planning. Options are to continue or terminate the pregnancy (if not beyond 20 to 24 weeks’ gestation). With the former, the adolescent may choose to parent the child or have the child adopted. Pregnant adolescents should be encouraged to involve their families to assist with decision making; parents may be more understanding than the adolescent expects.
Continuation of the Pregnancy
Adolescents who continue the pregnancy need early, consistent, and comprehensive prenatal care by a team of health care providers. Their socioeconomic situation should be evaluated in an effort to optimize the infant’s health and development. Although fewer than 5% of adolescents have their infants adopted, this option should be discussed. Pregnancy is the most common cause for females to drop out of school, so special attention should be given to keeping the adolescent in school during and after pregnancy.

Termination
If a pregnant adolescent chooses to terminate her pregnancy, she should be referred immediately to a nonjudgmental abortion service. The options for pregnancy termination depend on the gestational age. Surgical procedures include manual vacuum aspiration (<8 weeks’ gestational age), suction curettage (<12 to 14 weeks’ gestational age, depending on the provider), and dilation and evacuation (14 to 20 weeks’ gestational age). Early pregnancy (<8 weeks’ gestational age) can be terminated medically with oral mifepristone (RU-486) in combination with misoprostol, methotrexate with misoprostol, or misoprostol alone. Adolescents rarely present early enough to explore this option. In the second trimester (>12 weeks’ gestational age), labor induction and delivery can be effected by vaginal misoprostol or the intra-amniotic instillation of prostaglandins or hypertonic saline. Psychosocial support and subsequent contraceptive counseling and implementation should be available for adolescents who choose abortion.

CONTRACEPTION
Adolescents often begin intercourse without adequate birth control. Because unintended pregnancy can be associated with significant psychosocial morbidity for the mother, father, and child, prevention should be a primary goal. All methods of contraception significantly reduce the risk of pregnancy when used in a consistent and correct fashion. The best form of contraception is the one an individual will use. Contraceptives can be divided into user-based methods and LARCs. It is important to remind young women that steroidal contraception or LARCs do not provide any protection from STIs, and condoms should be used to reduce the risk of infection.

Abstinence
Abstaining from sexual intercourse is the most commonly used and most effective form of adolescent birth control. A degree of self-control, self-assuredness, and self-esteem is necessary. Adolescents who choose to be sexually active should be offered birth control, because there is a 70% chance of pregnancy in 1 year of regular, unprotected intercourse.

Steroidal Contraception
Combined Oral Contraceptives
Combined oral contraceptives (COCs) contain a synthetic estrogen and progesterone that suppress gonadotropin secretion and ovarian follicle development and ovulation. COCs also produce an atrophic endometrium (inhospitable for blastocyst implantation) and thicken cervical mucus to inhibit sperm penetration. COCs are 99% effective if taken regularly and have numerous noncontraceptive benefits (decreased acne, less dysmenorrhea, and lighter menstrual flow). After a history and physical examination, COCs can be started on the first day of the next menstrual period or as a Quick Start. The Quick Start method refers to starting on any day of the cycle, usually on the day of the visit to the health care provider, as long as pregnancy has been ruled out. Contraindications and relative contraindications to COCs are listed in Tables 69-4 and 69-5. Blood pressure measurement to rule out preexisting hypertension should be obtained before prescribing a COC. Initially the adolescent should be seen monthly to reinforce good contraceptive use and safer sex. Unless adolescents show the ability to take a pill daily, contraception with COCs should be avoided. When COCs are prescribed, 28-day packets are recommended because they encourage a daily routine. One novel contraceptive regimen has packaged 84 active tablets to be taken sequentially followed by a 7-day hormone-free interval and the next package. Any COC can be used in such a fashion to induce long intervals between withdrawal bleeding.

Initial side effects, such as nausea (pills should be taken at night to reduce this), breast tenderness, and breakthrough bleeding (especially if pills are missed), are common and usually transient. COCs do not generally cause weight gain. Usually 3 to 4 months on one COC are needed to determine acceptability. If there is breakthrough bleeding, the physician

<table>
<thead>
<tr>
<th>Table 69-4 Absolute Contraindications to Combined Hormonal Contraceptives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking and age &gt;35 yr</td>
</tr>
<tr>
<td>Hypertension (systolic ≥160 mm Hg or diastolic ≥100 mm Hg)</td>
</tr>
<tr>
<td>Current or history of venous thromboembolism</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>History of cerebrovascular accident</td>
</tr>
<tr>
<td>Complicated valvular heart disease (pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis)</td>
</tr>
<tr>
<td>Migraine with focal neurologic symptoms</td>
</tr>
<tr>
<td>Breast cancer (current)</td>
</tr>
<tr>
<td>Diabetes with retinopathy/nephropathy/neuropathy</td>
</tr>
<tr>
<td>Severe cirrhosis</td>
</tr>
<tr>
<td>Liver tumor (adenoma or hepatoma)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 69-5 Relative Contraindications to Combined Hormonal Contraceptives</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 month postpartum and breastfeeding or &lt;21 days postpartum not breastfeeding</td>
</tr>
<tr>
<td>Adequately controlled hypertension</td>
</tr>
<tr>
<td>Hypertension (systolic 140–159 mm Hg, diastolic 90–99 mm Hg)</td>
</tr>
<tr>
<td>Migraine and age &gt;35 yr</td>
</tr>
<tr>
<td>Currently symptomatic gallbladder disease</td>
</tr>
<tr>
<td>Mild cirrhosis</td>
</tr>
<tr>
<td>History of combined oral contraceptive-related cholestasis</td>
</tr>
<tr>
<td>History of malabsorptive bariatric surgery procedure</td>
</tr>
</tbody>
</table>
Contraceptive Vaginal Ring

The contraceptive vaginal ring (NuvaRing) is a flexible, Silastic ring. The ring releases a constant rate of 15 mg of ethinyl estradiol and 0.120 mg of etonogestrel per day. Each ring is used continuously for 3 weeks and then removed. A new ring is inserted 7 days later. The contraindications and side effects are the same as with COCs.

Contraceptive Patch

The contraceptive patch (norelgestromin [Evra]) is a 25-cm² pink patch that is applied, usually on the buttocks, for 1 week followed by removal and application of a new patch for a total of 3 weeks of patch use, then a patch-free week for a withdrawal bleed. The 4-week cycle is repeated. The daily dose is equivalent to a 35-mg ethinyl estradiol COC. In women weighing 90 kg or more, the contraceptive patch is less efficacious.

Long-Acting Reversible Contraceptives

Hormonal Injections and Implants

Intramuscular injection of 150 mg of medroxyprogesterone acetate (Depo-Provera) every 12 to 14 weeks is an effective form of birth control. Progestogen-only contraception is associated with menstrual irregularities (70% amenorrhea and 30% frequent menstrual bleeding). Medroxyprogesterone acetate (Depo-SubQ Provera 104) is designed for subcutaneous use every 12 to 14 weeks and may be self-administered with minimal training. An implant containing the progestin etonogestrel (Implanon) is now available on the U.S. market. This single rod implant is inserted subcutaneously and is effective for 3 years. These forms of contraception are user- and coital-independent and reduce failure secondary to missed doses.

Intrauterine Devices

Intrauterine devices (IUDs) are inserted into the uterus where they release either copper (ParaGard) that is spermicidal or levonorgestrel (Mirena) that prevents implantation by inducing an atrophic endometrium. The copper IUD, which lasts up to 10 years, may increase the amount and duration of bleeding as well as dysmenorrhea. The levonorgestrel-releasing intrauterine system is highly effective for up to 5 years while decreasing bleeding and dysmenorrhea, even causing amenorrhea. Although a small increased risk of pelvic inflammatory disease exists for 21 days after insertion of an IUD, the risk following that transient period lowers and continues at a low rate for the remainder of time that the young woman uses an IUD. Adolescents should be screened for STIs at the time of IUD insertion, with treatment provided as soon as possible for positive results or if there is a concern of compliance at the time of IUD insertion. Insertion in nulliparous women can be aided by the use of a paracervical block. IUDs require no active involvement by the user, thus eliminating error and can be considered as one of the first line options for adolescent contraception. Condoms should be encouraged to reduce the risk of STI.

Emergency Postcoital Contraception

Emergency postcoital contraception should be discussed at every visit. A prescription should be given in advance of need when no over-the-counter access is available. Emergency contraception reduces the risk of pregnancy after unprotected intercourse if used within 5 days, although efficacy is greatest when used as early as possible. Other indications and contraindications to emergency postcoital contraception are listed in Table 69-7. There are two forms of emergency contraception: (a) Plan B (0.75 mg of levonorgestrel), one pill taken twice, 12 hours apart, or two tablets given once and (b) using a CHC pill the equivalent of 50 mg of ethinyl estradiol and 250 μg of norgestrel, each repeated in 12 hours. Plan B is also associated with significantly less nausea and vomiting than the CHC regimen. Mifepristone is also an effective postcoital contraceptive; however it is not approved for this use in the United States. A copper IUD can be inserted 7 days from the act of unprotected intercourse and has an efficacy of greater than 99%. This method is not generally recommended for adolescents.
Barrier Methods

**Condoms and Foam**
When condoms and spermicide (foam, gel, film, sponge) are used together in a correct fashion (film must be placed 10 minutes before intercourse), they are almost as effective as COCs in the prevention of pregnancy, especially in individuals who have infrequent intercourse. This method is available over-the-counter (latex and polyurethane condoms) without the need for a physician visit or prescription and reduces the risk of STIs, including human immunodeficiency virus (HIV). The female condom (Reality) is an additional barrier method made of polyurethane that affords females more control, but adolescents usually do not consider it aesthetically pleasing.

**Sponge, Caps, and Diaphragm**
The vaginal sponge (Protectaid) is a spermicide-impregnated synthetic sponge that is effective for 24 hours of intercourse. The FemCap is a silicone cap fitted by a health care provider and then placed on the cervix by the user before intercourse. This method is technically difficult, especially for an adolescent. The diaphragm is fitted by a health care provider but is technically simpler to use than the cap because the edges go into the vaginal fornices. To be effective, the diaphragm should be used with spermicide applied to the cervical side and along the rim. The diaphragm needs additional spermicide with each act of intercourse. The Lea’s Shield is a silicone device, similar to a diaphragm, that covers the cervix and adheres to the vaginal vault by a mild vacuum generated by its design. All of these methods need to be left in place for 6 hours after the last act of intercourse for optimal efficacy.

**Coitus Interruptus**
Withdrawal is a common method of birth control used by sexually active adolescents, but it is ineffective because sperm are released into the vagina before ejaculation, and withdrawal may occur after ejaculation has begun.

**Rhythm Method (Periodic Coital Abstinence)**
The rhythm method is the practice of periodic abstinence just before, during, and just after ovulation. This method requires the user to have an accurate knowledge of her cycle, awareness of clues indicating ovulation, and discipline. Adolescents tend to have unpredictable cycles and consequently less predictable ovulation, so it is difficult to determine with any accuracy a time of the month that can be considered completely safe.

**Oral and Anal Sex**
Some adolescents engage in oral or anal sex because they believe that it eliminates the need for contraception. Many do not consider this activity to mean “having sex.” Condoms generally are not used during oral or anal sex, but the risk of acquiring an STI is still present. Adolescents should be asked specifically about nonvaginal forms of sexual activity, and adolescents who engage in oral and anal sex require STI and HIV counseling and screening.

**RAPE**
*Rape* is a legal term for nonconsensual intercourse. Almost half of rape victims are adolescents, and the perpetrator is known in 50% of cases. Although gathering historical and physical evidence for a criminal investigation is important, the physician’s primary responsibility is to perform these functions in a supportive, nonjudgmental manner. The history should include details of the sexual assault, time from the assault until presentation, whether the victim cleaned herself, date of last menstrual period, and previous sexual activity, if any.

For optimal results, forensic material should be collected within 72 hours of the assault. Clothes, especially undergarments, need to be placed in a paper bag for drying (plastic holds humidity, which allows organisms to grow, destroying forensic evidence). The patient should be inspected for bruises, bites, and oral, genital, and anal trauma. Photographs are the best record to document injuries. Specimens should be obtained from the fingernails, mouth, vagina, pubic hair, and anus. The sexual assault kit provides materials to obtain DNA from semen, saliva, blood, fingernail scrapings, and pubic hair. A wet mount of vaginal fluids shows the presence or absence of sperm under the microscope. Cultures for STIs should be taken but are often negative (unless previously infected), because 72 hours are needed for the bacterial load to be sufficient for a culture. Blood should be drawn for baseline HIV and syphilis (Venereal Disease Research Laboratories test). All materials must be maintained in a “chain of evidence” that cannot be called into question in court.

Therapy after a rape includes prophylaxis for emergency contraception and STI and, if indicated, hepatitis immune globulin and hepatitis vaccine. A single oral dose of cefixime, 400 mg, and azithromycin, 1 g, treats *Chlamydia*, gonorrhea, and syphilis. An alternative regimen is a single intramuscular dose of ceftriaxone, 125 mg, with a single oral dose of azithromycin, 1 g. For prophylaxis against bacterial vaginosis and *Trichomonas*, a single oral dose of metronidazole, 2 g, is recommended. Repeat cultures, wet mounts, and a pregnancy test should be performed 3 weeks after the assault, followed by serology for syphilis, hepatitis, and HIV at 12 weeks. Long-term sequelae are common; patients should be offered immediate and ongoing psychological support, such as that offered by local rape crisis services.
EATING DISORDERS

Eating disorders are common chronic diseases in adolescents, especially in females. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), classifies these as psychiatric illnesses. The diagnosis in young adolescents (pre-growth spurt, premenstrual) may not follow the typical diagnostic criteria (Table 70-1).

ANOREXIA NERVOSA

The prevalence of anorexia nervosa is 1.5% in teenage girls. The female-to-male ratio is approximately 20:1, and the condition shows a familial pattern. The cause of anorexia nervosa is unknown, but it involves a complex interaction between social, environmental, psychological, and biologic events (Fig. 70-1), with risk factors having been identified (Fig. 70-2).

Clinical Manifestations and Diagnosis

Screening for eating disorders is important and is best done as a part of the larger psychosocial screen for risk-taking factors (see Fig. 67-1). Although it is recommended that the adolescent be interviewed alone, he or she may minimize the problem; thus interviewing the parent(s) alone is also important. The first event usually described by an affected patient is a behavioral change in eating or exercise (i.e., food obsession, food-related ruminations, mood changes). The patient has an unrealistic body image and feels too fat, despite appearing excessively thin. Parents’ response to this situation can be anger, self-blame, focusing attention on the child, ignoring the disorder, or approving of the behavior.

The physician should be nonjudgmental, collect information, and assess the differential diagnosis. The differential diagnosis of weight loss includes gastroesophageal reflux, peptic ulcer, malignancy, chronic diarrhea, malabsorption, inflammatory bowel disease, increased energy demands, hypothalamic lesions, hyperthyroidism, diabetes mellitus, and Addison disease. Psychiatric disorders also need to be considered (e.g., drug abuse, depression, obsessive-compulsive disorders).

The clinical features of anorexia include wearing oversized layered clothing to hide appearance, fine hair on the face and trunk (lanugo-like hair), rough and scaly skin, bradycardia, hypothermia, decreased body mass index, erosion of enamel of teeth (acid from emesis), and acrocyanosis of hands and feet. Signs of hyperthyroidism should not be present (see Chapter 175). The diagnostic criteria for anorexia nervosa are listed in Table 70-2.

Treatment and Prognosis

Treatment requires a multidisciplinary approach, including a feeding program as well as individual and family therapy. Feeding is accomplished through voluntary intake of regular foods, nutritional formula orally or by nasogastric tube. When vital signs are stable, discussion and negotiation of a detailed treatment contract with the patient and the parents are essential. The first step is to restore body weight. Hospitalization may be necessary (Table 70-3). When 80% of normal weight is achieved, the patient is given freedom to gain weight at a personal pace. The prognosis includes a 3% to 5% mortality (suicide, malnutrition) rate, the development of bulimic symptoms (30% of individuals), and persistent anorexia nervosa syndrome (20% of individuals).

BULIMIA NERVOSA

Table 70-4 presents the diagnostic criteria for bulimia nervosa. The prevalence of bulimia nervosa is 5% in female college students. The female-to-male ratio is 10:1. Binge-eating episodes consist of large quantities of often forbidden foods or leftovers or both, consumed rapidly, followed by vomiting. Metabolic abnormalities result from the excessive vomiting or laxative

<table>
<thead>
<tr>
<th>Table 70-1</th>
<th>Normal Adolescent Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSYCHOLOGICAL STAGES</td>
<td>ISSUES THAT CAN TRIGGER EATING DISORDERS</td>
</tr>
<tr>
<td>Early adolescence—increased body awareness</td>
<td>Fear of growing up</td>
</tr>
<tr>
<td>Middle adolescence—increased self-awareness</td>
<td>Rebelliousness</td>
</tr>
<tr>
<td>Late adolescence—identity</td>
<td>Competition and achievement</td>
</tr>
<tr>
<td>Need for control</td>
<td></td>
</tr>
</tbody>
</table>

Table 70-2

Table 70-3

Table 70-4
Eating Disorders

and diuretic intake. Binge-eating episodes and the loss of control over eating often occur in young women who are slightly overweight with a history of dieting.

Nutritional, educational, and self-monitoring techniques are used to increase awareness of the maladaptive behavior, following which efforts are made to change the eating behavior. Patients with bulimia nervosa may respond to antidepressant therapy because they often have personality disturbances, impulse control difficulties, and family histories of affective disorders. Patients feel embarrassed, guilty, and ashamed of their actions. Attempted suicide and completed suicide (5%) are an important concern.

### Clinical Features

- Wearing oversized clothing
- Fine hair on the face and trunk (lanugo-like hair)
- Bradycardia, hypothermia
- Decreased body mass index
- Erosion of enamel of teeth (acid from emesis)
- Acrocyanosis of hands and feet.

### Risk Factors

**Familial**
- Personality types
- Previous overweight
- Affective disorders (family history)
- Impulsive/negative (bulimia nervosa)
- Psychiatric disease

**Feeling that something is not right:**
- With self
- With control (environment)

**Behavioral change**
- Exercise or Eating

**Eating disorder cycle**

### Figure 70-2

The slippery slope to eating disorders.

### Table 70-2

**Diagnostic Criteria for Anorexia Nervosa**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refusal to maintain body weight at or above</td>
<td>weight for age and height (e.g., weight loss leading to body weight &lt;85%</td>
</tr>
<tr>
<td>Intense fear of gaining weight or becoming fat,</td>
<td>of ideal)</td>
</tr>
<tr>
<td>Denial of the seriousness of the low body weight</td>
<td>—a disturbance in the way in which one's body weight or shape is experienced</td>
</tr>
<tr>
<td>Amenorrhea in postmenarche females*</td>
<td></td>
</tr>
</tbody>
</table>

*The diagnostic criteria may be difficult to meet in a young adolescent. Allow for a wide spectrum of clinical features.

### Table 70-3

**When to Hospitalize an Anorexic Patient**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss &gt;25% ideal body weight*</td>
<td></td>
</tr>
<tr>
<td>Risk of suicide</td>
<td></td>
</tr>
<tr>
<td>Bradycardia, hypothermia</td>
<td></td>
</tr>
<tr>
<td>Dehydration, hypokalemia, dysrhythmias</td>
<td></td>
</tr>
<tr>
<td>Outpatient treatment fails</td>
<td></td>
</tr>
</tbody>
</table>

*Less weight loss accepted in young adolescent.

### Table 70-4

**Diagnostic Criteria for Bulimia Nervosa**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent episodes of binge eating, at least</td>
<td>twice a week for 3 months, characterized by the following:</td>
</tr>
<tr>
<td>Intense fear of gaining weight or becoming fat</td>
<td></td>
</tr>
<tr>
<td>Denial of the seriousness of the low body</td>
<td></td>
</tr>
<tr>
<td>Amenorrhea in postmenarche females*</td>
<td></td>
</tr>
<tr>
<td>Compensatory behavior to prevent weight gain</td>
<td></td>
</tr>
<tr>
<td>Self-evaluation unduly influenced by body</td>
<td></td>
</tr>
<tr>
<td>Disturbance does not occur exclusively during</td>
<td></td>
</tr>
</tbody>
</table>

and episodes of anorexia nervosa.

*More weight loss accepted in young adolescent.
The age at which street drugs are first used is decreasing (<12 years), and females are overtaking males in terms of substance use. Ninety percent of adult smokers begin their habit during their adolescent years. Marijuana and stimulant drug use is increasing. Inhalant use (glue solvents, aerosol products) is prevalent in younger adolescents and in Native Americans. The use of club drugs by adolescents from upper income groups at rave parties (3,4-methylenedioxy-methamphetamine [Ecstasy]) and so-called date-rape drugs (gamma-hydroxybutyrate or flunitrazepam [Rohypnol]) has risen sharply. Anabolic steroid use has increased in adolescent boys seeking enhanced athletic performance.

A history of drug use should be taken in a nonjudgmental and supportive manner and include the types of substances, frequency, timing, circumstances, and outcomes of substance use. Table 71-1 is a helpful screening tool. There are few physical findings even with chronic adolescent substance use. An adolescent may present in an overdose or intoxicated state, or in a psychosis triggered by a hallucinogen, such as phencyclidine ("angel dust"). Club drugs have direct (coma and seizures) and indirect (sexual assault and dehydration) adverse effects. Anabolic steroids also have direct (gynecomastia and testicular atrophy) and indirect (mood swings and violence) adverse effects.

### Table 71-1: CRAFFT: A Screening Tool for Adolescent Substance Abuse

<table>
<thead>
<tr>
<th>C</th>
<th>Car</th>
<th>Driving under the influence of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Relax</td>
<td>Using drugs to relax, fit in, feel better</td>
</tr>
<tr>
<td>A</td>
<td>Alone</td>
<td>Drugs/alcohol consumption while alone</td>
</tr>
<tr>
<td>F</td>
<td>Forgetting</td>
<td>Forgetting things as a result of drugs/alcohol</td>
</tr>
<tr>
<td>F</td>
<td>Family/Friends</td>
<td>Family and friends tell teen to stop/cut down</td>
</tr>
<tr>
<td>T</td>
<td>Trouble</td>
<td>Getting into trouble because of drugs/alcohol</td>
</tr>
</tbody>
</table>

### Table 71-2: Substances Abused by Adolescents: Names and Acute Effects

<table>
<thead>
<tr>
<th>SUBSTANCE (STREET/ALTERNATIVE NAME)</th>
<th>EFFECTS AND FACTS</th>
<th>ROUTE OF ADMINISTRATION (TIME OF ACTION)</th>
<th>DETECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol (Meths)</td>
<td>Disinhibition, ataxia, slurred speech, respiratory and CNS depression</td>
<td>Ingested (depends on amount and tolerance)</td>
<td>Urine and blood</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Relaxation, CNS dependence, ↑ blood pressure, ↑ heart rate, ↓ temperature</td>
<td>Inhaled (minutes)</td>
<td>Snuffed, snorted, chewed</td>
</tr>
<tr>
<td>Marijuana (Cannabis, hashish, joints)</td>
<td>Euphoria, relaxation, ↑ appetite, ↓ reaction time</td>
<td>Inhaled (minutes) Tablets (30 min +)</td>
<td>Urine up to 1 mo</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Alertness, euphoria</td>
<td>Inhaled and snorted</td>
<td>Urine up to 48 h</td>
</tr>
<tr>
<td>Cocaine (crack)</td>
<td>Insomnia, ↑ appetite</td>
<td>(Quick high) Tablets (longer effect)</td>
<td></td>
</tr>
<tr>
<td>Amphetamines (ice)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Hallucination, anxiety</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Mescaline</td>
<td>Psychosis, dilated pupils</td>
<td>Injected, sniffed, ingested</td>
<td>Immunooassay</td>
</tr>
<tr>
<td>Psilocybin (magic mushrooms)</td>
<td>Dysphoria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSD</td>
<td>&quot;Artistic high&quot; &quot;Lucy in the sky with diamonds&quot;</td>
<td>2–12 h &quot;trip&quot;</td>
<td></td>
</tr>
<tr>
<td>Phencyclidine (PCP, angel dust)</td>
<td>Microdents in many colors Can induce suicide attempts</td>
<td></td>
<td>Immunooassay for PCP</td>
</tr>
<tr>
<td>EDMA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**ACUTE AND CHRONIC EFFECTS**

Heavy alcohol use can cause acute gastritis and acute pancreatitis. Intravenous drug use can result in hepatitis B, bacterial endocarditis, osteomyelitis, septic pulmonary embolism, infection, or acquired immunodeficiency syndrome (commonly known as AIDS). Chronic marijuana or tobacco use is associated with bronchoconstriction and bronchitis. Compulsive drug or alcohol use results in an adolescent being unable to help himself or herself out of the psychosocial sequelae that attend such habituation (e.g., stealing, prostitution, drug dealing, unemployment, school failure, social isolation).

**TREATMENT**

Specific management of substance use by adolescents depends on many individual patient factors. Because of the highly addictive (physical and psychological) nature of most substances, residential drug treatment facilities are suggested, especially for younger adolescents.

**Suggested Reading**


ASSESSMENT

The major components of host defense include anatomic barriers and the innate and adaptive immune systems. Integrity of the anatomic and mucociliary barrier (i.e., skin and mucous membranes) is essential for protection against infection, and defects in this barrier function can lead to infections (Table 72-1). The innate immune system acts as the first line of defense against pathogens, responding rapidly but nonspecifically before the development of the more versatile adaptive immune system. The innate immune system includes soluble factors, including acute-phase proteins, cytokines, chemokines, and complement, as well as cellular components, including neutrophils, monocytes/macrophages, and natural killer (NK) cells. The adaptive immune system is made up of T and B lymphocytes and their effector molecules (Table 72-2).

Recognition of pathogens by the innate immune system is facilitated by receptors on macrophages, NK cells, and neutrophils that recognize conserved pathogen motifs called pathogen-associated molecular patterns (PAMPs), including lipopolysaccharide of gram-negative bacteria, lipoteichoic acid of gram-positive bacteria, mannans of yeast, and specific nucleotide sequences of bacterial and viral DNA. Recognition of PAMPs by the innate immune system leads to the production of cytokines and chemokines that initiate inflammation and recruit inflammatory cells, induce an acute phase response (e.g., C-reactive protein, mannose binding lectin, complement), and activate the adaptive immune system. Complement proteins kill pathogens by facilitating uptake by phagocytic cells or by lysis of pathogens. Polymorphonuclear neutrophils ingest pyogenic bacteria and some fungi. Macrophages are effective in killing facultative intracellular organisms such as Mycobacterium, Toxoplasma, and Legionella. In addition NK lymphocytes mediate cytotoxic activity against virus-infected cells and cancer cells.

The key features of the adaptive immune system are antigen specificity and the development of immunologic memory, produced by expansion and maturation of antigen-specific T cells and B cells. Antibodies (immunoglobulin) produced by B cells neutralize toxins released by pathogens, opsonize pathogens to facilitate uptake by phagocytic cells, activate complement causing cytolysis of the pathogen, and direct NK cells to kill infected cells through antibody-mediated cytotoxicity. T cells kill virus-infected cells and cancer cells, activate macrophage to kill intracellular pathogens, and deliver the necessary signals for B-cell antibody synthesis and memory B-cell formation. Immunodeficiency can result from defects in one or more components of innate or adaptive immunity, leading to recurrent or opportunistic infections (Table 72-1).

### Table 72-1 Anatomic and Mucociliary Defects that Result in Recurrent or Opportunistic Infections

<table>
<thead>
<tr>
<th>ANATOMIC DEFECTS IN UPPER AIRWAYS</th>
<th>PHYSIOLOGIC DEFECTS IN UPPER AND LOWER AIRWAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Aspiration syndromes (gastroesophageal reflux, ineffective cough, foreign body)</td>
<td>- Primary ciliary dyskinesia syndromes, Young syndrome</td>
</tr>
<tr>
<td>- Cleft palate, eustachian tube dysfunction</td>
<td>- Cystic fibrosis</td>
</tr>
<tr>
<td>- Adenoidal hypertrophy</td>
<td>- Bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>- Nasal polyps</td>
<td>- Bronchiectasis</td>
</tr>
<tr>
<td>- Obstruction of paranasal sinus drainage (osteomeatal complex disease), encephaloceles</td>
<td>- Allergic disease (allergic rhinitis, asthma)</td>
</tr>
<tr>
<td>- Posttraumatic or congenital sinus tracts (CSF rhinorrhea)</td>
<td>- Chronic cigarette smoke exposure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANATOMIC DEFECTS IN THE TRACHEOBRONCHIAL TREE</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Tracheoesophageal fistula, bronchobiliary fistula</td>
</tr>
<tr>
<td>- Pulmonary sequestration, bronchogenic cysts</td>
</tr>
<tr>
<td>- Vascular ring</td>
</tr>
<tr>
<td>- Tumor, foreign body, or enlarged lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER DEFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Burns</td>
</tr>
<tr>
<td>- Chronic atopic dermatitis</td>
</tr>
<tr>
<td>- Ureteral obstruction, vesicoureteral reflux</td>
</tr>
<tr>
<td>- IV drug use</td>
</tr>
<tr>
<td>- Central venous line, artificial heart value, CSF shunt, peritoneal dialysis catheter, urinary catheter</td>
</tr>
<tr>
<td>- Dermal sinus tract</td>
</tr>
</tbody>
</table>

CSF, Cerebrospinal fluid.
to recurrent, opportunistic, or life-threatening infections. Primary immunodeficiency diseases are relatively rare individually, but together they cause significant chronic disease, morbidity, and mortality (Table 72-3).

**HISTORY**

The frequency, severity, and location of the infection and the pathogens involved can help differentiate infections in a normal host from infections in an immunodeficient patient (see Table 72-3). Although otitis media and sinopulmonary infections are common in children, recurrent infections, invasive or deep seeded infections, infections that require multiple rounds of oral antibiotics or need intravenous antibiotics, or infections with opportunistic infections suggest a primary immunodeficiency. Recurrent sinopulmonary infections with encapsulated bacteria suggest a defect in antibody-mediated immunity because these pathogens evade phagocytosis. Failure to thrive, diarrhea, malabsorption, and infections with opportunistic infections (i.e., fungi, *Candida* sp, *Pneumocystis jiroveci [carinii]*) suggest T-cell immunodeficiency. Recurrent viral infections can result from T-cell or NK-cell deficiency. Deep-seated abscesses and infections with *Staphylococcus aureus*, *Serratia marcescens*, and *Aspergillus* suggest a disorder of neutrophil function, such as chronic granulomatous disease (CGD). Delayed separation of the umbilical cord, especially in the presence of omphalitis and later onset periodontal disease, in addition to poorly formed abscesses, indicates leukocyte adhesion deficiency.

Age of onset of symptoms can be helpful in defining an immune deficiency, although significant variability does occur. Neutrophil defects (e.g., congenital neutropenia, leukocyte adhesion deficiency) typically present in the first several months of life. Antibody defects (e.g., agammaglobulinemia) and T-cell defects (e.g., severe combined immunodeficiency [SCID]) typically present after 3 months of life after maternal antibody levels have waned. Presentation with symptoms of an antibody deficiency in adolescence or young adulthood suggests common variable immunodeficiency (CVID) rather than agammaglobulinemia, although milder phenotypes of primary immunodeficiency disease may not present until later

### Table 72-2: Cytokines and Chemotactic Cytokines and Their Functions

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>SOURCE</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>Macrophages</td>
<td>Co-stimulatory effect on T cells, enhances antigen presentation, acute phase response, fever</td>
</tr>
<tr>
<td>IL-2</td>
<td>T cells</td>
<td>Primary T-cell growth factor; B-cell and NK-cell growth factors; required for T regulatory cell function and survival</td>
</tr>
<tr>
<td>IL-3</td>
<td>T cells</td>
<td>Mast cell growth factor; multiclonal-stimulating factor</td>
</tr>
<tr>
<td>IL-4</td>
<td>T cells</td>
<td>T-cell growth factor; enhances IgE synthesis; enhances B-cell differentiation; mast cell growth</td>
</tr>
<tr>
<td>IL-5</td>
<td>T cells</td>
<td>Enhances eosinophil differentiation; enhances immunoglobulin synthesis; enhances IgA synthesis</td>
</tr>
<tr>
<td>IL-6</td>
<td>T cells, macrophages, fibroblasts, endothelium</td>
<td>Enhances immunoglobulin synthesis, antiviral activity, induces acute phase response, fever, hematopoietic effects</td>
</tr>
<tr>
<td>IL-7</td>
<td>Stromal cells</td>
<td>Enhances growth of pre-T cells</td>
</tr>
<tr>
<td>IL-8</td>
<td>T cells, macrophages, epithelium</td>
<td>Neutrophil-activating protein; T lymphocyte and neutrophil chemotactic factor</td>
</tr>
<tr>
<td>IL-9</td>
<td>T cells</td>
<td>Acts in synergy with IL-4 to induce IgE production, mast cell growth</td>
</tr>
<tr>
<td>IL-10</td>
<td>T cells, including regulatory T cells, macrophages</td>
<td>Cytokine synthesis inhibitory factor; suppresses macrophage function; enhances B-cell growth; inhibits IL-12 production; suppresses inflammation at mucosal surfaces</td>
</tr>
<tr>
<td>IL-12</td>
<td>Macrophages, neutrophils</td>
<td>NK cell stimulatory factor; cytotoxic lymphocyte maturation factor; enhances IFN-γ synthesis; inhibits IL-4 synthesis</td>
</tr>
<tr>
<td>IL-13</td>
<td>T cells</td>
<td>Enhances IgE synthesis; enhances B-cell growth; inhibits macrophage activation; causes airway hyperreactivity</td>
</tr>
<tr>
<td>IL-17</td>
<td>T cells</td>
<td>Induces IL-1β and IL-6 synthesis, important in fungal infections</td>
</tr>
<tr>
<td>IL-18</td>
<td>Macrophages</td>
<td>Enhances IFN-γ synthesis</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>T cells</td>
<td>Macrophage activation; inhibits IgE synthesis; antiviral activity</td>
</tr>
<tr>
<td>TGF-β</td>
<td>T cells, including regulatory T cells, many other cells</td>
<td>Inhibits T-cell and B-cell proliferation and activation, induces T regulatory cells</td>
</tr>
<tr>
<td>RANTES</td>
<td>T cells, endothelium</td>
<td>Chemokine for monocytes, T cells, eosinophils</td>
</tr>
<tr>
<td>MIP-1α</td>
<td>Mononuclear cells, endothelium</td>
<td>Chemokine for T cells; enhances differentiation of CD4+ T cells</td>
</tr>
<tr>
<td>Eotaxin 1, 2, and 3</td>
<td>Epithelium, endothelium, eosinophils, fibroblasts, macrophages</td>
<td>Chemokine for eosinophils, basophils, and Th2 cells</td>
</tr>
<tr>
<td>IP-10</td>
<td>Monocytes, macrophages, endothelium</td>
<td>Chemokine for activated T cells, monocytes, and NK cells</td>
</tr>
</tbody>
</table>

*IFN*, Interferon; *NK*, natural killer; *RANTES*, regulated on activation, normal T expressed and secreted; *Th2*, T helper 2.
in life. The presence of associated problems, such as congenital heart disease and hypocalcemia (DiGeorge syndrome), atopic dermatitis (hyper-IgE syndrome, Omenn syndrome), and easy bruising or a bleeding disorder (Wiskott-Aldrich syndrome) can be informative in guiding an immune workup. Finally a family history of a primary immune deficiency or death of a young child due to infections should prompt an immune evaluation, particularly in the setting of recurrent infections.

### PHYSICAL EXAMINATION

Recurrent infection in immunologically deficient children is associated with pathology at sites of infection resulting in substantial morbidity, such as scarring tympanic membranes leading to hearing loss or chronic lung disease due to recurrent pneumonia. Height and weight percentiles, nutritional status, and presence of subcutaneous fat should be assessed. Oral thrush, purulent nasal or otic discharge, and chronic rales may be evidence of repeated or persistent infections. Absence of lymphoid tissue (e.g., tonsils) suggests agammaglobulinemia or SCID, whereas increased size of lymphoid tissue suggests CVID, CGD, or human immunodeficiency virus (HIV) infection. Cerebellar ataxia and telangiectasia indicate ataxia-telangiectasia. Severe eczema and inflammatory bowel disease are seen in some disorders of immune regulation with polyendocrinopathy and enteropathy that is X-linked (IPEX), whereas eczema and petechiae or bruises suggest Wiskott-Aldrich syndrome.

### DIFFERENTIAL DIAGNOSIS

There are many secondary causes of immunodeficiency that should be considered, particularly if the immunologic testing is nonrevealing (Table 72-4). In patients with primary immunodeficiencies, infections develop at multiple sites (e.g., ears, sinuses, lungs, skin), whereas in individuals with anatomic
problems (e.g., sequestered pulmonary lobe, ureteral reflux), infections are confined to a single anatomic site. Asplenia is associated with recurrent and severe infections, even in the presence of protective antibody titers. Infection with HIV should be considered in any patient presenting with a history suggesting a T-cell immunodeficiency.

**DIAGNOSTIC EVALUATION**

The diagnosis of patients with primary immunodeficiency diseases depends on early recognition of signs and symptoms, followed by laboratory tests to evaluate immune function. Recognizing the patient who may have an immunodeficiency disease prompts an evaluation and referral to an immunologist (see Table 72-3).

**Laboratory Tests**

A diagnosis of primary immunodeficiency disease cannot be established without the use of laboratory tests based on the clinical history (Table 72-5). A **complete blood count with differential** should always be obtained to identify patients with neutropenia or lymphopenia (SCID) as well as the presence of eosinophils (allergic disease) and anemia (chronic disease). **Serum immunoglobulin levels** are essential to the workup of suspected primary immunodeficiency. Antibody levels vary with age, with normal adult values of IgG at full-term birth from transplacental transfer of maternal IgG, a physiologic nadir occurring between 3 and 6 months of age, and a gradual increase to adult values over several years. IgA and IgM are low at birth, and levels increase gradually over several years, with IgA taking the longest to reach normal adult values. Low albumin levels with low immunoglobulin levels suggest low synthetic rates for all proteins or increased loss of proteins, as in protein-losing enteropathy. High immunoglobulin levels suggest intact B-cell immunity and can be found in diseases with recurrent infections, such as CGD, immotile cilia syndrome, cystic fibrosis, HIV infection, and autoimmune diseases. Elevated IgE levels can be found in a number of immune deficiencies such as hyper-IgE syndrome, as well as in atopic dermatitis.

**Specific antibody titers** after childhood vaccination (tetanus, diphtheria, *Haemophilus influenzae* type b, or *Streptococcus pneumoniae* vaccines) reflect the capacity of the immune system to synthesize specific antibodies and to develop memory B cells. If titers are low, immunization with a specific vaccine and titers obtained 4 to 6 weeks later confirm response to the immunization. Poor response to bacterial polysaccharide antigens is normal before 24 months of age but is also associated with IgG subclass deficiency or specific antibody deficiency. The development of protein-conjugate polysaccharide vaccines has prevented infections with these organisms in early childhood. Antibody responses to the *S. pneumoniae* serotypes found in the 23-valent polysaccharide vaccine, but not in the conjugate vaccine, can be used to test antibody responses to polysaccharide antigens.

**Delayed-type hypersensitivity** skin tests to protein antigens such as tetanus, diphtheria, *Candida*, or mumps demonstrate the presence of antigen-specific T cells and functional antigen-presenting cells. If delayed-type hypersensitivity skin test results are negative, patients should receive a booster vaccination and be retested 4 weeks later.

**Table 72-5**  
**Tests for Suspected Immune Deficiency**

<table>
<thead>
<tr>
<th>Category</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GENERAL</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete blood count, including hemoglobin, differential white blood count and morphology, and platelet count</td>
</tr>
<tr>
<td></td>
<td>Radiographs to document infection in chest, sinus, mastoids, and long bones, if indicated by clinical history</td>
</tr>
<tr>
<td></td>
<td>Cultures, if appropriate</td>
</tr>
<tr>
<td><strong>ANTIBODY-MEDIATED IMMUNITY</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quantitative immunoglobulin levels: IgG, IgA, IgM, IgE, Isohemagglutinin titers (anti-A, anti-B, measures IgM function)</td>
</tr>
<tr>
<td></td>
<td>Specific antibody levels:</td>
</tr>
<tr>
<td></td>
<td>Protein antigens: diphtheria, tetanus</td>
</tr>
<tr>
<td></td>
<td>Protein-conjugated antigens: <em>Haemophilus influenzae</em>, <em>Streptococcus pneumoniae</em> (conjugate vaccine)</td>
</tr>
<tr>
<td></td>
<td>Polysaccharide antigens: <em>S. pneumoniae</em> (unconjugated vaccine)</td>
</tr>
<tr>
<td></td>
<td>B-cell numbers and subsets by flow cytometry</td>
</tr>
<tr>
<td><strong>CELL-MEDIATED IMMUNITY</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphocyte count and morphology</td>
</tr>
<tr>
<td></td>
<td>Delayed hypersensitivity skin tests (Candida, tetanus toxoid, mumps): measure T-cell and macrophage function</td>
</tr>
<tr>
<td></td>
<td>T-cell and NK cell numbers and subsets by flow cytometry</td>
</tr>
<tr>
<td></td>
<td>T-lymphocyte functional analyses (mitogen responses, cytokines)</td>
</tr>
<tr>
<td></td>
<td>NK cell cytotoxicity assays</td>
</tr>
<tr>
<td><strong>PHAGOCYTOSIS</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutrophil cell count and morphology</td>
</tr>
<tr>
<td></td>
<td>Nitroblue tetrazolium dye test/dihydrorhodamine 123 using flow cytometry</td>
</tr>
<tr>
<td></td>
<td>Staphylococcal killing, chemotaxis assay</td>
</tr>
<tr>
<td></td>
<td>Myeloperoxidase stain</td>
</tr>
<tr>
<td><strong>COMPLEMENT</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total hemolytic complement CH50: measures classical and common pathway activity</td>
</tr>
<tr>
<td></td>
<td>AH50: measures alternative and common pathway activity</td>
</tr>
<tr>
<td></td>
<td>Levels of individual complement components</td>
</tr>
<tr>
<td></td>
<td>Cl-inhibitor level and function</td>
</tr>
</tbody>
</table>

NK, Natural killer.

**Lymphocyte phenotyping** by flow cytometry enumerates the percentage and absolute numbers of T-cell, B-cell, and NK-cell subsets. Flow cytometry can also test for the presence of surface proteins that are necessary for normal immunity, such as major histocompatibility complex molecules or adhesion molecules, as well as intracellular analysis of signaling proteins and cytokines. **T-cell proliferation** assays to mitogens (phytohemagglutinin, concanavalin A, or pokeweed mitogen) or antigens (tetanus toxoid or *Candida*) are in vitro assays that confirm the capacity of T cells to proliferate in response to a nonspecific stimulus (mitogens) or the presence of antigen-specific memory T cells (antigens). Such response requires prior vaccination (tetanus) or exposure (*Candida*) to the antigen. **Tests for cytokine synthesis or expression of activation markers** by T cells may be performed in specialized research laboratories and can help identify defects in T-cell function when, despite present T cells, the clinical history suggests a T-cell disorder.
Complement assays include the CH$_{50}$ test, which measures the presence of proteins in the classical pathway of complement (C1, C2, C3, C4), and the AH$_{50}$ test, which tests the proteins of the alternative pathway of complement (C3, factor B, properdin). If both the CH$_{50}$ and AH$_{50}$ levels are abnormal, a defect in the common pathway is likely (C5–C9). Specialized laboratories can measure the presence or function of specific complement proteins. Tests for C1-inhibitor antigen and function are used to diagnose hereditary or acquired angioneurotic edema.

Tests for neutrophil function include the nitroblue tetrazolium (NBT) or dihydrorhodamine 123 (DHR) test for CGD, in which oxygen radicals generated by activated neutrophils oxidize NBT to an insoluble blue dye and DHR to a fluorescent molecule. Patients with CGD have no blue-staining neutrophils with NBT and little fluorescence when DHR is used. In vitro tests for evaluation of neutrophil phagocytosis, chemotaxis, bacterial killing, and for the presence of myeloperoxidase activity are available in some laboratories. Tests for the expression of adhesion molecules such as CD18 (leukocyte function–associated antigen type 1, LFA-1) can be performed by flow cytometry.

Genetic testing to confirm the diagnosis of a primary immunodeficiency disease can be performed in specialized laboratories and may be helpful for deciding on a course of treatment, determining the natural history and prognosis of the disease, genetic counseling, and prenatal diagnosis. In patients in whom DiGeorge syndrome is suspected, fluorescent in situ hybridization studies for deletions of chromosome 22 can be helpful. In patients in whom ataxia-telangiectasia is suspected, chromosomal studies for breakage in chromosomes 7 and 14 are useful.

Diagnosis Imaging
The absence of a thymus on chest x-ray suggests DiGeorge syndrome or other defects in T-cell development. Abnormalities in the cerebellum are found in patients with ataxia-telangiectasia. Otherwise the use of diagnostic imaging in the evaluation of immunodeficiency diseases is essentially limited to the diagnosis of infectious diseases.

LYMPHOCYTE DISORDERS

Disorders that affect lymphocyte development or function result in significant immunodeficiency because lymphocytes provide antigen specificity and memory responses. Hematopoietic stem cells give rise to lymphoid precursors that develop into T lymphocytes in the thymus or B lymphocytes in the bone marrow (Fig. 73-1). Isolated B-cell disorders result in antibody deficiency diseases, whereas T-cell disorders usually cause combined immunodeficiency because they are necessary for cell-mediated immunity to clear intracellular pathogens and for antibody synthesis by B cells. NK cells are an important component of the innate immune response, develop from lymphoid precursors, and can kill virus-infected cells and tumor cells. Antibodies can enhance NK cell function by antibody-mediated cellular cytotoxicity.

ETIOLOGY AND CLINICAL MANIFESTATIONS

Antibody Deficiency Diseases

Disorders of B cells result in an increased susceptibility to infections by encapsulated bacteria.

Agammaglobulinemia results from the absence or defective function of B cells with subsequent severe decrease in immunoglobulin levels and a total absence of specific antibody.

X-linked agammaglobulinemia affects males and is characterized by a profound deficiency of B cells, severe hypogammaglobulinemia, and absence of lymphoid tissue (Table 73-1; see Fig. 73-1). The defect is caused by mutations in a gene encoding the tyrosine kinase Btk on chromosome Xq22 that is involved in a signaling of the pre-B-cell receptor and the B-cell antigen receptor. Autosomal recessive agammaglobulinemia results from a variety of defects in the pre-B-cell and B-cell antigen receptor complexes and includes mutations in the µ heavy chain gene, λ5, Igα, Igβ, and BLNK. X-linked agammaglobulinemia is more common than the autosomal recessive forms.

Patients with agammaglobulinemia usually present during the first 6 to 12 months of life as maternally derived antibodies wane, although patients can present years later. These patients develop infections with Streptococcus pneumoniae, Haemophilus influenzae type b, Staphylococcus aureus, and Pseudomonas, organisms for which antibody is an important opsonin. They also have increased susceptibility to giardiasis and enteroviral infections, leading to chronic enteroviral meningoencephalitis and vaccine-associated poliomyelitis (if immunized with oral live, attenuated poliovirus vaccine).

Common variable immunodeficiency (CVID) is a heterogeneous disorder characterized by hypogammaglobulinemia developing after an initial period of normal immune function, most commonly in the second and third decades of life (see Table 73-1). Serum IgG levels are less than 500 mg/dL (usually <300 mg/dL) with IgA levels less than 10 mg/dL and/or low IgM levels. Antibody titers to protein antigens, such as tetanus and diphtheria, and to polysaccharide antigens, such as pneumococcus, are low or absent. T-cell numbers and function are highly variable, and B-cell numbers can be normal or low. Patients exhibit normal-sized or enlarged tonsils and lymph nodes and may have splenomegaly. They are susceptible to frequent respiratory tract infections due to Streptococcus pneumoniae, Haemophilus influenzae type b, and Mycoplasma. Gastrointestinal infections with Giardia, Campylobacter, Salmonella, Helicobacter, and enteroviruses are common. Autoimmune hemolytic anemia and thrombocytopenia occur frequently, and granulomatous disease affecting the gastrointestinal tract, liver, and lungs leads to significant morbidity. Cancer, especially lymphoma, is a major cause of mortality.
The gene defects leading to the majority of cases of CVID are unknown. Some patients have a defect in the gene encoding for inducible co-stimulator (ICOS) on activated T cells, transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI), CD19, CD21, CD81, or BAFF-R. It is important to exclude X-linked agammaglobulinemia, X-linked lymphoproliferative disease, or hyper-IgM syndrome as well as other causes of hypogammaglobulinemia, such as hypogammaglobulinemia associated with thymoma, secondary to protein losing enteropathy, or secondary to medications, before making the diagnosis of CVID.

Selective IgA deficiency is defined as serum IgA levels less than 10 mg/dL with normal levels of other immunoglobulins. The diagnosis cannot be confirmed until the patient is at least 4 years of age when IgA levels should reach adult levels. Selective IgA deficiency occurs in approximately 1 in 500 individuals. Most patients with selective IgA deficiency are asymptomatic. In others it is associated with recurrent sinopulmonary infections, IgG2 subclass deficiency, specific antibody deficiency, food allergy, autoimmune disease, or celiac disease. IgA deficiency occurs in families, suggesting autosomal inheritance.

IgG subclass deficiency occurs when the level of antibodies in one or more of the four IgG subclasses is selectively decreased while total IgG levels are normal. Normal individuals can express low levels of one or more subclasses, so a history of recurrent infections is important. An inability to synthesize specific antibody titers to protein or polysaccharide antigens is the best marker of IgG subclass deficiency associated with recurrent infections and requiring therapy.

Transient hypogammaglobulinemia of infancy is a temporary condition characterized by delayed immunoglobulin production. The pathogenesis of this disorder is unknown but is thought to result from a prolongation of the physiologic hypogammaglobulinemia of infancy. The immunoglobulin nadir at 6 months of age is accentuated, with immunoglobulin levels less than 200 mg/dL. Immunoglobulin levels remain diminished throughout the first year of life and usually increase to normal, age-appropriate levels, generally by 2 to 4 years of age. The incidence of sinopulmonary infection is increased in some patients. The diagnosis is supported by normal levels of both B and T cells and by normal antibody responses to protein antigens such as diphtheria and tetanus toxoids. The transient nature of this disorder cannot be confirmed, however, until immunoglobulin levels return to normal ranges.

Specific antibody deficiency syndrome is characterized by recurrent infections with normal immunoglobulin levels and
normal lymphocyte numbers and subsets, but the disorder has an inability to synthesize specific antibody to polysaccharide antigens, such as to the 23-valent pneumococcal vaccine. The pathogenesis of this disorder is unknown. Lack of specific antibody titers explains the recurrent infections and justifies therapy.

### Combined Immunodeficiency Diseases

Disorders that affect T-cell development or function usually result in combined immunodeficiency because T cells provide necessary signals for B-cell differentiation. **X-linked hyper-IgM syndrome**, the most common form of hyper-IgM syndrome, is a combined immunodeficiency with deficient T-cell function due to defects in CD40 ligand. Defects in CD40 cause **autosomal recessive hyper-IgM syndrome** and present similarly to X-linked hyper-IgM syndrome (Fig. 73-2 and Table 73-2). Hyper-IgM syndrome is characterized by a failure of immunoglobulin isotype switching from IgM and IgD to IgG, IgA, or IgE, and a lack of memory responses. Affected patients have normal or elevated serum levels of IgM with low or absent levels of IgG, IgA, and IgE. Immunoglobulin isotype switching allows a B cell to maintain antigen specificity while altering immunoglobulin function, and is directed by cytokines and interaction between CD40 ligand on CD4 T cells and CD40 on B cells (see Fig. 73-2). Signal transduction via CD40 activates several signaling molecules and transcription factors, including nuclear factor κB (NF-κB) and two enzymes, activation-induced cytokine deaminase (AID) and uracil-DNA glycosylase (UNG), which are required for class switching. Deficiency of AID or UNG presents with a failure of immunoglobulin isotype switching without any abnormality in T-cell function. These forms of hyper-IgM are antibody deficiency diseases and not combined immunodeficiencies (see Table 73-1).

All patients with hyper-IgM syndrome have increased susceptibility to sinopulmonary infections, whereas patients with defects in CD40 ligand or CD40 are susceptible to opportunistic infections, such as P. jiroveci (carinii) and Cryptosporidium parvum. Signaling via CD40 on B cells and other antigen-presenting cells leads to upregulation of co-stimulatory molecules important for promoting T-cell differentiation and for activating cell-mediated immune responses. The hyper-IgM phenotype is also found in an X-linked disorder associated with ectodermal dysplasia, resulting from defects in the gene encoding the NF-κB essential modulator (NEMO). Patients with defects in NEMO are susceptible to a wider spectrum of infectious organisms, especially meningitis and infection with atypical mycobacteria, because NF-κB signaling is important for the function of both innate and adaptive immune systems.

**Severe combined immunodeficiency (SCID)** is characterized by a profound lack of T-cell numbers or function, and B-cell dysfunction resulting from the absence of B cells from the gene defect itself, or secondary to lack of T-cell function (see Table 73-2). T cells develop from bone marrow–derived...
Figure 73-2 Schematic representation of the interaction between a CD4 T cell and a B cell. T-cell activation follows T-cell receptor (TCR) recognition of peptide antigen presented via MHC class II molecules resulting in CD40 ligand (CD40L) expression and cytokine synthesis. CD40L stimulates the B cell via CD40, resulting in expression of co-stimulatory molecules (B7) that are important in T-cell priming and cytokine synthesis that drives T-cell differentiation. CD40 and cytokine signaling in B cells activate activation-induced cytidine deaminase (AID) and uracil-DNA glycosylase (UNG) to promote immunoglobulin isotype switching and somatic hypermutation. Defects in CD40L cause X-linked hyper-IgM (X-HIM), and defects in CD40, AID, or UNG cause autosomal recessive hyper-IgM (AR-HIM). Defects in either CD40L or CD40 affect T-cell co-stimulation and priming, leading to T-cell defects, whereas defects in AID and UNG maintain normal T-cell co-stimulation and function.

Table 73-2 Combined Immunodeficiency Diseases

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>GENETICS</th>
<th>ONSET</th>
<th>MANIFESTATIONS</th>
<th>PATHOGENESIS</th>
<th>ASSOCIATED FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyper-IgM syndrome</td>
<td>X-linked, AR</td>
<td>First year</td>
<td>Sinopulmonary infections, opportunistic infections, Pneumocystis jiroveci</td>
<td>Defect in CD40 ligand (X-linked) or CD40 (AR)</td>
<td>Neutropenia, liver disease, cancer</td>
</tr>
<tr>
<td>DiGeorge anomaly</td>
<td>22q11.2 (or 10p) deletion</td>
<td>Newborn, early infancy</td>
<td>Hypocalcemic tetany, pyogenic infections, partial or complete T-cell deficiency</td>
<td>Hypoplasia of third and fourth pharyngeal pouch</td>
<td>Congenital heart disease (aortic arch anomalies), hypoparathyroidism, micrognathia, hypertelorism</td>
</tr>
<tr>
<td>Severe combined immunodeficiency (T−B+ SCID)</td>
<td>X-linked; AR</td>
<td>1–3 mo</td>
<td>Candidiasis, all types of infections, failure to thrive, chronic diarrhea</td>
<td>Mutation in IL-2Rγ chain, Jak3 kinase, ZAP-70, IL-7Ra, CD3 subunits</td>
<td>GVHD from maternal-fetal transfusions, severe GVHD from nonirradiated blood transfusion</td>
</tr>
<tr>
<td>Severe combined immunodeficiency (T−B− SCID)</td>
<td>AR</td>
<td>1–3 mo</td>
<td>Same as T− B+ SCID</td>
<td>Mutation in RAG1/2, Artemis, ADA/PNP deficiency</td>
<td>Same as T− B+ SCID ADA deficiency: chondro-osseous dysplasia PNP deficiency: neurologic disorders</td>
</tr>
<tr>
<td>Omenn syndrome</td>
<td>AR</td>
<td>1–3 mo</td>
<td>Same as T− B− SCID, exfoliative erythroderma, lymphadenopathy, hepatosplenomegaly</td>
<td>Hypomorphic mutations in SCID-causing genes (RAG1/2, Artemis)</td>
<td>Restricted T-cell receptor heterogeneity, eosinophilia, elevated IgE</td>
</tr>
<tr>
<td>Reticular dysgenesis (T− B− SCID)</td>
<td>AR</td>
<td>1–3 mo</td>
<td>Same as T− B− SCID</td>
<td>Defective maturation of common stem cells due to AK2 mutations</td>
<td>Agammaglobulinemia, lymphocytosis, agranulocytosis</td>
</tr>
<tr>
<td>Bare lymphocyte syndrome (MHC class I deficiency)</td>
<td>AR</td>
<td>First decade</td>
<td>Sinopulmonary infections</td>
<td>Mutation in TAP1 or TAP2 (transporter associated with antigen processing)</td>
<td>Decreased CD8 T cells, chronic lung inflammation</td>
</tr>
<tr>
<td>Bare lymphocyte syndrome (MHC class II deficiency)</td>
<td>AR</td>
<td>Early infancy</td>
<td>Respiratory tract infections, chronic diarrhea, viral infections in central nervous system</td>
<td>Mutations in CIITA, RFX5, RFXAP, and RFX-B (DNA binding factors)</td>
<td>Decreased CD4 T cells, autoimmune disease</td>
</tr>
</tbody>
</table>

AD, Autosomal dominant; ADA, adenosine deaminase; AR, autosomal recessive; dATP, deoxyadenosine triphosphate; dGTP, deoxyguanosine triphosphate; GVHD, graft-versus-host disease; IL, interleukin; IL-2Rγ, interleukin-2 receptor gamma chain; MHC, major histocompatibility complex; PNP, purine nucleoside phosphorylase; SCID, severe combined immunodeficiency; T− B+, T cells absent and B cells present; T− B−, T cells absent and B cells absent.
precursors in the thymus (see Fig. 73-2), where they undergo several stages of development characterized by DNA recombination of the variable region of T-cell antigen receptor genes to generate a diverse T-cell receptor repertoire. A process of positive selection occurs in the thymus to select thymocytes with antigen receptors that can interact with major histocompatibility complex (MHC) molecules to ensure their survival (see Fig. 73-2). Thymocytes differentiate into CD4 or CD8 T cells if they interact with MHC class II or class I molecules, respectively. Some of the positively selected thymocytes, however, have antigen receptors that recognize self-antigens presented by MHC molecules in the thymus. These cells are deleted in the thymus by a process of negative selection. Positive selection and negative selection in the thymus ensure that the mature T cells that leave the thymus can function with the individual’s MHC molecules and recognize a multitude of foreign antigens without mounting autoimmune responses. SCID can result from any specific genetic mutation that interferes with T-cell development in the thymus or T-cell function in the periphery.

Clinical manifestations of SCID include failure to thrive, severe bacterial infections, chronic candidiasis and other fungal infections, chronic viral infections, infection with P. jiroveci (carinii) and other opportunistic organisms, and intractable diarrhea. Patients often have skin disease similar to eczema, possibly related to graft-versus-host disease (GVHD) from engraftment of maternal lymphocytes, which usually is not fatal. Patients with SCID are extremely susceptible to fatal GVHD from lymphocytes in blood transfusions and can be infected by cytomegalovirus-positive blood products. Patients with T-cell disorders always should receive irradiated blood products.

X-linked SCID, the most common form, is caused by mutations in the gene on chromosome Xq13.1 coding for the common gamma chain of the interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21 receptors. Affected patients have no T cells or NK cells in the peripheral blood but have normal numbers of B cells. Immunoglobulin levels are low or undetectable because there are no CD4 T cells to stimulate B cells. The defect in T-cell development results from a failure of signaling via the IL-7 receptor, and IL-15 is required for NK-cell development. There are many causes of autosomal recessive SCID. Defects in Janus kinase 3 (Jak3), which binds to the common gamma chain, result in a similar phenotype as X-linked SCID. Defects in the IL-7 receptor, ZAP-70, and subunits of the CD3 molecule result in a deficiency of T cells with normal B- and NK-cell numbers. In addition there is a variety of defects that affect DNA recombination in T and B cells, including two genes called recombinase activating gene (RAG) 1 and 2 as well as other genes important in DNA excision and repair such as Artemis. Defects in any of the genes that abolish DNA recombination or DNA repair result in autosomal recessive SCID with no T cells or B cells present. Mutations in RAG1, RAG2, or Artemis that preserve limited function result in Omenn syndrome, a variant form of SCID that is characterized by exfoliative erythroderma, lymphadenopathy, hepatosplenomegaly, marked eosinophilia, elevated serum IgE, and impaired T-cell function. Patients with Omenn syndrome have T cells in the periphery, but these T cells have a limited repertoire.

Deficiencies in adenosine deaminase (ADA) and purine nucleoside phosphorylase, two enzymes involved in the purine salvage pathway, also result in SCID. Accumulation of nucleoside substrates or their metabolic products in the plasma and urine is toxic to lymphocytes, including T, B, and NK cells. Most patients exhibit severe infection early in life, although the diagnosis in patients with partial enzyme function may not be established until after 5 years of age or, occasionally, in adulthood. Patients with late-onset diagnosis are generally lymphopenic; they may have B cells and normal total immunoglobulin levels but little functional antibody (Nezelof syndrome). All patients with ADA or purine nucleoside phosphorylase deficiency SCID have lymphopenia and loss of immune function over time.

Bare lymphocyte syndrome results from defects in transcription factors that regulate expression of class II molecules or genes that affect transport of antigen peptides, which leads to the absence of either MHC class I or MHC class II molecules. Lymphoid tissue and B cells may be present in normal amounts, but CD4 T cells are decreased or absent in class II deficiency, whereas CD8 cells are decreased or absent in class I deficiency. Some patients may have normal numbers of CD4 or CD8 T cells, but none of the T cells are functional because peptide antigens cannot be presented to T cells.

DiGeorge syndrome, also known as velocardiofacial syndrome or CATCH 22 syndrome (cardiac anomalies, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia), is the result of dysmorphogenesis of the third and fourth pharyngeal pouches, resulting in hypoplasia of the thymus required for T-cell maturation. Most, but not all, patients with DiGeorge syndrome have a defect on chromosome 22q11.2. DiGeorge syndrome is classically characterized by hypocalcemic tetany, conotruncal and aortic arch anomalies, and increased infections. The diagnosis is established by fluorescent in situ hybridization or a polymerase chain reaction with a DNA probe to detect deletions in chromosome 22q11.2. Most patients have partial immune defects with low T-cell numbers and function that generally improve with age. Severe T-cell deficiency is rare, but it results in SCID due to a complete lack of T cells. Most important, DiGeorge syndrome and bare lymphocyte syndrome do not respond well to bone marrow transplantation as do other forms of SCID because the defects are in the thymus, although transfer of mature T cells during transplant may confer some immune function.

Wiskott-Aldrich syndrome is an X-linked disorder characterized by thrombocytopenia, eczema, defects in cell-mediated and humoral immunity, and a predisposition to lymphoproliferative disease (Table 73-3). It is caused by mutations of the gene on chromosome Xp11.22 coding for the Wiskott-Aldrich syndrome protein (WASP), expressed in lymphocytes, platelets, and monocytes. Deficiency of this protein results in elevated levels of IgE and IgA, decreased IgM, poor responses to polysaccharide antigens, waning T-cell function, and profound thrombocytopenia. Opportunistic infections and autoimmune cytophenias become problematic in older children. Isolated X-linked thrombocytopenia also results from mutations of the identical gene. One third of patients with Wiskott-Aldrich syndrome die as a result of hemorrhage, and two thirds die as a result of recurrent infection caused by bacteria, cytomegalovirus, P. jiroveci (carinii), or herpes simplex virus. Stem cell transplantation has corrected the immunologic and hematologic problems in some patients.

Ataxia-telangiectasia is a syndrome caused by the ATM (ataxia-telangiectasia, mutated) gene on chromosome 11q22.3 (see Table 73-3). Patients have cutaneous and conjunctival
Table 73-3  Other Immunodeficiency Diseases

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>GENETICS</th>
<th>ONSET</th>
<th>MANIFESTATIONS</th>
<th>PATHOGENESIS</th>
<th>ASSOCIATED FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>X-linked,</td>
<td>Early</td>
<td>Thrombocytopenia, atopic dermatitis,</td>
<td>53-kD protein (WASP) defect</td>
<td>Polysaccharide antibody deficiency, small</td>
</tr>
<tr>
<td></td>
<td>(Xp11.22)</td>
<td>infancy</td>
<td>recurrent infections</td>
<td></td>
<td>platelets, decreased cell-mediated immunity,</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>AR (11q22.3)</td>
<td>2–5 yr</td>
<td>Recurrent otitis media, pneumonia,</td>
<td>ATM gene mutation</td>
<td>Neurologic and endocrine dysfunction,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>meningitis with encapsulated</td>
<td>Disorder of cell cycle</td>
<td>malignancy, telangiectasia; sensitivity to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>organisms</td>
<td>checkpoint and of DNA double-strand break</td>
<td>radiation</td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
<td>AR (8q21)</td>
<td>Infancy</td>
<td>Sinopulmonary infections, bronchiectasis,</td>
<td>Defect in chromosomal repair mechanisms;</td>
<td>Sensitivity to ionizing radiation; microcephaly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>urinary tract infections</td>
<td>hypomorphic mutation in NBS1 (Nibrin)</td>
<td>with mild neurologic impairment; malignancy</td>
</tr>
<tr>
<td>Cartilage-hair</td>
<td>AR (9p13–21)</td>
<td>Birth</td>
<td>Variable susceptibility to infections</td>
<td>Mutation in RMRP</td>
<td>Metaphyseal dysplasia, short extremities</td>
</tr>
<tr>
<td>hypoplasia (short-limbed dwarf)</td>
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<td></td>
<td></td>
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<tr>
<td>Chronic mucocutaneous</td>
<td>AR</td>
<td>3–5 yr</td>
<td>Candidal infections of mucous</td>
<td>Mutations in AIRE gene</td>
<td>Autoimmune endocrinopathies</td>
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<tr>
<td>candidiasis (APECED)</td>
<td></td>
<td></td>
<td>membranes, skin, and nails</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-linked-lymphoproliferative</td>
<td>X-linked</td>
<td>Variable</td>
<td>Variable decrease in T, B, and NK cell function,</td>
<td>Mutation in SH2D1A (SAP: SLAM-associated protein) or XIAP</td>
<td>Life-threatening Epstein-Barr virus infection,</td>
</tr>
<tr>
<td>syndromes</td>
<td></td>
<td></td>
<td>hypogammaglobulinemia</td>
<td></td>
<td>lymphoma or Hodgkin disease, aplastic anemia,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>lymphohistiocytic disorder</td>
</tr>
<tr>
<td>Hyper-IgE syndrome</td>
<td>AD, AR</td>
<td>Variable</td>
<td>Skin and pulmonary abscesses, fungal</td>
<td>Mutation in STAT3 (AD), TYK2 (AR), and DOCK8 (AR)</td>
<td>Coarse facial features, failure to shed primary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>infections, eczema, elevated IgE</td>
<td></td>
<td>teeth, frequent fractures (STAT3), viral and other</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>infections (TYK2 and DOCK8)</td>
</tr>
</tbody>
</table>

AD, Autosomal dominant; AR, autosomal recessive; NK, natural killer.

Telangiectasias and progressive cerebellar ataxia with degeneration of Purkinje cells. IgA deficiency, IgG2 subclass deficiency of variable severity, low IgE levels, and variably depressed T-cell function may be seen. The normal function of the ATM gene is not clear but appears to be involved in detecting DNA damage, blocking cell growth division until the damage is repaired, or both. Ataxia-telangiectasia cells are exquisitely sensitive to irradiation. Leukemias, lymphomas, and diabetes also may be present. Sexual maturation is delayed. There is no uniformly effective therapy, but antimicrobial therapy and intravenous immunoglobulin (IVIG) replacement therapy may be helpful.

Chronic mucocutaneous candidiasis (autoimmune-polyendocrinopathy-candidiasis-ectodermal dystrophy [APECED]) is characterized by chronic or recurrent candidal infections of the mucous membranes, skin, and nails (see Table 73-3). There is normal antibody production but significantly decreased or absent lymphocyte proliferation and delayed skin reactivity to Candida. Patients usually do not respond to topical antifungal therapy and must be treated with oral antifungal agents. In most patients, an autoimmune endocrine disorder, such as hypoparathyroidism and Addison disease, develops by early adulthood. Other autoimmune disorders have been reported. The insidious onset requires the need for frequent evaluation for autoimmune endocrine disorders. This disease results from a defect in the gene for the transcription factor autoimmune regulator (AIRE), which is necessary for expression of peripheral tissue antigens in the thymus, resulting in a negative selection in the thymus and in tolerance to these tissues in normal individuals.

Patients with X-linked lymphoproliferative disease (see Table 73-3) have a defect in immune responsiveness to Epstein-Barr virus (EBV). Boys with this disease are normal until infected with EBV, which is acutely fatal in 80% of patients. The disease is caused by a mutation in the gene called SH2D1A at chromosome Xq25, which codes for an adapter protein involved in signal transduction of lymphocytes. With EBV infection, the mutation results in an extensive expansion of CD8 T cells, hepatic necrosis, and death. Boys who survive initial EBV infection have significant hypogammaglobulinemia and are at high risk for developing aplastic anemia and lymphoma. A similar disorder is seen in boys with mutations in XIAP, which results in X-linked lymphoproliferative disorder type 2.
Hyper-IgE syndrome is characterized by markedly elevated serum IgE levels, a rash that resembles atopic dermatitis, eosinophilia, and staphylococcal abscesses of the skin, lungs, joints, and viscera (see Table 73-3). Infections with H. influenzae type b, Candida, and Aspergillus also may occur. These patients have coarse facial features, develop osteopenia, and may have giant pneumatoceles in the lungs after staphylococcal pneumonias. Although serum IgG, IgA, and IgM levels are normal, humoral immune responses to specific antigens are reduced, as is cell-mediated immunity. Long-term treatment with antistaphylococcal medications is indicated, and immunoglobulin replacement therapy may be helpful. Most patients have an autosomal dominant form of inheritance, whereas some patients appear to have an autosomal recessive inheritance. Defects in the TYK2 and DOCK8 genes have been found in a patient with an autosomal recessive hyper-IgE syndrome, and defects in the STAT3 (signal transducer and activator of transcription 3) gene were identified in autosomal dominant hyper-IgE syndrome.

**Table 73-4 General Management of Patients with Immunodeficiency**

Avoid transfusions with blood products unless they are irradiated and cytomegalovirus-negative.

Avoid live virus vaccines, especially in patients with severe T-cell deficiencies or agammaglobulinemia, and in household members.

Use prophylaxis to *Pneumocystis jiroveci* (carinii) in T-cell immunodeficiency, and in X-linked hyper-IgM, consider antifungal prophylaxis in T-cell immunodeficiency.

Follow pulmonary function in patients with recurrent pneumonia.

Use chest physiotherapy and postural drainage in patients with recurrent pneumonia.

Consider using prophylactic antibiotics because minor infections can quickly disseminate.

Examine diarrheal stools for *Giardia lamblia* and *Clostridium difficile.*

Avoid unnecessary exposure to individuals with infection.

Boil water for T-cell defects and hyper-IgM syndrome (Cryptosporidium risk).

Use immunoglobulin for severe antibody deficiency states (400–600 mg/kg q3–4 wk IV).

**TREATMENT**

The approach to therapy of lymphocyte disorders depends on the diagnosis, clinical findings, and laboratory findings (Table 73-4). When immunodeficiency is suspected and while the evaluation is in process, all blood products need to be irradiated and negative for cytomegalovirus. Lymphocytes present in blood products can cause fatal GVHD in patients with SCID. Cytomegalovirus infection can be fatal in an immunodeficiency patient undergoing stem cell transplantation. Live virus vaccines should be withheld from patients and household members until a diagnosis is established.

Infections should be treated with appropriate antibiotics; prophylactic antibiotics can be used to prevent recurrent infections, provide a better quality of life, and decrease possible consequences. Antibiotic prophylaxis can be provided with once-daily administration of trimethoprim-sulfamethoxazole or amoxicillin at one half of the total daily therapeutic dose. Patients with severe T-cell deficiencies should receive prophylaxis against *Pneumocystis* and fungi until treated with stem cell transplantation. Patients with milder forms of antibody deficiency diseases may benefit from vaccination with protein-conjugate vaccines to *H. influenzae* type b and *S. pneumoniae,* assaying post vaccination titers at least 1 month later. These vaccines are administered routinely to young children; older children and adults with antibody deficiency syndrome should also receive them to generate protective antibody levels.

**Immunoglobulin replacement therapy,** intravenously or subcutaneously, is a lifesaving therapy for patients with severe antibody deficiency diseases and SCIDs. It provides passive immunity against common microorganisms and reduces the frequency and severity of infection in most patients. Immunoglobulin replacement therapy is usually administered at a total monthly dose of 400 to 600 mg/kg of body weight administered intravenously every 3 to 4 weeks, or subcutaneously by infusion pump every 1 to 2 weeks. IVIG therapy should be monitored by regularly measuring trough immunoglobulin levels and, more important, the patient’s clinical course. Patients who continue to have recurrent infections, especially in the last week before the administration of IVIG, may require higher doses or more frequent administration. A combination of prophylactic antibiotics and immunoglobulin replacement therapy may be indicated in patients who continue to have recurrent infections. **Complications of IVIG** therapy include transfusion reactions with chills, fever, and myalgias. They usually can be prevented in subsequent infusions by pretreatment with an antihistamine, an antipyretic, and by a slower rate of infusion. Headache from aseptic meningitis can develop after IVIG therapy, usually in the first 24 hours. It most often responds to treatment with ibuprofen. Allergic reactions to IVIG can occur in patients with absent IgA. Allergic reactions are rare and should not occur in patients who have detectable serum IgA levels or patients who cannot synthesize any antibodies. Subcutaneous administration of immunoglobulin has fewer adverse effects but may be complicated by local reactions at the site(s) of infusion. The risk of transmission of infectious agents, despite preparation from large numbers of selected donors, is extremely low.

Therapy for severe T-cell disorders is stem cell transplantation, preferably from a human leukocyte antigen–matched sibling (see Chapter 76). Immunoglobulin replacement provides passive antibody-mediated immunity. Some patients continue to have poor B-cell function after stem cell transplantation and require lifelong immunoglobulin replacement therapy. GVHD, in which the transplanted cells initiate an immune response against the host tissues, is the main complication of stem cell transplantation. Patients with the ADA deficiency form of SCID who lack matched sibling donors can receive repeated intramuscular replacement doses of ADA, stabilized by coupling to polyethylene glycol. Gene therapy has been performed in several patients with common gamma chain deficiency and ADA deficiency by transfer of a normal gene into bone marrow stem cells, which are infused into the patient. Gene therapy for common gamma chain deficiency was successful in most of the treated patients; however, it was complicated by the development of leukemia in some patients.
PREVENTION AND NEWBORN SCREENING

Population-based screening programs for SCID is underway because early identification of SCID prior to infectious complications improves outcomes. Polymerase chain reaction amplification of T-cell receptor excision circles (TRECs) formed during T-cell receptor recombination can be performed on newborn screening blood spots to detect severe T-cell lymphopenia. Newborn screening for TRECs has been shown to detect SCID at birth, and this test has been recommended for universal screening.

Chapter 74

NEUTROPHIL DISORDERS

Neutrophils play important roles in immunity and wound healing; their primary function is ingesting and killing pathogens. Neutrophil disorders can result from deficient cell numbers or defective function (Table 74-1). Patients with neutrophil disorders are susceptible to a variety of bacterial infections and certain fungi. Suggestive signs include mucous membrane infections (gingivitis), abscesses in the skin and viscera, lymphadenitis, poor wound healing, delayed umbilical cord separation, or absence of pus. Neutrophils develop in the bone marrow from hematopoietic stem cells by the action of several colony-stimulating factors, including stem cell factor, granulocyte-monocyte colony-stimulating factor, granulocyte colony-stimulating factor (G-CSF), and interleukin-3. On leaving the bone marrow, mature neutrophils are found in the circulation or reside in the marginating pool. Adhesion molecules are necessary for neutrophils to roll and adhere to vascular endothelium and extravasate from the blood into sites of infection, where they phagocyte and kill pathogens, especially those coated by complement or antibodies. Chemotactic factors, including the complement fragment C5a, interleukin-8, and bacterial formulated peptides, mobilize neutrophils to enter tissues and sites of infections. Neutrophils kill ingested pathogens using granular enzymes or by activation of oxygen radicals.

ETIOLOGY AND CLINICAL MANIFESTATIONS

Disorders of Neutrophil Numbers

The normal neutrophil count varies with age. Neutropenia is defined as an absolute neutrophil count (ANC) less than 1500/mm³ for white children 1 year of age or older. African American children normally have lower total white blood cell and neutrophil counts. The effect of neutropenia depends on its severity. The susceptibility to infection is minimally increased until the ANC is less than 1000/mm³. Most patients do well with an ANC greater than 500/mm³. At these levels, localized infections are more common than generalized bacte remia. Serious bacterial infections are more common with an ANC less than 200/mm³. The major types of infections associated with neutropenia are cellulitis, pharyngitis, gingivitis, lymphadenitis, abscesses (cutaneous or perianal), enteritis (typhilitis), and pneumonia. The sites of the infection usually are colonized heavily with normal bacterial flora that becomes invasive in the presence of neutropenia. Neutropenia may be congenital or acquired (Table 74-2) and may be associated with specific diseases, especially infections (Table 74-3), or result from drug reactions (Table 74-4).

There are several forms of congenital neutropenia. Severe congenital neutropenia (Kostmann syndrome) is an autosomal recessive disorder in which myeloid cells fail to mature beyond the early stages of the promyelocyte due to mutations in the HAX-1 gene. The peripheral blood may show an impressive monocytosis. Although endogenous G-CSF levels are increased, exogenous G-CSF produces a rise in the neutrophil count, improving the care of these children. Acute myeloid leukemia has developed in a few patients who have survived into adolescence. Stem cell transplantation may be curative. Defects in G6PC3 and GFI1 have also been shown to cause severe congenital neutropenia. Cyclic neutropenia is a stem cell disorder in which all marrow elements cycle. It may be transmitted as an autosomal dominant, recessive, or sporadic disorder. Because of the short half-life of neutrophils in the blood (6 to 7 hours) compared to platelets (10 days) and red blood cells (120 days), neutropenia is the only clinically significant abnormality. The usual cycle is 21 days, with neutropenia lasting 4 to 6 days, accompanied by monocytosis and often by eosinophilia. Severe, debilitating bone pain is common when the neutrophil count is low. G-CSF results in increasing neutrophil numbers and a shorter duration of neutropenia. Defects in ELA2, the gene encoding for neutrophil elastase, has been found in patients with cyclic neutropenia. Further analysis has demonstrated ELA2 mutations in some cases of severe congenital neutropenia.

Severe congenital neutropenia that may be either persistent or cyclic also is a component of Shwachman-Diamond syndrome, an autosomal recessive syndrome of pancreatic insufficiency accompanying bone marrow dysfunction. This is a panmyeloid disorder in which neutropenia is the most prominent manifestation. Metaphyseal dysostosis and dwarfism may occur. Patients usually respond to G-CSF. Other congenital neutropenia caused by deficient neutrophil production vary in severity and are poorly characterized. A gain of function mutation in the Wiskott-Aldrich syndrome protein has also been associated with an X-linked form of severe congenital neutropenia. Benign congenital neutropenia is a functional diagnosis for patients with significant neutropenia in whom major infectious complications do not develop. Many patients whose ANC ranges from 100 to 500/mm³ have an increased frequency of infections, particularly respiratory infections, but the major problem is the slow resolution of infections that develop. These disorders may be sporadic or familial and, in some instances, are transmitted as an autosomal dominant disorder. Severe congenital neutropenia may be associated with severe combined immunodeficiency in reticular dysgenesis, a
Disorders of Neutrophil Migration

Neutrophils normally adhere to endothelium and migrate to areas of inflammation by the interaction of membrane proteins, called integrins and selectins, with endothelial cell adhesion molecules. A hallmark of defects in neutrophil migration is the absence of pus at sites of infection. In leukocyte adhesion deficiency type I (LAD-I), infants lacking the β2 integrin CD18 exhibit the condition early in infancy with failure of separation of the umbilical cord (often 2 months after birth) with attendant omphalitis and sepsis (see Table 74-1). The neutrophil count usually is greater than 20,000/mm³ because of failure of the neutrophils to adhere normally to vascular endothelium and to migrate out of blood to the tissues (Fig. 74-1). Cutaneous, respiratory, and mucosal infections occur. Children with this condition often have severe gingivitis. Septicemia usually leads to death in early childhood. This disorder is transmitted as an autosomal recessive trait. Stem cell transplantation can be lifesaving.

LAD-II results from impairment of neutrophil rolling along the vascular wall, which is the first step in neutrophil migration into tissues and sites of infection. Rolling is mediated by sialylated and fucosylated tetrasaccharides related to the sialylated Lewis X (S-LeX) blood group found on the surface of neutrophils, monocytes, and activated lymphocytes binding to selectin molecules on vascular endothelium (see Fig. 74-1). LAD-II results from a general defect in fucose metabolism leading to the absence of S-LeX blood group on the surface of neutrophils and other leukocytes. LAD-III is a rare disorder caused by defects in the KINDLIN-3 protein resulting in defective neutrophil adhesion as well as platelet defects. Defective migration of neutrophils has also been described in Hyper-IgE syndrome and with mutations in the RAC2 gene (see Chapter 73 and Table 74-1).

Disorders of Neutrophil Function

<table>
<thead>
<tr>
<th>NAME</th>
<th>DEFECT</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic granulomatous disease</td>
<td>Bactericidal</td>
<td>X-linked recessive (66%), autosomal recessive (33%); eczema, osteomyelitis, granulomas, abscesses caused by <em>Staphylococcus aureus</em>, <em>Burkholderia cepacia</em>, <em>Aspergillus fumigatus</em></td>
</tr>
<tr>
<td>Chédiak-Higashi syndrome (1q421-44)</td>
<td>Bactericidal plus chemotaxis; poor natural killer function</td>
<td>Autosomal recessive; oculocutaneous albinism, neuropathy, giant neutrophilic cytoplasmic inclusions; malignancy, neutropenia</td>
</tr>
<tr>
<td>Hyperimmunoglobulin E (Job syndrome)</td>
<td>Chemotaxis, opsonization</td>
<td>Autosomal dominant (STAT3 mutation), autosomal recessive (TYK2, DOCK8 mutation), eczema, staphylococcal abscesses, granulocyte and monocyte chemotaxis affected</td>
</tr>
<tr>
<td>Myeloperoxidase deficiency</td>
<td>Bactericidal, fungicidal</td>
<td>Reduced chemiluminescence; autosomal recessive (1:4000); persistent candidiasis in diabetic patients</td>
</tr>
<tr>
<td>Glucose-6-phosphate dehydrogenase deficiency</td>
<td>Bactericidal</td>
<td>Phenotypically similar to chronic granulomatous disease</td>
</tr>
<tr>
<td>Burns, malnutrition</td>
<td>Bactericidal plus chemotaxis</td>
<td>Reversible defects</td>
</tr>
<tr>
<td>Lazy leukocyte syndrome</td>
<td>Chemotaxis</td>
<td>Normal bone marrow cells but poor migration; granulocytopenia</td>
</tr>
<tr>
<td>Leukocyte adhesion deficiency</td>
<td>Adherence, chemotaxis, phagocytosis; reduced lymphocyte cytotoxicity</td>
<td>Delayed separation or infection of umbilical cord; lethal bacterial infections without pus; autosomal recessive; neutrophilia; deficiency of LFA-1, Mac-1, CR3</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td>Chemotaxis, neutropenia</td>
<td>Pancreatic insufficiency, metaphyseal chondrodysplasia; autosomal recessive</td>
</tr>
</tbody>
</table>

Disorder of hematopoietic stem cells affecting all bone marrow lineages due to mutations in the AK2 gene.

Isoimmune neutropenia occurs in neonates as the result of transplacental transfer of maternal antibodies to fetal neutrophil antigens. The mother is sensitized to specific neutrophil antigens on fetal leukocytes that are inherited from the father and are not present on maternal cells. Isoimmune neonatal neutropenia, similar to isoimmune anemia and thrombocytopenia, is a transient process (see Chapters 62 and 151). Cutaneous infections are common, and sepsis is rare. Early treatment of infection while the infant is neutropenic is the major goal of therapy. Intravenous immune globulin may decrease the duration of neutropenia.

Autoimmune neutropenia usually develops in children 5 to 24 months of age and often persists for prolonged periods. Neutrophil autoantibodies may be IgG, IgM, IgA, or a combination of these. Usually the condition resolves in 6 months to 4 years. Although intravenous immune globulin and corticosteroids have been used, most patients respond to G-CSF. Autoimmune neutropenia rarely may be the early manifestation of systemic lupus erythematosus, rheumatoid arthritis, or autoimmune lymphoproliferative disease.

CR3, Complement receptor 3; LFA-1, leukocyte function-associated antigen type 1; Mac-1, macrophage 1 antigen.
from defective intracellular killing of bacteria and intracellular pathogens by neutrophils and macrophages because of an inability to activate the “respiratory burst,” the catalytic conversion of molecular oxygen to superoxide (O$_2^–$). Reduced nicotinamide adenine dinucleotide phosphate oxidase, the enzyme that catalyzes the respiratory burst, consists of four subunits; gp91phox, p22 phox, p47 phox, and p67 phox. Defects in any of these enzymes lead to an inability to kill catalase-positive pathogens such as $S$. aureus and enteric gram-negative bacteria (Burkholderia) and fungi (Aspergillus fumigatus, Candida albicans). The gp91phox gene is located on chromosome Xp21.1 and is responsible for the most common form of the disease. The other gene defects are inherited in an autosomal recessive manner. The chromosome locations for these genes are 16q24 for p22phox, 7q11.23 for p47phox, and 1q25 for p67phox. Glucose-6-phosphate dehydrogenase also is involved in the production of superoxide, and severe forms of glucose-6-phosphate dehydrogenase deficiency also result in CGD. Patients characteristically have lymphadenopathy, hypergammaglobulinemia, hepatosplenomegaly, dermatitis, failure to thrive, anemia, chronic diarrhea, and abscesses. Infections occur in the lungs, the middle ear, gastrointestinal tract, skin, urinary tract, lymph nodes, liver, and bones.

### Table 74-2

<table>
<thead>
<tr>
<th>Mechanisms of Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABNORMAL BONE MARROW</strong></td>
</tr>
<tr>
<td>Marrow Injury</td>
</tr>
<tr>
<td>Drugs: idiosyncratic, cytotoxic (myelosuppressive)</td>
</tr>
<tr>
<td>Radiation</td>
</tr>
<tr>
<td>Chemicals: DDT, benzene</td>
</tr>
<tr>
<td>Immune-mediated: T and B cell and immunoglobulin</td>
</tr>
<tr>
<td>Infections (viruses, rickettsia)</td>
</tr>
<tr>
<td>Infiltrative processes: tumor, storage disease</td>
</tr>
<tr>
<td>Myelodysplasia</td>
</tr>
<tr>
<td>Aplastic anemia</td>
</tr>
<tr>
<td><strong>Maturation Defects</strong></td>
</tr>
<tr>
<td>Folic acid deficiency</td>
</tr>
<tr>
<td>Vitamin B$_12$</td>
</tr>
<tr>
<td>Copper</td>
</tr>
<tr>
<td><strong>Congenital Disorders</strong></td>
</tr>
<tr>
<td>Kostmann syndrome (HAX-1, G6PC3, ELA-2, G-CSF, GFI-1)</td>
</tr>
<tr>
<td>Cyclic neutropenia (ELA-2)</td>
</tr>
<tr>
<td>Cartilage hair hypoplasia</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
</tr>
<tr>
<td>Diamond-Blackfan syndrome</td>
</tr>
<tr>
<td>Griscelli syndrome</td>
</tr>
<tr>
<td>Chédiak-Higashi syndrome</td>
</tr>
<tr>
<td>WHIM syndrome (warts, hypogammaglobulinemia, infections, myelokathexis)</td>
</tr>
<tr>
<td>Glycogen storage disease type Ib</td>
</tr>
<tr>
<td>Methylmalonicacidemia</td>
</tr>
</tbody>
</table>

| **PERIPHERAL CIRCULATION** |
| Pseudoneutropenia: Shift to Bone Marrow |
| Hereditary |
| Severe infection |
| Intravascular |
| Destruction: neonatal isoimmune, autoimmune, hypersplenism |
| Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome) |
| Leukoagglutination: lung, after cardiac bypass surgery |

### Table 74-3

<table>
<thead>
<tr>
<th>Infection-Associated Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BACTERIAL</strong></td>
</tr>
<tr>
<td>Typhoid-paratyphoid</td>
</tr>
<tr>
<td>Brucellosis</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
</tr>
<tr>
<td>Meningococcemia</td>
</tr>
<tr>
<td>Overwhelming sepsis</td>
</tr>
<tr>
<td>Congenital syphilis</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td><strong>VIRAL</strong></td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Hepatitis B</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Rubella</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Influenza</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td><strong>RICKETTSIAL</strong></td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
</tr>
<tr>
<td>Typhus</td>
</tr>
<tr>
<td>Ehrlichiosis</td>
</tr>
<tr>
<td>Ricketsialpox</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus.

### Table 74-4

<table>
<thead>
<tr>
<th>Drug-Associated Neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYTOTOXIC</strong></td>
</tr>
<tr>
<td>Myelosuppressive, chemotherapeutic agents</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
</tr>
<tr>
<td><strong>IDIOSYNCRATIC</strong></td>
</tr>
<tr>
<td>Indomethacin</td>
</tr>
<tr>
<td>Para-aminophenol derivatives</td>
</tr>
<tr>
<td>Pyrazolone derivatives (aminopyrine, dipyrone, oxyphenbutazone)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Antithyroid drugs (propylthiouracil, methimazole, carbimazole)</td>
</tr>
<tr>
<td>Phenothiazines (chlorpromazine, phenothiazines)</td>
</tr>
<tr>
<td>Penicillins and semisynthetic penicillins</td>
</tr>
</tbody>
</table>

Granulomas are prominent and may obstruct the pylorus or ureters.

Chédiak-Higashi syndrome, an abnormality of secondary granules, is an autosomal recessive disorder caused by a mutation in a cytoplasmic protein (CHS1) thought to be involved in organelar protein trafficking, resulting in a fusion of the primary and secondary granules in neutrophils. Giant granules are present in many cells, including lymphocytes, platelets, and melanocytes. Patients usually have partial oculocutaneous albinism. The defect in Chédiak-Higashi syndrome results in defective neutrophil and natural killer cell function, leading to recurrent and sometimes fatal infections with streptococci and staphylococci. Most patients progress to an accelerated phase associated with Epstein-Barr virus infection and characterized by a lymphoproliferative syndrome with generalized lymphohistiocytic infiltrates, fever, jaundice, hepatomegaly, lymphadenopathy, and pancytopenia. The condition resembles hemophagocytic lymphohistiocytosis.

**LABORATORY DIAGNOSIS**

The evaluation of a neutropenic child depends on clinical signs of infection, family and medication history, age of the patient, cyclic or persistent nature of the condition, signs of bone marrow infiltration (malignancy or storage disease), and evidence of involvement of other cell lines. Neutropenia is confirmed by a complete blood count and differential. A bone marrow aspirate and biopsy may be necessary to determine whether the neutropenia is due to a failure of production in the bone marrow, infiltration of the bone marrow, or loss of neutrophils in the periphery. Antineutrophil antibodies help diagnose autoimmune neutropenia.

Neutrophil chemotactic defects can be excluded by the presence of neutrophils at the site of infection. The Rebuff skin window is a 4-hour in vivo test for neutrophil chemotaxis that is not performed routinely by most laboratories. In vitro studies of neutrophil migration are available in specialized laboratories. Flow cytometry for the presence of adhesion molecules, such as CD18 or CD15, can help diagnose leukocyte adhesion defects. Point mutations that affect the function of the adhesion molecule but do not alter antibody binding are missed using flow cytometry. CGD can be diagnosed by the flow cytometry-based test using dihydrorhodamine 123 or the nitroblue tetrazolium test (see Chapter 72). Light microscopy of neutrophils for the presence of giant granules can help diagnose Chédiak-Higashi syndrome.

**TREATMENT**

Therapy for neutropenia depends on the underlying cause. Patients with severe bacterial infections require broad-spectrum antibiotics; the resolution of neutropenia is the most important prognostic factor. Most patients with severe congenital neutropenia or autoimmune neutropenia respond to therapy with G-CSF. Granulocyte transfusion should be reserved for life-threatening infection. Chronic mild neutropenia not associated with immunosuppression can be managed expectantly with prompt antimicrobial treatment of soft tissue infections, which usually are caused by *S. aureus* or group A streptococcus.

Frequent courses of antibiotics, including trimethoprim-sulfamethoxazole prophylaxis, and surgical débridement of infections are required in CGD. Because *A. fumigatus* can cause serious infection in patients with CGD, moldy hay, decomposing compost, and other nests of fungi must be avoided, and prophylactic antifungals can be helpful. The frequency of infection in CGD is lessened by treatment with recombinant interferon-γ administered subcutaneously three times a week. Stem cell transplantation (see Chapter 76) may be lifesaving in CGD, LAD-1, and Chédiak-Higashi syndrome.

**PROGNOSIS AND PREVENTION**

The prognosis depends on the particular defect. Milder and transient defects in neutrophil numbers have a better prognosis. Prolonged absence of neutrophils or their function has a poor prognosis, especially with the risk of bacterial and fungal sepsis. Treatment with prophylactic antibiotics and interferon-γ has improved the prognosis of patients with CGD. Stem cell transplantation is the only currently available mode of therapy that can reverse the poor prognosis of severe neutrophil defects. As in other genetic defects, prenatal diagnosis and genetic counseling are possible for all known gene mutations.

**COMPLEMENT SYSTEM**

The complement system consists of plasma and membrane proteins that function in the innate immune response as well as facilitate adaptive immunity. Complement proteins can kill pathogens with or without antibodies, opsonize pathogens...
to facilitate their uptake by phagocytes, or mediate inflammation. The complement system can be activated through three pathways—classic, alternative, or lectin—that involve a cascade-like, sequential activation of complement factors resulting in an amplified response (Fig. 75-1). Disorders of the complement system predispose to recurrent infection, autoimmunity, and angioedema (Table 75-1).

ETIOLOGY
The three pathways for complement activation are initiated by different mechanisms. The classic pathway is activated by antigen-antibody complexes or by C-reactive protein. The alternative pathway may be activated by C3b generated through classic complement activation or by spontaneous hydrolysis of C3 on microbial surfaces. The lectin pathway is initiated by the interaction of mannose-binding lectin with microbial carbohydrate. Activation of the classic pathway by an antigen-antibody complex is initiated by the binding of C1q to the Fc portion of an antibody molecule in the immune complex. C1r auto-activates and cleaves C1s, which cleaves C4 and then C2, forming the C3 convertase, C4b2a. C4b2a is activated by the lectin pathway when mannose-binding protein binds to sugar residues on the surface of pathogens, and mannose-binding protein–associated proteases (MASP) cleave C4 and C2. The alternative pathway is always active at a low level and is amplified when active C3 binds to a surface that lacks regulatory proteins. C3b generated from C3 binds to factor B, which is cleaved by factor D to form the alternative pathway C3 convertase, C3bBb. Properdin binds to and stabilizes the C3 convertase (see Fig. 75-1). The C3 convertase can cleave C3 resulting in further C3b deposition and activation of the alternative pathway that acts as an amplification loop by generating more C3b, or it can form the C5 convertase which initiates the formation of a membrane attack complex (MAC). The MAC is a complex of C5b, C6, C7, C8, and several C9 molecules that is common to all three pathways (see Fig. 75-1). The MAC generates pores in the cell membrane, leading to lysis of the cells. C3a and C5a, produced by cleavage of C3 and C5 respectively, can release histamine from mast cells and basophils, leading to increased vascular permeability and smooth muscle contraction. In addition, C5a has chemotactic
Deficiency of Complement and Associated Disease

<table>
<thead>
<tr>
<th>DEFICIENT PROTEIN</th>
<th>ASSOCIATED DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1q, C1r</td>
<td>SLE, glomerulonephritis; encapsulated bacterial infections</td>
</tr>
<tr>
<td>C2</td>
<td>SLE, glomerulonephritis; encapsulated bacterial infections</td>
</tr>
<tr>
<td>C3</td>
<td>Recurrent bacterial infections, rare glomerulonephritis, or SLE</td>
</tr>
<tr>
<td>C4</td>
<td>SLE, glomerulonephritis; encapsulated bacterial infections</td>
</tr>
<tr>
<td>C5</td>
<td>Recurrent meningococcal infections</td>
</tr>
<tr>
<td>C6</td>
<td>Recurrent meningococcal infections</td>
</tr>
<tr>
<td>C7</td>
<td>Recurrent meningococcal infections</td>
</tr>
<tr>
<td>C8</td>
<td>Recurrent meningococcal infections</td>
</tr>
<tr>
<td>C9</td>
<td>Occasional meningococcal infection</td>
</tr>
<tr>
<td>Properdin</td>
<td>Recurrent infections, severe meningococcal infection</td>
</tr>
<tr>
<td>MBL</td>
<td>Increased susceptibility to infections</td>
</tr>
<tr>
<td>Factor H</td>
<td>Glomerulonephritis, atypical HUS</td>
</tr>
<tr>
<td>Factor I</td>
<td>Recurrent infections, glomerulonephritis</td>
</tr>
<tr>
<td>MCP</td>
<td>Glomerulonephritis, atypical HUS</td>
</tr>
<tr>
<td>C1 inhibitor</td>
<td>Hereditary angioedema</td>
</tr>
</tbody>
</table>

HUS, hemolytic uremic syndrome; MBL, mannose binding lectin; MCP, membrane cofactor protein; SLE, systemic lupus erythematosus.

C2 deficiency may present with milder recurrent infections. Patients with C1, C2, or C4 deficiency are susceptible to autoimmune diseases, especially systemic lupus erythematosus. The exact mechanism of this susceptibility is not known but is thought to arise from the role of these early components in clearing immune complexes.

**Deficiency of properdin, C3, or the terminal components** predisposes patients to severe recurrent infections. Deficiency of C3, the major opsonin, due to a genetic defect or secondary to excessive consumption, predisposes patients to infections, especially with encapsulated organisms. Deficiency of one of the terminal components that compose the MAC predisposes patients to infection with *Neisseria meningitidis*. Complement deficiency may be found in 40% of patients presenting with recurrent neisserial infections. Deficiency of mannose-binding lectin also is associated with an increased frequency of bacterial infections, including sepsis.

Congenital deficiency of C1-inhibitor results in hereditary angioedema, characterized by recurrent episodes of nonpuritic angioedema lasting 48 to 72 hours, which occur spontaneously or after minor trauma, stress, or anxiety. Abdominal edema can cause acute abdominal pain; edema of the upper airway can be life threatening and may necessitate emergency tracheostomy. The disorder is inherited as an autosomal dominant disease and results from a heterozygous deficiency of C1-inhibitor leading to serum levels less than 30% of normal values. Some mutations (type II hereditary angioedema) result in normal levels of C1-inhibitor with defective function. An acquired form of angioedema results from autoantibodies to C1-inhibitor in lymphoid malignancies or autoimmune disorders but is uncommon in childhood. C1-inhibitor is a regulator of Hageman factor (clotting factor XIIa), clotting factor Xla, plasma kallikrein, and plasmin in addition to C1r and C1s. Lack of inhibition of the contact system, Hageman factor and plasma kallikrein, is responsible for the development of angioedema. Deficiencies in the complement regulatory proteins factor H, factor I, and MCP result in atypical hemolytic uremic syndrome, membranoproliferative glomerulonephritis type II, and have been linked to age-related macular degeneration.

**LABORATORY STUDIES**

The CH50 test is a widely available test of classic complement pathway function, based on an antibody-dependent hemolytic assay, which measures the serum dilution that results in lysis of 50% of sheep red blood cells. The CH50 test depends on the function of all nine complement proteins, C1 through C9. The AH50 test, which measures complement activation using red blood cells from different species (e.g., rabbit) that can activate the alternative pathway without antibody, is less widely available than the CH50 test and requires the alternative pathway components and C5 to C9. Abnormal results of both tests indicate a deficiency in a terminal component common to both pathways, whereas an abnormal result of one or the other test indicates a deficiency of an early component of the respective pathway. If the CH50 or AH50 levels are abnormal, individual components can be analyzed in specialized laboratories.

Determination of C1-inhibitor levels and function is needed to diagnose hereditary angioedema. Some functional tests miss rare mutations that allow C1-inhibitor to bind C1s, but not one or more of the other enzymes with which it interacts. Low C1-inhibitor levels or function results in chronically decreased
C4 levels and decreased C2 levels during acute attacks. Low C1q levels are found in acquired C1-inhibitor deficiency, which distinguishes it from hereditary angioedema. Tests for autoantibodies to C1-inhibitor and C1q can be performed by enzyme-linked immunosorbent assay.

**TREATMENT**

Specific treatment of complement deficiencies with component replacement is not available. Long, frequent courses of antibiotics constitute the primary therapy. Immunization of patients and close contacts with pneumococcal and meningococcal vaccines may be useful, but infections may still occur in immunized complement-deficient patients. Replacement of complement proteins by plasma transfusion has been used in some patients with C2 deficiency, factor H deficiency, or factor I deficiency. MCP deficiency is treated with renal transplantation because it is a membrane protein.

Patients with C1-inhibitor deficiency and frequent episodes of angioedema respond to prophylactic use of an oral attenuated androgen (stanozolol or danazol), which increases serum concentrations of C1-inhibitor. Adverse effects, including masculinization in females, growth arrest, and hepatitis, limit their use. Prophylactic administration of fresh frozen plasma before surgery can prevent angioedema, but administration during an acute episode may exacerbate the episode. Angioedema of the airway can present as an acute emergency, necessitating a tracheostomy because administration of epinephrine, antihistamines, or corticosteroids is ineffective in reversing this type of angioedema. Purified C1-inhibitor is available and can be used prophylactically (before surgery) and during acute episodes of angioedema. Angiotensin-converting enzyme inhibitors, such as captopril, should be avoided in patients with C1-inhibitor deficiency because these drugs can precipitate episodes of angioedema by inhibiting degradation of kinins that mediate edema formation. Novel therapeutic agents, including a kallikrein inhibitor and a bradykinin receptor 2 antagonist, are being investigated as potential therapy for hereditary angioedema.

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### Table 76-1: Immunodeficiency Diseases Curable by Stem Cell Transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe combined immunodeficiency (SCID)</td>
<td>X-linked SCID (γc deficiency)</td>
</tr>
<tr>
<td>Jak 3 kinase deficiency</td>
<td>ZAP 70 deficiency and other T-cell activation defects</td>
</tr>
<tr>
<td>RAG1/RAG2 deficiency and other T- B- SCID</td>
<td>Omenn syndrome</td>
</tr>
<tr>
<td>Purine nucleoside phosphorylase deficiency</td>
<td>Adenosine deaminase deficiency</td>
</tr>
<tr>
<td>Reticular dysgenesis</td>
<td>Purified C1-inhibitor</td>
</tr>
<tr>
<td>Bare lymphocyte syndrome</td>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>X-linked hyper-IgM</td>
<td>X-linked lymphoproliferative syndromes</td>
</tr>
<tr>
<td>X-linked lymphoproliferative syndromes</td>
<td>Cartilage hair hypoplasia</td>
</tr>
<tr>
<td>Autoimmune lymphoproliferative syndrome (Fas defect)</td>
<td>Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)</td>
</tr>
<tr>
<td>Severe congenital neutropenia</td>
<td>Cyclic neutropenia</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td>Chédiak-Higashi syndrome</td>
</tr>
<tr>
<td>Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)</td>
<td>Leukocyte adhesion deficiency type I</td>
</tr>
<tr>
<td>Leukocyte adhesion deficiency</td>
<td>Familial hemophagocytic lymphohistiocytosis</td>
</tr>
</tbody>
</table>

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The principle of HSCT is to replace a patient’s defective bone marrow stem cells with normal stem cells. Hematopoietic stem cells reside in the bone marrow but can also be obtained from peripheral blood or cord blood. Peripheral blood does not contain a significant proportion of stem cells unless the donor’s bone marrow is actively stimulated to generate stem cells. Cord blood is a good source of stem cells and is used for sibling and unrelated HSCT.

**Major histocompatibility complex (MHC) compatibility** is crucial in the choice of a stem cell donor to avoid rejection of the donor cells by the host immune system and to prevent graft-versus-host disease (GVHD) caused by contaminating mature T cells. The donor stem cells give rise to T cells that develop in the host thymus and need to interact with donor and host antigen-presenting cells. In cases with MHC mismatched donors, mature T cells need to be removed from the donor to reduce the risk of GVHD; this complication outweighs the disadvantage of a prolonged time of 90 to 120 days before T-cell development. Patients are at risk for developing **B-cell lymphoproliferative disease**, usually associated with Epstein-Barr virus, when T-cell–depletion techniques are used, likely due to the delay in T-cell engraftment.

The most important factor affecting outcomes in HSCT is the similarity of the donor MHC. The best outcomes are obtained using MHC-identical siblings (25% chance of a matched sibling) as donors, followed by matched unrelated donors. Unlike transplantation for other disorders, MHC haploidal bone marrow from a parent (preferred) or a sibling...
can be used to treat severe combined immunodeficiency (SCID), likely the result of these patients lacking functioning T cells. Stem cells from a partially mismatched donor, such as a parent, can give rise to a functioning immune system because the patient shares at least half of the MHC molecules with the donor stem cells.

MHC molecules are highly polymorphic, and typing is currently performed on DNA rather than by serology. Bone marrow and cord blood registries are available worldwide. Searching and identifying a donor can be a lengthy process, especially for some underrepresented ethnic backgrounds. Finding a suitable cord blood donor is faster because the cord blood already has been obtained and stored, whereas bone marrow donors have to be identified, located, and tested. A matched sibling, if available, is the preferred source of hematopoietic stem cells.

Patients with SCID are ideal candidates for HSCT, which is the only option for treatment of SCID at this time. Patients are unlikely to survive beyond 1 to 2 years of age without transplantation, and they have no T-cell function to reject donor cells. Thus they may not need to undergo conditioning with chemotherapy or irradiation before transplantation. The development of transplantation using T-cell–depleted, haploidentical bone marrow from a parent for SCID has provided almost every patient with SCID a potential donor. The mother is the preferred source for haploidentical bone marrow, if she is able to donate, because some transfer of maternal T cells can occur during pregnancy, and these maternal T cells can reject cells obtained from the father. The survival rate after HSCT for SCID is approximately 90% with MHC-identical and 60% with haploidentical bone marrow transplantation. Early transplantation before the acquisition of infection improves outcomes. Because newborn screening for SCID is now possible, stem cell transplantation can occur as early as possible when the infants are healthy, providing the best opportunity for a cure.

The decision to treat other primary immunodeficiency diseases with HSCT is more difficult because it is difficult to predict the prognosis of a particular patient because of the variability in clinical course of most primary immunodeficiency diseases. This must be weighed with the risks of transplantation. In addition, HSCT for other primary immunodeficiencies is less successful than for SCID because patients typically have some T-cell function and require conditioning with the risks that it entails. The availability of a matched related sibling favors the decision to perform HSCT. Disorders of B cells have not been treated with HSCT because, in many cases, donor B cells do not engraft, and patients usually do well with intravenous immunoglobulin. Regardless a variety of primary immunodeficiencies have been treated with HSCT (see Table 76-1).

### COMPLICATIONS

Rejection of the grafted cells is the first potential complication of HSCT and depends on the immunocompetence of the patient, the degree of MHC incompatibility, and the number of cells administered. Preconditioning with myeloablative drugs, such as busulfan and cyclophosphamide, can prevent graft rejection but may be complicated by pulmonary toxicity and by venoocclusive disease of the liver, which results from damage to the hepatic vascular endothelium and can be fatal. Myeloablation results in anemia, leukopenia, and thrombocytopenia, making patients susceptible to infection and bleeding disorders. Neutropenic precautions should be maintained and patients supported with red blood cell and platelet transfusions until the red blood cell, platelet, and neutrophil lineages engraft. Reduced intensity preconditioning has been used recently to prevent graft rejection and decrease the adverse effects of myeloablation. B-cell lymphoproliferative disorder can develop after T-cell–depleted bone marrow transplantation. GVHD can arise from an MHC-mismatched transplantation or from mismatch in minor histocompatibility antigens that are not tested for before transplantation. T-cell depletion of haploidentical bone marrow reduces the risk of GVHD. Patients with SCID transplanted with T-cell–depleted haploidentical bone marrow do not usually develop severe GVHD. Acute GVHD begins 6 or more days after transplantation and can result from transfusion of non-irradiated blood products in patients with no T-cell function. Acute GVHD presents with fever, skin rash, and severe diarrhea. Patients develop a high, unrelenting fever; a morbilliform maculopapular erythematous rash that is painful and pruritic; hepatosplenomegaly and abnormal liver function tests; and nausea, vomiting, abdominal pain, and watery diarrhea. Acute GVHD is staged from grades 1 to 4, depending on the degree of skin, fever, gastrointestinal, and liver involvement. Chronic GVHD results from acute GVHD lasting longer than 100 days and can develop without acute GVHD or after acute GVHD has resolved. Chronic GVHD is characterized by skin lesions (hyperkeratosis, reticular hyperpigmentation, fibrosis, and atrophy with ulceration), limitation of joint movement, interstitial pneumonitis, and immune dysregulation with autoantibody and immune complex formation.

### Suggested Reading


Atopy is a result of a complex interaction between multiple genes and environmental factors. It implies specific IgE-mediated diseases, including allergic rhinitis, asthma, and atopic dermatitis. An allergen is an antigen that triggers an IgE response in genetically predisposed individuals.

Hypersensitivity disorders of the immune system are classified into four groups, based on the mechanism that leads to tissue inflammation (Table 77-1). Type I reactions are triggered by the binding of antigen to high-affinity IgE receptors on the surface of tissue mast cells, circulating basophils, or both, causing the release of preformed chemical mediators, such as histamine and tryptase, and newly generated mediators, such as leukotrienes, prostaglandins, and platelet-activating factor. These mediators contribute to the development of allergic symptoms, with anaphylaxis as the most profound symptom. Several hours after the initial response, a late-phase reaction may develop with an influx of other inflammatory cells such as basophils, eosinophils, monocytes, lymphocytes, and neutrophils, and their inflammatory mediators. Recruitment of these cells leads to more persistent and chronic symptoms.

Type II (antibody cytotoxicity) reactions involve IgM, IgG, or IgA antibodies binding to the cell surface and activating the entire complement pathway resulting in lysis of the cell or release of anaphylatoxins, such as C3a, C4a, and C5a (see Chapter 75). These anaphylatoxins trigger mast cell degranulation, resulting in inflammatory mediator release. The target can be cell surface membrane antigens, such as red blood cells (hemolytic anemia); platelet cell surface molecules (thrombocytopenia); basement membrane molecules in the kidney (Goodpasture syndrome); the alpha chain of the acetylcholine receptor at the neuromuscular junction (myasthenia gravis); and thyroid-stimulating hormone receptor on thyroid cells (Graves disease).

Type III (immune complex) reactions involve the formation of antigen-antibody or immune complexes that enter into the circulation and are deposited in tissues such as blood vessels and filtering organs (i.e., liver, spleen, and kidney). These complexes initiate tissue injury by activating the complement cascade and recruiting neutrophils that release their toxic mediators. Local reactions caused by the injection of antigen

<table>
<thead>
<tr>
<th>TYPE</th>
<th>INTERVAL BETWEEN EXPOSURE AND REACTION</th>
<th>EFFECTOR CELL</th>
<th>TARGET OR ANTIGEN</th>
<th>EXAMPLES OF MEDIATORS</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>I—Anaphylactic immediate late phase</td>
<td>&lt;30 min 2–12 h</td>
<td>IgE</td>
<td>Pollens, food, venom, drugs</td>
<td>Histamine, tryptase, leukotrienes, prostaglandins, platelet-activating factor</td>
<td>Anaphylaxis, urticaria, allergic rhinitis, allergic asthma</td>
</tr>
<tr>
<td>II—Cytotoxic antibody</td>
<td>Variable (minutes to hours)</td>
<td>IgG, IgM, IgA</td>
<td>Red blood cells, platelets</td>
<td>Complement</td>
<td>Rh hemolytic anemia, thrombocytopenia, hemolysis (quinidine), Goodpasture syndrome</td>
</tr>
<tr>
<td>III—Immune complex reactions</td>
<td>1–3 weeks after drug exposure</td>
<td>Antigen-antibody/ aggregates</td>
<td>Blood vessels, liver, spleen, kidney, lung</td>
<td>Complement, anaphylatoxin</td>
<td>Serum sickness (cefaclor), hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>IV—Delayed type</td>
<td>2–7 days after drug exposure</td>
<td>Lymphocytes</td>
<td>Mycobacterium tuberculosis, chemicals</td>
<td>Cytokines (IFN-γ, TNF-α, GM-CSF)</td>
<td>TB skin test reactions, contact dermatitis (neomycin), graft-versus-host disease</td>
</tr>
</tbody>
</table>

CSF, Cerebrospinal fluid; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-γ; TB, tuberculosis; TNF-α, tumor necrosis factor-α.
into tissue are called Arthus reactions. The administration of large amounts of antigen leads to serum sickness, a classic example of a type III reaction. Other type III–mediated reactions include hypersensitivity pneumonitis and some vasculitic syndromes.

Type IV (cellular immune–mediated or delayed-hypersensitivity) reactions involve recognition of antigen by sensitized T cells. Antigen-presenting cells form peptides that are expressed on the cell surface in association with major histocompatibility complex class II molecules. Memory T cells recognize the antigen peptide/major histocompatibility complex class II complexes. Cytokines, such as interferon-γ, tumor necrosis factor-α, and granulocyte-macrophage colony-stimulating factor, are secreted from this interaction, which activates and attracts tissue macrophages. Contact allergies (nickel, poison ivy, topical medications) and immunity to tuberculosis are type IV reactions.

HISTORY

A family history of allergic disease is often present in affected patients. Multiple genes predispose to atopy. If one parent has allergies, the risk that a child will develop an allergic disease is 25%. If both parents have allergies, the risk increases to 50% to 70%. Similar atopic diseases tend to occur in families.

PHYSICAL EXAMINATION

Children with allergic rhinitis exhibit frequent nasal itching and rubbing of the nose with the palm of the hand, the allergic salute, which can lead to a transverse nasal crease found across the lower bridge of the nose. Allergic shiners, bluish to purple discoloration below the lower eyelids that is attributed to venous congestion, along with swollen eyelids or conjunctival injection are often present in children. Dermatologic findings of atopy include hyperlinearity of the palms and soles, white dermatographism, pityriasis alba, prominent creases under the lower eyelids (Dennie−Morgan folds or Dennie lines), and keratosis pilaris (asymptomatic horny follicular papules on the extensor surfaces of the arms).

COMMON MANIFESTATIONS

Cutaneous manifestations are most common and range from generalized xerosis (dry skin) to urticaria to the pruritic, erythematous papules, and vesicles of atopic dermatitis. There may be involvement of the upper respiratory tract with allergic rhinitis and the lower respiratory tract with asthma. Allergic disease may involve only the skin or the nose, eyes, lungs, and gastrointestinal tract alone or in combination. It is distinguished by environmental exposure to an inciting trigger and usually a history of previous similar disease or development of symptoms after a suspected trigger. Many patients have more than one allergic symptom.

INITIAL DIAGNOSTIC EVALUATION

Screening Tests

Atopy is characterized by elevated levels of IgE (Table 77-2) and eosinophilia (3% to 10% of white blood cells or an absolute eosinophil count of >250 eosinophils/mm³) with a predominance of Th2 cytokines, including interleukin (IL)-4, IL-5, and IL-13. Extreme eosinophilia suggests a nonallergic disorder such as infections with tissue-invasive parasites, drug reactions, or malignancies (Table 77-3). A classic example of a type IV reaction is the tuberculin skin test. A small amount of purified protein derivative from Mycobacterium tuberculosis is injected intradermally (see Chapter 124). In a previously sensitized individual, a type IV inflammatory reaction (induration) develops over the next 24 to 72 hours.

There are two methods for identifying allergen-specific IgE: in vivo skin testing and in vitro serum testing (Table 77-4). In vivo skin testing introduces allergen into the skin via a prick/puncture or intradermal injection. The allergen diffuses through the skin to interact with IgE that is bound to mast cells. Cross-linking of IgE causes mast cell degranulation, which results in a histamine release; this prompts the development of a central wheal and erythematous flare. The wheal and flare are measured 15 to 20 minutes after the allergen has been placed. Properly performed skin tests are the best available method for detecting the presence of allergen-specific IgE.

In vitro serum testing, such as immunoassays like the radioallergosorbent test (also known as RAST) and enzyme-linked immunosorbent assay (also known as ELISA), measures levels of antigen-specific IgE. Many allergists and laboratories regard the ImmunoCAP System as the method of choice. This method uses a solid phase and shows higher sensitivity,
### Table 77-3  Disorders Associated with Eosinophilia

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALLERGIC DISEASE</strong></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td></td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic gastroenteritis</td>
<td></td>
</tr>
<tr>
<td>Allergic colitis</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td><strong>INFECTIOUS</strong></td>
<td></td>
</tr>
<tr>
<td>Tissue-invasive helminthic infections</td>
<td></td>
</tr>
<tr>
<td><strong>NEOPLASTIC</strong></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic leukemia</td>
<td></td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td></td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic pneumonia</td>
<td></td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td></td>
</tr>
<tr>
<td><strong>SYSTEMIC</strong></td>
<td></td>
</tr>
<tr>
<td>Idiopathic hypereosinophilic syndrome</td>
<td></td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td></td>
</tr>
<tr>
<td>Mastocytosis</td>
<td></td>
</tr>
<tr>
<td><strong>IATROGENIC</strong></td>
<td></td>
</tr>
<tr>
<td>Drug-induced</td>
<td></td>
</tr>
</tbody>
</table>

### Table 77-4  Comparison of In Vivo Skin Tests and In Vitro Serum IgE Antibody Immunoassay in Allergic Diagnosis

<table>
<thead>
<tr>
<th>In Vivo Skin Test</th>
<th>In Vitro Serum IgE Antibody Immunoassay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less expensive</td>
<td>No patient risk</td>
</tr>
<tr>
<td>Greater sensitivity</td>
<td>Patient/physician convenience</td>
</tr>
<tr>
<td>Wide allergen selection</td>
<td>Not suppressed by antihistamines</td>
</tr>
<tr>
<td>Results available immediately</td>
<td>Preferable to skin testing for dermatogaphism</td>
</tr>
<tr>
<td></td>
<td>Widespread dermatitis</td>
</tr>
<tr>
<td></td>
<td>Uncooperative children</td>
</tr>
</tbody>
</table>


### DIAGNOSTIC IMAGING

Diagnostic imaging has a limited role in the evaluation of allergic disease. Chest radiography is helpful with the differential diagnosis of asthma. Sinus radiography and computed tomography may be useful, but when these images are abnormal, they do not distinguish allergic disease from nonallergic disease.

### ASTHMA

#### ETIOLOGY

Inflammatory cells (mast cells, eosinophils, T lymphocytes, neutrophils), chemical mediators (histamine, leukotrienes, platelet-activating factor, bradykinin), and chemotactic factors (cytokines, eotaxin) mediate the underlying inflammation found in asthmatic airways. Inflammation contributes to **airway hyperresponsiveness** (airways constricting in response to allergens, irritants, viral infections, and exercise). It also results in edema, increased mucus production in the lungs, influx of inflammatory cells into the airway, and epithelial cell denudation. Chronic inflammation can lead to **airway remodeling**, which results from a proliferation of extracellular matrix proteins and vascular hyperplasia and may lead to irreversible structural changes and a progressive loss of pulmonary function.

#### EPIDEMIOLOGY

Asthma is the most common chronic disease of childhood in industrialized countries, affecting nearly 7 million children younger than 18 years of age in the United States. The number of people with asthma continues to grow. One in 11 children (7 million) had asthma, and 1 in 12 (18.7 million) adults (totaling over 25 million or 8% of U.S. population) had asthma in 2010 compared to 1 in 14 people (about 20 million, or 7%) in 2001. One in 5 children went to the emergency department for an asthma-related visit in 2009. Women are more likely than men to have asthma, and boys are more likely than girls to have asthma.

### CLINICAL MANIFESTATIONS

Children with asthma have symptoms of coughing, wheezing, shortness of breath or rapid breathing, and chest tightness. The history should elicit the frequency, severity, and factors that worsen the child’s symptoms as well as a family history of
asthma and allergy. Exacerbating factors include viral infections, exposure to allergens and irritants (e.g., smoke, strong odors, fumes), exercise, emotions, and change in weather/humidity. Nighttime symptoms are common. Rhinosinusitis, gastroesophageal reflux, and nonsteroidal anti-inflammatory drugs (especially aspirin) can aggravate asthma. Treatment of these conditions may lessen the frequency and severity of the asthma.

During acute episodes, tachypnea, tachycardia, cough, wheezing, and a prolonged expiratory phase may be present. Physical findings may be subtle. Classic wheezing may not be prominent if there is poor air movement from airway obstruction. As the attack progresses, cyanosis, diminished air movement, retractions, agitation, inability to speak, tripod sitting position, diaphoresis, and pulsus paradoxus (decrease in blood pressure of >15 mm Hg with inspiration) may be observed. Physical examination may show evidence of other atopic diseases such as eczema or allergic rhinitis.

**LABORATORY AND IMAGING STUDIES**

Objective measurements of pulmonary function (spirometry) help establish the diagnosis and direct the treatment of asthma. Spirometry is used to monitor response to treatment, assess degree of reversibility with therapeutic intervention, and measure the severity of an asthma exacerbation. Children older than 5 years of age can perform spirometry maneuvers. Variability in predicted peak flow reference values make spirometry preferred to peak flow measures in the diagnosis of asthma. For younger children who cannot perform spirometry maneuvers or peak flow, a therapeutic trial of controller medications helps in the diagnosis of asthma.

**Allergy skin testing** should be included in the evaluation of all children with persistent asthma but not during an exacerbation of wheezing. Positive skin tests results, identifying immediate hypersensitivity to aeroallergens (e.g., as tree and grass pollens, and dust), correlate strongly with bronchial allergen provocative challenges. In vitro serum tests, such as radioallergosorbent test (also known as RAST), fluorescent enzyme immunoassay (also known as FEIA), or enzyme-linked immunosorbent assay, are generally less sensitive in defining clinically pertinent allergens, are more expensive, and require several days for results compared to several minutes for skin testing (see Table 77-4).

A **chest radiograph** should be performed with the first episode of asthma or with recurrent episodes of undiagnosed cough or wheeze to exclude anatomic abnormalities. Repeat chest radiographs are not needed with new episodes unless there is fever (suggesting pneumonia) or localized findings on physical examination.

Two novel forms of monitoring asthma and airway inflammation directly include **exhaled nitric oxide analysis** and quantitative analysis of expectorated sputum for eosinophilia.

**DIFFERENTIAL DIAGNOSIS**

Many childhood conditions can cause wheezing and coughing of asthma (Table 78-1) but not all cough and wheeze is asthma. Misdiagnosis delays correcting the underlying cause and exposes children to inappropriate asthma therapy (Table 78-2).

**Allergic bronchopulmonary aspergillosis** is a hypersensitivity type of reaction to antigens of the mold *Aspergillus fumigatus*. It occurs primarily in patients with steroid-dependent asthma and in patients with cystic fibrosis.

**TREATMENT**

Optimal medical treatment of asthma includes several key components: environmental control, pharmacologic therapy, and patient education, including attainment of
self-management skills. Because many children with asthma have coexisting allergies, steps to minimize allergen exposure should be taken (Table 78-3). For all children with asthma, exposures to tobacco and wood smoke and to persons with viral infections should be minimized. Influenza immunizations are indicated. Asthma medications can be divided into long-term control medications and quick-relief medications.

### Long-Term Control Medications

#### Inhaled Corticosteroids

Inhaled corticosteroids are the most effective anti-inflammatory medications for the treatment of chronic, persistent asthma and are the preferred therapy when initiating long-term control therapy. Early intervention with inhaled corticosteroids reduces morbidity but does not alter the natural history of asthma. Regular use reduces airway hyperreactivity, the need for rescue bronchodilator therapy, risk of hospitalization, and risk of death from asthma. Inhaled corticosteroids are available as an inhalation aerosol, dry powder inhaler, and nebulizer solution.

The potential risks of inhaled corticosteroids are favorably balanced with their benefits. A reduction in growth velocity may occur with poorly controlled asthma or inhaled corticosteroids use. Low-to-medium dose inhaled corticosteroids may decrease growth velocity, although these effects are small (approximately 1 cm in the first year of treatment), generally not progressive, and may be reversible. Regularly scheduled height measurements should be monitored. Inhaled corticosteroids do not have clinically significant adverse effects on hypothalamic-pituitary-adrenal axis function, glucose metabolism, or subcapsular cataracts or glaucoma when used at low-to-medium doses in children. Rinsing the mouth after inhalation and using spacers help lessen the local adverse effects of dysphonia and candidiasis and decrease systemic absorption from the gastrointestinal tract. Inhaled corticosteroids should be titrated to the lowest dose needed to maintain control of a child’s asthma. For children with severe asthma, higher dose inhaled corticosteroids may be needed to minimize the oral corticosteroid dose, but other “add-on” therapy should be considered (see the following sections).

#### Leukotriene Modifiers

Leukotrienes, synthesized via the arachidonic acid metabolism cascade, are potent mediators of inflammation and smooth muscle bronchoconstriction. Leukotriene modifiers are oral, daily-use medications that inhibit these biologic effects in the airway. Two classes of leukotriene modifiers include cysteinyl leukotriene receptor antagonists (zafirlukast and montelukast) and leukotriene synthesis inhibitors (zileuton). The leukotriene receptor antagonists have much wider appeal than zileuton. Zafirlukast is approved for children older than 5 years of age and is given twice daily. Montelukast is dosed once daily, at night, as 4-mg granules or chewable tablets (for children 6 months to 5 years), 5-mg chewable tablets (6 to 14 years), and 10-mg tablets (15 years of age or older). Pediatric studies show the usefulness of leukotriene modifiers in mild asthma

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**Table 78-2**  
**Mnemonic of Causes of Cough in the First Months of Life**

<table>
<thead>
<tr>
<th>C</th>
<th>Cystic fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Respiratory tract infections</td>
</tr>
<tr>
<td>A</td>
<td>Aspiration (swallowing dysfunction, gastroesophageal reflux, tracheoesophageal fistula, foreign body)</td>
</tr>
<tr>
<td>D</td>
<td>Dyskinetic cilia</td>
</tr>
<tr>
<td>L</td>
<td>Lung and airway malformations (laryngeal webs, laryngotracheomalacia, tracheal stenosis, vascular rings and slings)</td>
</tr>
<tr>
<td>E</td>
<td>Edema (heart failure, congenital heart disease)</td>
</tr>
</tbody>
</table>

**Table 78-3**  
**Controlling Factors Contributing to Asthma Severity**

<table>
<thead>
<tr>
<th>Major Indoor Triggers for Asthma</th>
<th>Suggestions for Reducing Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral upper respiratory tract (RSV, influenza virus)</td>
<td>Limit exposure to viral infections (day care with fewer children)</td>
</tr>
<tr>
<td>Tobacco smoke, wood smoke</td>
<td>No smoking around the child or in child’s home</td>
</tr>
<tr>
<td>Dust mites</td>
<td>Essential actions</td>
</tr>
<tr>
<td>Animal dander</td>
<td>Avoid sleeping or lying on upholstered furniture</td>
</tr>
<tr>
<td>Cockroach allergens</td>
<td>Minimize number of stuffed toys in child’s bedroom</td>
</tr>
<tr>
<td>Indoor mold</td>
<td>Reduce indoor humidity to &lt;50%</td>
</tr>
<tr>
<td>Mold</td>
<td>If possible, remove carpets from bedroom and play areas; if not possible, vacuum frequently</td>
</tr>
<tr>
<td>SUGGESTIONS FOR REDUCING EXPOSURE</td>
<td></td>
</tr>
<tr>
<td>Desirable actions</td>
<td></td>
</tr>
<tr>
<td>Essential actions</td>
<td></td>
</tr>
</tbody>
</table>

---


*From American Academy of Allergy Asthma & Immunology: Pediatric Asthma: Promoting Best Practice, Milwaukee, Wisconsin, 1999, American Academy of Allergy Asthma & Immunology.*

*RSV, Respiratory syncytial virus.*
and the attenuation of exercise-induced bronchoconstriction. These agents may be helpful as steroid-sparing agents in patients with asthma that is more difficult to control.

**Long-Acting $\beta_2$-Agonists**

Long-acting $\beta_2$-agonists, formoterol and salmeterol, have twice-daily dosing and relax airway smooth muscle for 12 hours but do not have any significant anti-inflammatory effects. Adding a long-acting bronchodilator to inhaled corticosteroid therapy is more beneficial than doubling the dose of inhaled corticosteroids. Multiple formulations are available. Formoterol is approved for use in children older than 5 years of age for maintenance asthma therapy and for prevention of exercise-induced asthma. It has a rapid onset of action similar to albuterol (15 minutes). Salmeterol is approved for children 4 years of age or older and has an onset of 30 minutes. Because combination agents administer two medications simultaneously, compliance is generally improved.

**Omalizumab**

Omalizumab (Xolair) is a humanized anti-IgE monoclonal antibody that prevents binding of IgE to high-affinity receptors on basophils and mast cells. It is approved for moderate to severe allergic asthma in children 12 years of age and older. Xolair is delivered by subcutaneous injection every 2 to 4 weeks, depending on body weight and pretreatment serum IgE level.

**Quick-Relief Medications**

**Short-Acting $\beta_2$-Agonists**

Short-acting $\beta_2$-agonists, such as albuterol, levalbuterol, and pirbuterol, are effective bronchodilators that exert their effect by relaxing bronchial smooth muscle within 5 to 10 minutes of administration. They last for 4 to 6 hours. Generally a short-acting $\beta_2$-agonist is prescribed for acute symptoms and as prophylaxis before allergen exposure and exercise. The inhaled route is preferred because adverse effects—tremor, prolonged tachycardia, and irritability—are less. *Overuse* of $\beta_2$-agonists implies inadequate control; a change in medications may be warranted. The definition of *overuse* depends on the severity of the child’s asthma; use of more than one metered dose inhaler canister per month or more than eight puffs per day suggests poor control.

**Anticholinergic Agent**

Ipratropium bromide is an anticholinergic bronchodilator that relieves bronchoconstriction, decreases mucus hypersecretion, and counteracts cough-receptor irritability by binding acetylcholine at the muscarinic receptors found in bronchial smooth muscle. It seems to have an additive effect with $\beta_2$-agonists when used for acute asthma exacerbations. Long-term use of anticholinergic medications in asthma is not supported by the literature.

**Oral Corticosteroids**

Short bursts of oral corticosteroids (3 to 10 days) are administered to children with acute exacerbations. The initial starting dose is 1 to 2 mg/kg/day of prednisone followed by 1 mg/kg/day over the next 2 to 5 days. Oral corticosteroids are available in liquid or tablet formulations. Prolonged use of oral corticosteroids can result in systemic adverse effects such as hypothalamic-pituitary-adrenal suppression, cushingoid features, weight gain, hypertension, diabetes, cataracts, glaucoma, osteoporosis, and growth suppression. Children with severe asthma may require oral corticosteroids over extended periods. The dose should be tapered as soon as possible to the minimum effective dose, preferably administered on alternate days.

**Approach to Therapy**

Therapy is based on the concept that chronic inflammation is a fundamental feature of asthma and that the processes underlying asthma can vary in intensity over time, requiring treatment to be adjusted accordingly. Classification of asthma severity is emphasized for initiation of therapy in patients not currently receiving controller medications. Assessing control is emphasized for monitoring and adjusting therapy. A stepwise approach is used for management of infants and young children 0 to 4 years, children 5 to 11 years (Fig. 78-1), youths 12 years or older, and adults (Fig. 78-2). Medication type, amount, and scheduling are determined by the level of asthma severity or asthma control. Therapy is then increased (*stepped up*) as necessary and decreased (*stepped down*) when possible. A short-acting bronchodilator should be available for all children with asthma. A child with intermittent asthma has asthma symptoms less than two times per week. To determine whether a child is having more persistent asthma, using the **Rules of Two** is helpful: daytime symptoms occurring two or more times per week or nighttime awakening two or more times per month implies a need for daily anti-inflammatory medication.

Inhaled corticosteroids are the preferred initial long-term control therapy for children of all ages (Fig. 78-3). Daily long-term control therapy is recommended for infants and young children 0 to 4 years of age who had four or more episodes of wheezing in the previous year that lasted more than 1 day, affected sleep, and who have a positive asthma predictive index. For children over 5 years of age with moderate persistent asthma, combining long-acting bronchodilators with low-to-medium doses of inhaled corticosteroids improves lung function and reduces rescue medication use. For children with severe persistent asthma, a high-dose inhaled corticosteroid and a long-acting bronchodilator are the preferred therapy. The guidelines also recommend that treatment be reevaluated within 2 to 6 weeks of initiating therapy. Once asthma is under control, control should be assessed on an ongoing basis every 1 to 6 months. The asthma should be well controlled for at least 3 months before stepping down therapy. Note that asthma management guidelines are based on review of the published evidence, not solely on age recommendations and dosages approved by the U.S. Food and Drug Administration.
**Stepwise long-term approach for managing asthma in children, 0 to 4 years of age and 5 to 11 years of age.**


### Each Step: Patient Education and Environmental Control

#### Intermittent Asthma

**Preferred**
- SABA PRN
- Low-dose ICS
- Medium-dose ICS
- Medium-dose ICS + LABA or Montelukast
- High-dose ICS + LABA or Montelukast
- High-dose ICS + LABA or Montelukast + Oral corticosteroids

**Alternative**
- Cromolyn or Montelukast

### Quick-Relief Medication

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms.
- With viral respiratory symptoms: SABA q 4–6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.

**Key:** Alphabetical listing is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, Inhaled corticosteroid; LABA, Inhaled long-acting beta2-agonist; LTRA, Leukotriene receptor antagonist, oral corticosteroids, oral systemic corticosteroids; SABA, inhaled short-acting beta2-agonist

### Persistent Asthma: Daily Medication

**Consult with asthma specialist if Step 3 care or higher is required. Consider consultation at Step 2.**

**Steps 2–4:** Consider subcutaneous allergen immunotherapy for patients who have persistent, allergic asthma.

#### Intermittent Asthma

**Preferred**
- SABA PRN
- Low-dose ICS
- Low-dose ICS + LABA, LTRA, or Theophylline
- Medium-dose ICS + LABA
- Medium-dose ICS + LABA or LTRA or Theophylline
- High-dose ICS + LABA
- High-dose ICS + LABA or LTRA or Theophylline
- High-dose ICS + LABA or LTRA or Theophylline + Oral corticosteroids

**Alternative**
- Cromolyn
- LTRA
- Nedocromil, or Theophylline

**Key:** Alphabetical listing is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, Inhaled corticosteroid; LABA, Inhaled long-acting beta2-agonist; LTRA, Leukotriene receptor antagonist, oral corticosteroids, oral systemic corticosteroids; SABA, inhaled short-acting beta2-agonist

### Management of Comorbidities

**Steps 2–4:** Consider consultation at Step 2.

- Immunotherapy for Steps 2–4 is based on Evidence B for efficacy of each treatment with extrapolation from comparator trials in older children and adults–comparator trials are not available for this age group; Steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.

**Key:**
- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If an alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks, and patient’s/family’s medication technique and adherence are satisfactory, consider adjusting therapy or an alternative diagnosis. Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.
- Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

### Notes

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If an alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks, and patient’s/family’s medication technique and adherence are satisfactory, consider adjusting therapy or an alternative diagnosis. Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.
- Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.
**Intermittent asthma**

Consult with asthma specialist if Step 4 care or higher is required. Consider consultation at Step 3.

**Step 1**

Preferred: SABA PRN

Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 2**

Preferred: Low-dose ICS + LABA

Alternative: Medium-dose ICS + LABA

**Step 3**

Preferred: Medium-dose ICS + LABA

Alternative: Low-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 4**

Preferred: High-dose ICS + LABA AND Consider Omalizumab for patients who have allergies

**Step 5**

Preferred: High-dose ICS + LABA AND Oral corticosteroid AND Consider Omalizumab for patients who have allergies

**Step 6**

Step up if needed (first, check adherence, environmental control, and comorbid conditions)

Assess control

Step down if possible (and asthma is well controlled at least 3 months)

Key: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, Inhaled corticosteroid; LABA, long-acting inhaled beta2-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta2-agonist

Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function.
- Theophylline requires monitoring of serum concentration levels.
- In Step 6, before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, Theophylline, or Zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A; Step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for Theophylline, and Evidence D for Zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and Theophylline and Evidence D Zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR–2 1997) and Evidence B for Omalizumab.
- Immunotherapy for Steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or Omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.

**Quick-relief medication for all patients**

- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

**Each step: Patient education, environmental control, and management of comorbidities.**

Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see Notes).

**Figure 78-2** Stepwise approach for managing asthma in youths 12 years of age or older and adults. (From National Heart Lung Blood Institute, National Asthma Education and Prevention Program: Expert panel report 3: guidelines for the diagnosis and management of asthma. Summary report 2007, NIH Publication No. 08-5846, Bethesda, MD, 2007, U.S. Department of Health and Human Services, p 45, http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf.)

**COMPLICATIONS**

Most asthma exacerbations can be successfully managed at home. **Status asthmaticus** is an acute exacerbation of asthma that does not respond adequately to therapeutic measures and may require hospitalization. Exacerbations may progress over several days or occur suddenly and can range in severity from mild to life threatening. Significant respiratory distress, dyspnea, wheezing, cough, and a decrease in peak expiratory flow rate (PEFR) characterize deterioration in asthma control. During severe episodes of wheezing, pulse oximetry is helpful in monitoring oxygenation. In status asthmaticus, arterial blood gases may be necessary for measurement of ventilation. As airway obstruction worsens and chest compliance decreases, carbon dioxide retention can occur. In the face of tachypnea, a normal pCO2 (40 mm Hg) indicates impending respiratory arrest.

First-line management of asthma exacerbations includes supplemental oxygen, repetitive, or continuous administration of short-acting bronchodilators. Early administration of oral or intravenous corticosteroids (Fig. 78-4) is important in treating the underlying inflammation. Administration of anticholinergic agents (ipratropium) with bronchodilators decreases rates of hospitalization and duration of time in the emergency department. Intravenous magnesium sulfate is given in the emergency department if there is clinical deterioration, despite treatment with β2-agonists, ipratropium, and systemic glucocorticoids. The typical dose is 25 to 75 mg/kg (maximum 2.0 g) intravenously administered over 20 minutes. Epinephrine (intramuscular) or terbutaline (subcutaneous) is rarely used except when severe asthma is associated with anaphylaxis or unresponsive to continuous administration of short-acting bronchodilators.

**PROGNOSIS**

For some children, symptoms of wheezing with respiratory infections subside in the preschool years, whereas others have more persistent asthma symptoms. Prognostic indicators for children younger than 3 years of age who are at risk for asthma include eczema, parental asthma, or two of the
Asthma management plan (Fig. 78-5) for daily care and for exacerbations. Ingesting patient skills in the use of spacer devices for metered dose inhalers and peak flow monitoring. Families should have an asthma management plan that is helpful for children over 5 years of age. It is advisable for children who are poor perceivers of airway obstruction, have moderate limitations, teaching basic asthma facts, explaining the role of medications, teaching environmental control measures, and improving patient skills in the use of spacer devices for metered dose inhalers and peak flow monitoring. Families should have an asthma management plan (Fig. 78-5) for daily care and for exacerbations.

### PREVENTION

Education plays an important role in helping patients and their families adhere to the prescribed therapy and needs to begin at the time of diagnosis. Successful education involves the following: allergic rhinitis, wheezing with a cold, or eosinophilia of greater than 4%. Atopy is the strongest predictor for wheezing continuing into persistent asthma.

#### Table 78-4

<table>
<thead>
<tr>
<th>Drug</th>
<th>Medium Daily Dose</th>
<th>High Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 Years of Age</td>
<td>12 Years of Age</td>
</tr>
<tr>
<td>Beclomethasone HFA 40</td>
<td>&gt;240–480 µg</td>
<td>&gt;480 µg</td>
</tr>
<tr>
<td>or 80 µg/puff</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide DPI 90</td>
<td>&gt;320 µg</td>
<td>&gt;1,200 µg</td>
</tr>
<tr>
<td>or 180, or 200 µg/inh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone DPI 200 µg</td>
<td>&gt;1,250 µg</td>
<td>&gt;2,000 µg</td>
</tr>
<tr>
<td>DPI: 50, 100, or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 µg/inhalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunisolide HFA 80 µg</td>
<td>&gt;600–1,200 µg</td>
<td>&gt;2,000 µg</td>
</tr>
<tr>
<td>Fluticasone HFA/MDI: 44</td>
<td>&gt;600–1,200 µg</td>
<td>&gt;2,000 µg</td>
</tr>
<tr>
<td>or 110, or 220 µg/puff</td>
<td>&gt;600–1,200 µg</td>
<td>&gt;2,000 µg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 µg/inhalation</td>
<td>&gt;600–1,200 µg</td>
<td>&gt;2,000 µg</td>
</tr>
<tr>
<td>Mometasone DPI 200 µg</td>
<td>&gt;1,250 µg</td>
<td>&gt;2,000 µg</td>
</tr>
<tr>
<td>DPI: 50, 100, or 250 µg/inhalation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone acetonide 75 µg/puff</td>
<td>&gt;600–900 µg</td>
<td>&gt;1,500 µg</td>
</tr>
</tbody>
</table>

Key: DPI: Dry powder inhaler; HFA: hydrofluoroalkane; MDI, metered-dose inhaler; NA, not available (either not approved, no data available, or safety and efficacy not established for this age group)

#### Therapeutic Issues:

- The most important determinant of appropriate dosing is the clinician’s judgment of the patient’s response to therapy. The clinician must monitor the patient’s response on several clinical parameters and adjust the dose accordingly. Once control of asthma is achieved, the dose should be carefully titrated to the minimum dose required to maintain control.

- Preparations are not interchangeable on a µg or per puff basis. This figure presents estimated comparable daily doses. See EPR–3 Full Report 2007 for full discussion.

- Some doses may be outside package labeling, especially in the high-dose range. Budesonide nebulizer suspension is the only inhaler corticosteroid (ICS) with FDA-approved labeling for children <4 years of age.

- For children <4 years of age: The safety and efficacy of ICSs in children <1 year has not been established. Children <4 years of age generally require delivery of ICS (budesonide and fluticasone HFA) through a face mask that should fit snugly over nose and mouth and avoid nebulizing in the eyes. Wash face after each treatment.

- Potential Adverse Effects of Inhaled Corticosteroids:
  - Cough, dysphonia, oral thrush (candidiasis).
  - Spacer or valved holding chamber with non-breath-actuated MDIs and mouthwashing and spitting after inhalation decrease local side effects.
  - A number of the ICSs, including Fluticasone, Budesonide, and Mometasone, are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as Ritonavir and Ketoconazole, have the potential for increasing systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported.
  - In high doses, systemic effects may occur, although studies are not conclusive, and clinical significance of these effects has not been established (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising). In low-to-medium doses, suppression of growth velocity has been observed in children, but this effect may be transient, and the clinical significance has not been established.

#### Figure 78-3

Initial assessment
Brief history, physical examination (auscultation, use of accessory muscles, heart rate, respiratory rate), PEF or FEV₁, oxygen saturation, and other tests as indicated

FEV₁ or PEF 40% (mild-to-moderate)
- Oxygen to achieve SaO₂ ≥ 90%
- Inhaled SABA by nebulizer or MDI with valved holding chamber, up to 3 doses in first hour
- Oral systemic corticosteroids if no immediate response or if patient recently took oral systemic corticosteroids

FEV₁ or PEF <40% (severe)
- Oxygen to achieve SaO₂ ≥ 90%
- High-dose inhaled SABA plus Ipratropium by nebulizer or MDI plus valved holding chamber, every 20 minutes or continuously for 1 hour
- Oral systemic corticosteroids

Impending or actual respiratory arrest
- Intubation and mechanical ventilation with 100% oxygen
- Nebulized SABA and Ipratropium
- Intravenous corticosteroids
- Consider adjunct therapies

Repeat assessment
Symptoms, physical examination, PEF, O₂ saturation, other tests as needed

Moderate exacerbation
FEV₁ or PEF 40–69% predicted/personal best
Physical exam: moderate symptoms
- Inhaled SABA every 60 minutes
- Oral systemic corticosteroid
- Continue treatment 1–3 hours, provided there is improvement; make admit decision in <4 hours

Severe exacerbation
FEV₁ or PEF <40% predicted/personal best
Physical exam: severe symptoms at rest, accessory muscle use, chest retraction
History: high-risk patient
No improvement after initial treatment
- Oxygen
- Nebulized SABA plus Ipratropium, hourly or continuous
- Oral systemic corticosteroids
- Consider adjunct therapies

Good response
- FEV₁ or PEF ≥ 70%
- Response sustained 60 minutes after last treatment
- No distress
- Physical exam: normal

Incomplete response
- FEV₁ or PEF 40–69%
- Mild-to-moderate symptoms

Poor response
- FEV₁ or PEF <40%
- PCO₂ ≥ 42 mm Hg
- Physical exam: symptoms severe, drowsiness, confusion

Individualized decision re: hospitalization (see text)

Discharge home
- Continue treatment with inhaled SABA
- Continue course of oral systemic corticosteroid
- Patient education
  - Review medications, including inhaler technique
  - Review/initiate action plan
  - Recommend close medical follow-up

Admit to hospital ward
- Oxygen
- Inhaled SABA
- Systemic (oral or intravenous) corticosteroid
- Consider adjunct therapies
- Monitor vital signs, FEV₁ or PEF, SaO₂

Admit to hospital intensive care
- Oxygen
- Inhaled SABA hourly or continuously
- Intravenous corticosteroid
- Consider adjunct therapies
- Possible intubation and mechanical ventilation

Discharge home
- Continue treatment with inhaled SABAs.
- Continue course of oral systemic corticosteroid.
- Continue on ICS. For those not on long-term-control therapy, consider initiation of an ICS.
- Patient education (e.g., review medications, including inhaler technique: review/initiate action plan and, whenever possible, environmental control measures; and recommend close medical follow-up).
- Before discharge, schedule follow-up appointment with primary care provider and/or asthma specialist in 1–4 weeks.

Key: FEV₁, Forced expiratory volume in 1 second; ICS, inhaled corticosteroid; MDI, metered-dose inhaler; PCO₂, partial pressure carbon dioxide; PEF, peak expiratory flow; SABA, short-acting beta-agonist; SaO₂, oxygen saturation

**Asthma Action Plan**

For: ___________________________  Doctor: ___________________________  Date: ___________________________

Doctor’s Phone Number ___________________________  Hospital/Emergency Department Phone Number ___________________________

**GREEN ZONE**

**Doing Well**
- No cough, wheeze, chest tightness, or shortness of breath during the day or night
- Can do usual activities

**And, if a peak flow meter is used,**
- **Peak flow:** more than __________ (60 percent or more of my best peak flow)
- My best peak flow is: __________

Take these long-term-control medicines each day (include an anti-inflammatory).

<table>
<thead>
<tr>
<th>Medicine</th>
<th>How much to take</th>
<th>When to take it</th>
</tr>
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</table>

Identify and avoid and control the things that make your asthma worse, like (list here):

- ___________________________
- ___________________________
- ___________________________

Before exercise, if prescribed, take: ☐ 2 or ☐ 4 puffs __________ 5 to 60 minutes before exercise

**YELLOW ZONE**

**Asthma Is Getting Worse**
- Cough, wheeze, chest tightness, or shortness of breath, or
- Waking at night due to asthma, or
- Can do some, but not all, usual activities

- **First**
  - **Peak flow:** ________ to ________ (50 to 79 percent of my best peak flow)

  Add: quick-relief medicine—and keep taking your GREEN ZONE medicine.

  - 2 or 4 puffs, every 20 minutes for up to 1 hour (short-acting beta2-agonist)
  - Nebulizer, once

  If applicable, remove yourself from the thing that made your asthma worse.

  - If your symptoms (and peak flow, if used) return to GREEN ZONE after 1 hour of above treatment:
    - ☐ Continue monitoring to be sure you stay in the green zone.

  - **Second**
    - If your symptoms (and peak flow, if used) do not return to GREEN ZONE after 1 hour of above treatment:
      - Take: ___________________________ 2 or 4 puffs or Nebulizer (short-acting beta2-agonist)
      - Add: ___________________________ mg per day. For ________ (3–10) days (oral corticosteroid)
      - Call the doctor __________ ☐ before/☐ within ________ hours after taking the oral corticosteroid.

**RED ZONE**

**Medical Alert!**
- Very short of breath, or
- Quick-relief medicines have not helped, or
- Cannot do usual activities, or
- Symptoms are same or get worse after 24 hours in Yellow Zone.

- **First**
  - **Peak flow:** less than ________ (50 percent of my best peak flow)

  Take this medicine:

  - □ ___________________________ 4 or 6 puffs or Nebulizer (short-acting beta2-agonist)
  - □ ___________________________ mg (oral corticosteroid)

  Then call your doctor NOW. Go to the hospital or call an ambulance if
  - You are still in the red zone after 15 minutes AND
  - You have not reached your doctor.

**DANGER SIGNS**
- Trouble walking and talking due to shortness of breath
- Lips or fingernails are blue
- Take □ 4 or □ 6 puffs of your quick-relief medicine **AND**
- Go to the hospital or call for an ambulance ___________________________ NOW!
to severe asthma, or have a history of severe exacerbations. Peak flow monitoring also can be useful in children who are still learning to recognize asthma symptoms.

To use a peak flow meter, a child should be standing with the indicator placed at the bottom of the scale. The child must inhale deeply, place the device in the mouth, seal the lips around the mouthpiece, and blow out forcefully and rapidly. The indicator moves up the numeric scale. The PEFR is the highest number achieved. The test is repeated three times to obtain the best possible effort. Peak flow meters are available as low range (<300 L/sec) and high range (<700 L/sec). It is important to provide the appropriate range meter so that accurate measurements can be obtained and children do not become discouraged because their exhalations barely move the indicator.

A child’s personal best is the highest PEFR achieved over a 2-week period when stable. Based on the child’s personal best, a written action plan can be established, which is divided into three zones, similar to a stoplight. The green zone indicates a PEFR 80% to 100% of the child’s personal best value. In this zone, the child is likely asymptomatic and should continue with medications as usual. The yellow zone indicates a PEFR 50% to 80% of the child’s personal best value, which generally coincides with more asthma symptoms. Rescue medications, such as albuterol, are added. A call to the physician may be warranted if the peak flows do not return to the green zone within 24 to 48 hours or if asthma symptoms are increasing. The red zone indicates a PEFR below 50% and is a medical emergency. Rescue medication should be taken immediately. If the PEFR remains in the red zone or the child has significant airway compromise, a call to the physician or emergency care is needed.

Children with asthma should be seen not only when they are ill but also when they are healthy. Regular office visits allow the health care team to review adherence to medication and control measures and to determine whether doses of medications need adjustment.

### ALLERGIC RHINITIS

#### ETIOLOGY

Rhinitis describes diseases that involve inflammation of the nasal epithelium and is characterized by sneezing, itching, rhinorrhea, and congestion. There are many different causes of rhinitis in children, but approximately half of all cases of asthma are caused by allergies.

Allergic rhinitis, commonly known as hay fever, is caused by an IgE-mediated allergic response. During the early allergic phase, mast cells degranulate and release preformed chemical mediators, such as histamine and tryptase, and newly generated mediators, such as leukotrienes, prostaglandins, and platelet-activating factor. After a quiescent phase in which other cells are recruited, a late phase occurs approximately 4 to 8 hours later. Eosinophils, basophils, CD4 T cells, monocytes, and neutrophils release their chemical mediators, which leads to the development of chronic nasal inflammation.

Allergic rhinitis can be seasonal, perennial, or episodic depending on the particular allergen and the exposure. Some children experience perennial symptoms with seasonal exacerbations. Seasonal allergic rhinitis is caused by airborne pollens, which have seasonal patterns. Typically trees pollinate in the spring, grasses in late spring to summer, and weeds in the summer and fall. The pollen, microscopic in size, can travel airborne hundreds of miles and be inhaled easily into the respiratory tract. Perennial allergic rhinitis is primarily caused by indoor allergens, such as house dust mites, animal dander, mold, and cockroaches. Episodic rhinitis occurs with intermittent exposure to allergens, such as visiting a friend’s home where a pet dwells.

#### EPIDEMIOLOGY

Chronic rhinitis is one of the most common disorders encountered in infants and children. Overall allergic rhinitis is observed in 10% to 25% of the population, with children and adolescents more commonly affected than adults. The prevalence of physician-diagnosed allergic rhinitis may be 40%.

#### CLINICAL MANIFESTATIONS

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinorrhea</td>
</tr>
<tr>
<td>Red Eye</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Hoarseness</td>
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</tbody>
</table>

### Table 78-4: Risk Factors for Persistent Asthma

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Allergy</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
</tr>
<tr>
<td>Elevated total serum IgE levels (first year of life)</td>
</tr>
<tr>
<td>Peripheral blood eosinophilia &gt;4% (2–3 yr of age)</td>
</tr>
<tr>
<td>Food and inhalant allergen sensitization</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Boys</td>
</tr>
<tr>
<td>Transient wheezing</td>
</tr>
<tr>
<td>Persistent allergy-associated asthma</td>
</tr>
<tr>
<td>Girls</td>
</tr>
<tr>
<td>Asthma associated with obesity and early-onset puberty</td>
</tr>
<tr>
<td>Triad asthma (adulthood)</td>
</tr>
<tr>
<td>Parental asthma</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
</tr>
<tr>
<td>Respiratory syncytial virus, parainfluenza</td>
</tr>
<tr>
<td>Severe bronchiolitis (e.g., requiring hospitalization)</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Environmental tobacco smoke exposure (including prenatal)</td>
</tr>
</tbody>
</table>

The hallmarks of allergic rhinitis are clear: thin rhinorrhea; nasal congestion; paroxysms of sneezing; and pruritus of the eyes, nose, ears, and palate. Postnasal drip may result in frequent attempts to clear the throat, nocturnal cough, and hoarseness. It is important to correlate the onset, duration, and severity of symptoms with seasonal or perennial exposures, changes in the home or school environment, and exposure to nonspecific irritants, such as tobacco smoke.

The physical examination includes a thorough nasal examination and an evaluation of the eyes, ears, throat, chest, and skin. Physical findings may be subtle. Classic physical findings include pale pink or bluish gray, swollen, boggy nasal turbinates with clear, watery secretions. Frequent nasal itching and rubbing of the nose with the palm of the hand, the allergic salute, can lead to a transverse nasal crease found across the lower bridge of the nose. Children may produce clucking sounds by rubbing the soft palate with their tongue. Oropharyngeal examination may reveal lymphoid hyperplasia of the soft palate and posterior pharynx or visible mucus or both. Orthodontic abnormalities may be seen in children with chronic mouth breathing. Allergic shiners, dark periorbital swollen areas caused by venous congestion, along with swollen eyelids or conjunctival injection, are often present in children. Retracted tympanic membranes from eustachian tube dysfunction or serous otitis media also may be present. Other atopic diseases, such as asthma or eczema, may be present, which helps lead the clinician to the correct diagnosis.

### LABORATORY AND IMAGING STUDIES

Allergy testing can be performed by in vivo skin tests or by in vitro serum tests (radioallergosorbent test [RAST], fluorescent enzyme immunoassay [FEIA], or enzyme linked immunoassay [ELISA]) to pertinent allergens found in the patient’s environment (see Table 77-4). Skin tests (prick/puncture) provide immediate and accurate results. Positive tests correlate strongly with nasal and bronchial allergen provocative challenges. In vitro serum tests are useful for patients with abnormal skin conditions, for those with a tendency for anaphylaxis, or for those taking medications that interfere with skin testing. Disadvantages of serum tests include increased cost, inability to obtain immediate results, and reduced sensitivity compared with skin tests. Widespread screening with serum testing without regard to symptoms is not recommended. Measurement of total serum IgE or blood eosinophils generally is not helpful. The presence of eosinophils on the nasal smear suggests a diagnosis of allergy, but eosinophils also can be found in patients with nonallergic rhinitis with eosinophilia. Nasal smear eosinophilia is often predictive of a good clinical response to nasal corticosteroid sprays.

### DIFFERENTIAL DIAGNOSIS

Rhinitis can be divided into allergic and nonallergic rhinitis (Table 79-1). Nonallergic rhinitis describes a group of nasal diseases in which there is no evidence of allergic etiology. It can be divided further into nonanatomic and anatomic etiologies. The most common form of nonallergic rhinitis in children is infectious rhinitis, which may be acute or chronic. Acute infectious rhinitis (the common cold) is caused by viruses, including rhinoviruses and coronaviruses, and typically resolves within 7 to 10 days (see Chapter 102). An average child has three to six common colds per year, with the most affected being younger children and children attending day care. Infection is suggested by the presence of sore throat, fever, and poor appetite, especially with a history of exposure to others with colds. Chronic infectious rhinosinusitis, or sinusitis, should be suspected if there is mucopurulent nasal discharge with symptoms that persist beyond 10 days (see Chapter 104). Classic signs of acute sinusitis in older children include facial tenderness, tooth pain, headache, and fever. Classic signs are usually not present in young children who may present with postnasal drainage with cough, throat clearing, halitosis, and rhinorrhea. The character of the nasal secretions with infectious rhinitis varies from purulent to minimal or absent. Coexistence of middle ear disease, such as otitis media or eustachian tube dysfunction, may be additional clues of infection.

Nonallergic, noninfectious rhinitis (formerly known as vasomotor rhinitis) can manifest as rhinorrhea and sneezing in children with profuse clear nasal discharge. Exposure to irritants, such as cigarette smoke and dust, and strong fumes and odors, such as perfumes and chlorine in swimming pools, can trigger these nasal symptoms. Nonallergic rhinitis with eosinophilia syndrome is associated with clear nasal discharge and eosinophilia on nasal smear and is seen infrequently in

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**Table 79-1** Classification of the Etiology of Rhinitis in Children

<table>
<thead>
<tr>
<th>ALLERGIC</th>
<th>NONANATOMIC</th>
<th>ANATOMIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal</td>
<td>Nonallergic, noninfectious (vasomotor) rhinitis</td>
<td>Adenoidal hypertrophy</td>
</tr>
<tr>
<td>Perennial</td>
<td>Infectious rhinosinusitis</td>
<td>CSF rhinorrhea</td>
</tr>
<tr>
<td>Episodic</td>
<td>Nonallergic rhinitis with eosinophilia</td>
<td>Choanal atresia</td>
</tr>
<tr>
<td>Physical rhinitis</td>
<td>Congenital anomalies</td>
<td></td>
</tr>
<tr>
<td>Rhinitis medicamentosa</td>
<td>Foreign body</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal polyps</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Septal deviation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Turbinate hypertrophy</td>
<td></td>
</tr>
</tbody>
</table>

CSF, Cerebrospinal fluid.
children. Cold air (skier's nose), hot/spicy food ingestion (gustatory rhinitis), and exposure to bright light (reflex rhinitis) are examples of physical rhinitis. Treatment with topical ipratropium before exposure may be helpful.

Rhinitis medicamentosa, which is due primarily to overuse of topical nasal decongestants, such as oxymetazoline, phenylephrine, or cocaine, is not a common condition in younger children. Adolescents or young adults may become dependent on these over-the-counter medications. Treatment requires discontinuation of the offending decongestant spray, topical corticosteroids, and, frequently, a short course of oral corticosteroids.

The most common anatomic problem seen in young children is obstruction secondary to adenoidal hypertrophy, which can be suspected from symptoms such as mouth breathing, snoring, hyponasal speech, and persistent rhinitis with or without chronic otitis media. Infection of the nasopharynx may be secondary to infected hypertrophied adenoid tissue.

Choanal atresia is the most common congenital anomaly of the nose and consists of a bony or membranous septum between the nose and pharynx, either unilateral or bilateral. Bilateral choanal atresia classically presents in neonates as cyclic cyanosis because neonates are preferential nose breathers. Airway obstruction and cyanosis are relieved when the mouth is opened to cry and recurs when the calming infant reattempts to breathe through the nose. Some newborns show respiratory difficulty while feeding only. Nearly half of infants with choanal atresia have other congenital anomalies as a part of the CHARGE association (coloboma, congenital heart disease, choanal atresia, retardation, genitourinary defects, ear anomalies). Unilateral choanal atresia may go undiagnosed until later in life and presents with symptoms of unilateral nasal obstruction and discharge.

Nasal polyps typically appear as bilateral, gray, glistening sacs originating from the ethmoid sinuses and may be associated with clear or purulent nasal discharge. Nasal polyps are rare in children younger than 10 years of age but, if present, warrant evaluation for an underlying disease process, such as cystic fibrosis or primary ciliary dyskinesia. Triad asthma is asthma, aspirin sensitivity, and nasal polyps with chronic or recurrent sinusitis.

Foreign bodies are seen more commonly in young children who place food, small toys, stones, or other things in their nose. The index of suspicion should be raised by a history of unilateral, purulent nasal discharge, or foul odor. The foreign body can often be seen on examination with a nasal speculum.

### Treatment

Management of allergic rhinitis is based on disease severity, impact of the disease on the patient, and the ability of the patient to comply with recommendations. Treatment modalities include allergen avoidance, pharmacologic therapy, and immunotherapy. Environmental control and steps to minimize allergen exposure, similar to preventive steps for asthma, should be implemented whenever possible (see Table 78-3).

#### Pharmacotherapy

**Intranasal corticosteroids** are the most potent pharmacologic therapy for treatment of allergic and nonallergic rhinitis. These include beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone, and triamcinolone. These topical agents work to reduce inflammation, edema, and mucus production. They are effective for symptoms of nasal congestion, rhinorrhea, itching, and sneezing but less helpful for ocular symptoms. Nasal corticosteroid sprays have been used safely in long-term therapy. Deleterious effects on adrenal function or nasal membranes have not been reported when these agents are used appropriately. The most common adverse effects include local irritation, burning, and sneezing, which occur in 10% of patients. Nasal bleeding from improper technique (spraying the nasal septum) can occur. Rare cases of nasal septal perforation have been reported.

**Antihistamines** are the medications used most frequently to treat allergic rhinitis. They are useful in treating rhinorrhea, sneezing, nasal itching, and ocular itching but are less helpful in treating nasal congestion. **First-generation antihistamines**, such as diphenhydramine and hydroxyzine, easily cross the blood-brain barrier, with sedation as the most common reported adverse effect. Use of first-generation antihistamines in children has an adverse effect on cognitive and academic function. In very young children, a paradoxical stimulatory central nervous system effect, resulting in irritability and restlessness, has been noted. Other adverse effects of first-generation antihistamines include anticholinergic effects, such as blurred vision, urinary retention, dry mouth, tachycardia, and constipation. **Second-generation antihistamines**, such as cetirizine, loratadine, desloratadine, fexofenadine, and levocetirizine, are less likely to cross the blood-brain barrier, resulting in less sedation. Cetirizine, fexofenadine, and loratadine are over-the-counter medications. Azelastine and olopatadine, topical nasal antihistamine sprays, are approved for children older than 5 years and older than 6 years, respectively.

**Decongestants**, taken orally or intranasally, may be used to relieve nasal congestion. Oral medications, such as pseudoephedrine and phenylephrine, are available either alone or in combination with antihistamines. Adverse effects of oral decongestants include insomnia, nervousness, irritability, tachycardia, tremors, and palpitations. For older children participating in sports, oral decongestant use may be restricted. Topical nasal decongestant sprays are effective for immediate relief of nasal obstruction but should be used for less than 5 to 7 days to prevent rebound nasal congestion (rhinitis medicamentosa).

Topical ipratropium bromide, an anticholinergic nasal spray, is used primarily for nonallergic rhinitis and rhinitis associated with viral upper respiratory infection. Leukotriene modifiers have been studied in the treatment of allergic rhinitis. Montelukast is approved for use in seasonal allergic rhinitis.

#### Immunotherapy

If environmental control measures and medication intervention are only partially effective or produce unacceptable adverse effects, immunotherapy may be recommended. The mechanism of action for allergen immunotherapy is complex but includes increased production of an IgG-blocking antibody, decreased production of specific IgE, and alteration of cytokine expression produced in response to an allergen challenge. Immunotherapy is effective for desensitization to pollens, dust mites, and cat and dog proteins. Use in young
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children may be limited by the need for frequent injections. Immunotherapy must be administered in a physician’s office with 20 to 30 minutes of observation after the allergen injection. Anaphylaxis may occur, and the physician must be experienced in the treatment of these severe adverse allergic reactions.

**COMPLICATIONS**
Approximately 60% of children with allergic rhinitis have symptoms of reactive airways disease/asthma (see Chapter 78). Chronic allergic inflammation leads to chronic cough from postnasal drip; eustachian tube dysfunction and otitis media; sinusitis; and tonsillar and adenoid hypertrophy, which may lead to obstructive sleep apnea. Children with allergic rhinitis may experience sleep disturbances, limitations of activity, irritability, and mood and cognitive disorders that adversely affect their performance at school and their sense of well-being.

**PROGNOSIS AND PREVENTION**
Seasonal allergic rhinitis is a common and prominent condition that may not improve as children grow older. Patients become more adept at self-management. Perennial allergic rhinitis improves with allergen control of indoor allergens.

Removal or avoidance of the offending allergen is advised. The only effective measure for minimizing animal allergens from pets is removal of the pet from the home. Avoidance of pollen and outdoor molds can be accomplished by staying indoors in a controlled environment. Air conditioning and keeping windows and doors closed lower exposure to pollen. High-efficiency particle air filters reduce exposure to allergens (e.g., pet dander). Sealing the mattress, pillow, and covers in allergen-proof encasings is the most effective strategy for reduction of mite allergen. Bedding should be washed in hot water (>130 °F) every week.

**ATOPIC DERMATITIS**

**ETIOLOGY**
Atopic dermatitis is a chronic, pruritic, relapsing inflammatory skin condition. The pathogenesis is multifactorial and involves a complex interplay of factors, including genetic predisposition, immunologic abnormalities, disturbances in skin barrier function, environmental interactions, and infectious triggers. Several genes encoding epidermal (filaggrin) or other epithelial structural proteins and genes encoding major elements of the immune system play a major role in atopic dermatitis.

Several immunoregulatory abnormalities have been described in patients with atopic dermatitis. There is an exaggerated cutaneous inflammatory response to environmental triggers, including irritants and allergens. Activated Langerhans cells in the dermis expressing surface-bound IgE stimulate T cells. In acute lesions, activated Th2 lymphocytes infiltrate the dermis. They initiate and maintain local tissue inflammation primarily through interleukin-4 (IL-4) and IL-13, which promote IgE production, and IL-5, which promotes eosinophil differentiation. As the disease progresses from an acute to a chronic phase, there is a switch from Th2 to Th1/Th0 cellular response. Chronic lesions are characterized by increased IL-12 and IL-18.

Patients with atopic dermatitis have hyperirritable skin, and many factors can cause the disease to worsen or relapse. Known triggers include anxiety and stress, climate (extremes of temperature and humidity), irritants, allergens, and infections. Approximately 35% to 40% of infants and young children with moderate to severe atopic dermatitis have coexisting food allergies. The more severe the atopic dermatitis and the younger the patient, the more likely a food allergy will be identified as a contributing factor. Egg allergy is the most common cause of food-induced eczematous reactions.

**EPIDEMIOLOGY**
The prevalence of atopic dermatitis increased twofold to threefold over the past 30 years. Approximately 15% to 20% of children and 2% to 10% of adults are affected. Atopic dermatitis often starts in early infancy. Approximately 50% of affected children show symptoms in the first year of life, and 80% of these children experience disease onset before 5 years of age. Atopic dermatitis is often the first manifestation of other atopic diseases. Approximately 80% of children with atopic dermatitis develop other allergic diseases, such as asthma or allergic rhinitis. Symptoms of dermatitis often disappear at the onset of respiratory allergy.

**CLINICAL MANIFESTATIONS**
The clinical manifestations of atopic dermatitis vary with age. In infants, atopic dermatitis involves the face, scalp, cheeks, and extensor surfaces of the extremities (Fig. 80-1). The
Allergy

Table 80-1  Criteria for the Diagnosis of Atopic Dermatitis

The diagnosis requires evidence of itchy skin (or parental report of scratching or rubbing) plus three or more of the following:
1. History of involvement of skin creases
2. History of asthma or allergic rhinitis (or history of atopic disease in a first-degree relative if child is <4 years of age)
3. History of generally dry skin in the past year
4. Onset in a child <2 years of age (criterion not used if child is <4 years of age)
5. Visible flexural dermatitis (including dermatitis affecting cheeks, forehead, and outer aspects of limbs in children <4 years of age)


Table 80-2  Differential Diagnosis of Atopic Dermatitis

<table>
<thead>
<tr>
<th>CONGENITAL DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherton syndrome</td>
</tr>
<tr>
<td>Familial keratosis pilaris</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CHRONIC DERMATOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seborrheic dermatitis</td>
</tr>
<tr>
<td>Contact dermatitis (allergic or irritant)</td>
</tr>
<tr>
<td>Nummular eczema</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Ichthyoses</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>INFECTIONS AND INFESTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scabies</td>
</tr>
<tr>
<td>HIV-associated dermatitis</td>
</tr>
<tr>
<td>Dermatophytosis</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>MALIGNANCIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous T-cell lymphoma (mycosis fungoides/Sezary syndrome)</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AUTOIMMUNE DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
</tr>
<tr>
<td>Graft-versus-host disease</td>
</tr>
<tr>
<td>Dermatomyositis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IMMUNODEFICIENCIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiskott-Aldrich syndrome</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
</tr>
<tr>
<td>Hyper-IgE syndromes</td>
</tr>
<tr>
<td>IPEX</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>METABOLIC DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinc deficiency</td>
</tr>
<tr>
<td>Pyridoxine (vitamin B6) and niacin deficiency</td>
</tr>
<tr>
<td>Multiple carboxylase deficiency, phenylketonuria</td>
</tr>
</tbody>
</table>


IPEX, Immunodeficiency polyendocrinopathy X-linked.

diaper area is spared. In older children, the rash localizes to the antecubital and popliteal flexural surfaces, head, and neck. In adolescents and adults, lichenified plaques are seen in the flexural areas (Fig. 80-2) and the head and neck regions. Itching or pruritus has a significant impact on the child and family’s quality of life; it is often worse at night, interrupting sleep. Physical examination may show hyperlinearity of the palms and soles, white dermatoglyphism, pityriasis alba, creases under the lower eyelids (Dennie–Morgan folds or Dennie lines), and keratosis pilaris (asymptomatic horny follicular papules on the extensor surfaces of the arms).

LABORATORY AND IMAGING STUDIES
The diagnosis of atopic dermatitis is based on clinical features rather than laboratory tests (Table 80-1). Skin biopsy is of little value, but it may be used to exclude other skin diseases that mimic atopic dermatitis. Skin testing or, alternatively, CAP fluorescent immunoassay (also known as FEIA) may be helpful in assessing the contribution of food or environmental allergies to disease expression.

DIFFERENTIAL DIAGNOSIS
Many conditions share signs and symptoms of atopic dermatitis (Table 80-2). Infants presenting in the first year of life with failure to thrive, recurrent skin or systemic infections, and scaling, erythematous rash should be evaluated for immunodeficiency disorders. Wiskott-Aldrich syndrome is an X-linked recessive syndrome characterized by atopic
dramatizes, thrombocytopenia, small-sized platelets, and recurrent infections. Langerhans cell histiocytosis is characterized by hemorrhagic or petechial lesions. Scabies is an intensely pruritic skin condition caused by the human scabies mite. The presence of a burrow found in the web spaces of the fingers, the flexor surfaces of the wrists, elbows, axilla, or genitals is pathognomonic. Burrows may be few in number or absent, however.

TREATMENT
The goals of therapy are to reduce the number and severity of flares and to increase the number of disease-free periods. Successful management involves skin hydration, pharmacologic therapy to reduce pruritus, and identification and avoidance of triggers. Patients with atopic dermatitis have a decrease in skin barrier function and enhanced transepidermal water loss. Daily, lukewarm baths for 15 to 20 minutes followed immediately by the application of fragrance-free emollients to retain moisture are a major component of therapy. Prevention of xerosis is important for control of pruritus and for maintaining the integrity of the epithelial barrier. Emollients should be ointments or creams, such as petrolatum, Aquaphor, Eucerin, or Cetaphil. Lotions are not as effective because they contain water or alcohol and may have a drying effect owing to evaporation. A mild nonsoap cleanser also is recommended.

Topical anti-inflammatory agents, including corticosteroids and immunomodulators, are the cornerstone of therapy for acute flares and prevention of relapses. Topical corticosteroids are used for reducing inflammation and pruritus; they are effective for the acute and chronic phases of the disease. Ointments generally are preferred over creams and lotions because of enhanced potency and skin penetration. Corticosteroids are ranked by potency into seven classes. The least potent corticosteroid that is effective should be used. Higher potency corticosteroids may be necessary to diminish the dermatitis flare but should be used for limited periods. Low-potency, nonfluorinated corticosteroids should be used on the face, intertriginous areas (groin, axilla), and large areas to reduce the risk of adverse effects. Reduced efficacy of topical corticosteroids may be related to disease severity rather than glucocorticoid resistance. Local adverse effects, such as skin atrophy and striae, and systemic adverse effects, such as hypothalamic-pituitary-adrenal axis and growth suppression and hyperglycemia, are related to the potency, length of use, and extent of medication application. In infants and younger children, the possibility of corticosteroid-induced adverse effects may be greater. When control of inflammatory lesions is achieved, most patients can be managed with emollients and low-potency topical corticosteroids.

The topical immunomodulating drugs, tacrolimus and pimecrolimus, are approved as second-line agents for short-term and intermittent treatment of atop dermatitis in patients unresponsive to or intolerant of other therapies. They are approved for use in children older than 2 years of age. These agents may be used on all body locations and are especially useful on delicate skin sites, such as the face, neck, and axilla without the adverse effect of cutaneous atrophy seen with topical corticosteroids. These medications have a potential increased cancer risk, and their long-term safety has not been established. Other less serious adverse effects include local burning and the need for sun protection.

COMPLICATIONS
Defective cell-mediated immunity leads to increased susceptibility to many bacterial, viral, and fungal infections of the skin. More than 90% of patients with atopic dermatitis have colonization of lesional skin with *Staphylococcus aureus*, and more than 75% of patients have colonization of uninvolved skin. Colonization and infection by *S. aureus* are associated with disease severity. *S. aureus* secretes exotoxins that act as a superantigen, stimulating T cells and increasing IgE production. Secondarily infected atopic dermatitis often presents as impetiginous, pustular lesions with crusting and honey-colored exudate. Topical antibiotics, such as mupirocin or retapamulin, can be used to treat local areas of infection, or oral antibiotics (such as cephalaxin, dicloxacillin, or amoxicillin-clavulanate) can be used for multifocal disease or for infection around the eyes and mouth that is difficult to treat topically. Bacterial cultures may be helpful in patients who do not respond to oral antibiotics or who have infection after multiple antibiotic courses. The incidence of community-acquired methicillin-resistant *S. aureus* is increasing.

Herpes simplex superinfection of affected skin, or *Kaposi varicelliform eruption* or *eczema herpeticum*, results in vesiculopustular lesions that appear in clusters and can become hemorrhagic. Herpes simplex virus infection can be misdiagnosed as bacterial infection and should be considered if skin lesions fail to respond to antibiotics.

In individuals with atopic dermatitis, smallpox vaccination or exposure to a vaccinated individual may lead to *eczema vaccinatum*, a localized vaccinal superinfection of affected skin. Eczema vaccinatum may progress to generalized vaccinia with vaccinal lesions appearing at sites distant from the inoculation. In patients with underlying immunodeficiencies, it may be life threatening.

Widespread infections with human papillomavirus (warts) and molluscum contagiosum are also common in children with atopic dermatitis.

PROGNOSIS
Atopic dermatitis is a chronic, relapsing skin disorder that tends to be more severe and prominent in young children. Symptoms become less severe in two thirds of children, with complete remission for approximately 20%. Early onset disease that is more widespread, concomitant asthma and allergic rhinitis, family history of atopic dermatitis, and elevated serum IgE levels may predict a more persistent course. Patients and families should be taught that a single cause and cure for atopic dermatitis is unlikely but that good control is possible for the majority of affected patients.

PREVENTION
An important step in the management of atopic dermatitis is to identify and avoid allergens and irritants. Common irritants include soaps, detergents, fragrances, chemicals, smoke, and extremes of temperature and humidity. Wool and synthetic fabrics can be irritating to the skin; 100% cotton fabric is preferred. Sweating is a recognized trigger. Fingernails should be trimmed frequently to minimize excoriation from scratching.

In infants and younger children who do not respond to the usual therapies, identifying and removing a food allergen from the diet may lead to clinical improvement. Food allergy is not
a common trigger for older patients. Other environmental exposures, such as dust mites, pet dander, or pollens, can also contribute to the disease state.

**Etiology**

Urticaria, commonly referred to as hives, is swelling of the dermis and one of the most common skin conditions seen in clinical practice. Angioedema results from a process similar to urticaria, but the reaction extends below the dermis. Urticaria and angioedema occur in response to the release of inflammatory mediators, including histamine, leukotrienes, platelet-activating factor, prostaglandins, and cytokines from mast cells present in the skin. A variety of stimuli can trigger mast cells and basophils to release their chemical mediators. Typically mast cells degranulate when cross-linking of the membrane-bound IgE occurs. Release of these mediators results in vasodilation, increased vascular leakage, and pruritus. Basophils from the circulatory system also can localize in tissue and release mediators similar to mast cells. Patients with urticaria have elevated histamine content in the skin that is more easily released.

Anaphylaxis is mediated by IgE, whereas anaphylactoid reactions result from mechanisms that are due to nonimmunologic mechanisms. Both reactions are acute, severe, and can be life threatening due to a massive release of inflammatory mediators. Urticaria, angioedema, and anaphylaxis are best considered as symptoms because they have a variety of causes.

Not all mast cell activation is IgE-mediated. Immunologic, nonimmunologic, physical, and chemical stimuli can produce degranulation of mast cells and basophils. Anaphylatoxins, C3a and C5a, can cause histamine release in a non–IgE-mediated reaction. Anaphylatoxins are generated in serum sickness (reactions to blood transfusions) (see Chapter 82) and in infectious, neoplastic, and rheumatic diseases. In addition mast cell degranulation can occur from a direct pharmacologic effect or physical or mechanical activation, such as urticaria after exposure to opiates medications, and dermatographism.

Urticaria/angioedema can be classified into three subcategories: acute, chronic, and physical. By definition acute urticaria and angioedema are hives and diffuse swelling that last less than 6 weeks. Often the history is quite helpful in eliciting the cause of the acute reaction (Table 81-1). An IgE mechanism is more commonly found in acute urticaria than in chronic urticaria. Chronic urticaria and angioedema are characterized by persistence of symptoms beyond 6 weeks (Table 81-2). Some have daily symptoms of hives and swelling, whereas others have intermittent or recurrent episodes. Chronic urticaria can be idiopathic with unknown causal

<table>
<thead>
<tr>
<th>Table 81-1</th>
<th>Etiology of Acute Urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods</td>
<td>Egg, milk, wheat, peanuts, tree nuts, soy, shellfish, fish, strawberries (direct mast cell degranulation)</td>
</tr>
<tr>
<td>Medications</td>
<td>Suspect all medications, even over-the-counter or homeopathic medications</td>
</tr>
<tr>
<td>Insect stings</td>
<td>Hymenoptera (honeybee, yellow jacket, hornets, wasp, fire ants), biting insects (papular urticaria)</td>
</tr>
<tr>
<td>Infections</td>
<td>Bacterial (group A streptococcus pharyngitis, Mycoplasma, sinusitis); viral (hepatitis B, mononucleosis [EBV], coxsackieviruses A and B); parasitic (Ascaris, Ancylostoma, Echinococcus, Fasciola, Filaria, Schistosoma, Strongyloides, Toxocara, Trichinella); fungal (dermatophytes, Candida)</td>
</tr>
<tr>
<td>Contact allergy</td>
<td>Latex, pollen, animal saliva, nettle plants, caterpillars</td>
</tr>
<tr>
<td>Transfusion reactions</td>
<td>Blood, blood products, or IVIG administration</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
</tbody>
</table>


EBV, Epstein-Barr virus; IVIG, intravenous immunoglobulin.

<table>
<thead>
<tr>
<th>Table 81-2</th>
<th>Etiology of Chronic Urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>75%–90% of cases</td>
</tr>
<tr>
<td>Physical</td>
<td>25%–50% of adult patients have IgG, anti-IgE, and anti-FcεR1 (high-affinity IgE receptor alpha chain) autoantibodies</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Angioedema</td>
<td>Hereditary angioedema (autosomal dominant inherited deficiency of Cl-esterase inhibitor)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

factors; 35% to 40% of chronic urticaria cases have an autoimmune process due to IgG autoantibodies binding directly to IgE or to the IgE receptor. Physical urticaria and angioedema are characterized by known eliciting external factors that may include pressure, cold, heat, exercise, or exposure to sun or water.

The most common physical urticaria is dermatographism, affecting 2% to 5% of persons. Dermatographism means “writing on the skin” and is easily diagnosed by firmly scratching the skin with a blunt point, such as the wooden tip of a cotton swab or tongue depressor. It is characterized by an urticarial reaction localized to the site of skin trauma. It has been suggested that trauma induces an IgE-mediated reaction causing histamine to be released from the mast cells.

Cholinergic urticaria, characterized by the appearance of 1- to 3-mm wheals surrounded by large erythematous flares after an increase in core body temperature, occurs commonly in young adults. Lesions may develop during strenuous exercise, after a hot bath, or emotional stress. The lack of airway symptoms differentiates it from exercise-induced anaphylaxis.

Cold urticaria occurs with exposure to cold and may develop within minutes on areas directly exposed to cold or on rewarming of the affected parts. Ingestion of cold drinks may result in lip swelling. Cold urticaria syndromes can be categorized into acquired and familial disorders. Severe reactions resulting in death can occur with swimming or diving into cold water. Patients must never swim alone, avoid total body exposure to cold, and have injectable epinephrine available.

Hereditary angioedema (HAE) is an autosomal dominant disease due to a deficiency of Cl inhibitor. The genetic defect may be caused by spontaneous mutation; approximately 25% of cases occur in patients without any family history. The disease is estimated to affect approximately 10,000 persons in the United States. It is characterized by unpredictable, recurrent attacks of episodic swelling that involves the face, peripheral extremities, genitalia, abdomen, oropharynx, and pharynx. Episodes are often triggered by trauma. Asphyxiation from laryngeal attacks is a significant cause of mortality. Patients with HAE rarely have urticaria associated with angioedema. The majority of patients (85%) have type I disease, which is due to decreased production of Cl-esterase inhibitor. A minority of patients (15%) have type II disease, which is due to production of dysfunctional Cl-esterase inhibitor. A low C4 level serves as an initial screening test. Patients with reduced C4 should have quantitative and functional levels of Cl-esterase inhibitor measured. C2 levels are low during an acute attack. Type III HAE patients have normal laboratory evaluation. These patients are more typically females, but some males have been reported in the literature. Three products are approved to treat HAE attacks: Berinert (for acute facial or abdominal attacks in children ≥13 years old), Kalbitor (for acute attacks in children ≥16 years of age), and Cinryze (for prophylaxis in adolescents and adults).

Anaphylactic reactions are type I, IgE-mediated reactions and result from many causes (Table 81-3). Cross-linking of the IgE molecule with the allergen leads to IgE receptor activation on the mast cell and basophil and release of mediators, including histamine, tryptase, tumor necrosis factor, platelet-activating factor, leukotrienes, prostaglandins, and cytokines. Other cell types involved in the reactions include monocytes, macrophages, eosinophils, neutrophils, and platelets. The mediator release results in the clinical picture of anaphylaxis.

### Table 81-3: Common Causes of Anaphylaxis in Children

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foods</strong></td>
<td>Peanuts, tree nuts, milk, eggs, fish, shellfish, seeds, fruits, grains</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td>Penicillins, cephalosporins, sulfonamides, nonsteroidal anti-inflammatory drugs, opiates, muscle relaxants, vancomycin, dextran, thiamine, vitamin B12, insulin, thiopental, local anesthetics</td>
</tr>
<tr>
<td><strong>Hymenoptera venom</strong></td>
<td>Honeybee, yellow jacket, wasp, hornet, fire ant</td>
</tr>
<tr>
<td><strong>Latex</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Allergen immunotherapy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
<td>Food-specific exercise, postprandial (nonfood-specific) exercise</td>
</tr>
<tr>
<td><strong>Vaccinations</strong></td>
<td>Tetanus, measles, mumps, influenza</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>Radiographic media, immunoglobulin, cold temperature, chemotherapeutic agents, blood products, inhalants</td>
</tr>
</tbody>
</table>

Anaphylactoid reactions are due to nonimmunologic mechanisms. Mast cells and basophils can be activated by direct, nonspecific stimulation, although the exact underlying mechanism is unknown. Reactions to agents, such as opiates and radiographic contrast material, are classic examples. Complement system activation also can result in mast cell and basophil activation. Anaphylatoxins, C3a and C5a, are named because of their ability to trigger mediator release and are generated in serum sickness. The most common cause of this type of reaction is transfusion with blood products. There are other causes of anaphylactoid reactions for which the mechanism has not been clarified.

### EPIDEMIOLOGY

Urticaria and angioedema are common skin conditions affecting 15% to 25% of individuals at some point in their lives. Most cases of urticaria are self-limited, but, for some patients, they are chronic. In approximately 50% of patients, urticaria and angioedema occur together. In the remaining 50%, 40% have urticaria alone and 10% have angioedema alone. The incidence of anaphylaxis in children is unknown.

### CLINICAL MANIFESTATIONS

Raised, erythematous lesions with pale centers that are intensely pruritic characterize urticaria, commonly called hives (Fig. 81-1). The lesions vary in size and can occur anywhere on...
the body. Typically urticaria arises suddenly and may resolve within 1 to 2 hours or may persist for 24 hours. **Angioedema** is a similar process that involves the deeper dermis or subcutaneous tissue, with swelling as the principal symptom. Generally angioedema is not pruritic, may be mildly painful, and persists for longer than 24 hours. In rare cases it may become life threatening if swelling affects the upper airway.

The clinical manifestations of **anaphylaxis** and **anaphylactoid** reactions are the same for children and adults. The signs and symptoms vary and can range from mild skin findings to a fatal reaction. Ninety percent of patients present with cutaneous symptoms, including urticaria, angioedema, flushing, and warmth; the absence of dermal symptoms does not exclude the diagnosis of anaphylaxis. Other affected organ systems include the respiratory tract (rhinorrhea, oropharyngeal edema, laryngeal edema, hoarseness, stridor, wheezing, dyspnea, and asphyxiation), cardiovascular system (tachycardia, hypotension, shock, syncope, and arrhythmias), gastrointestinal tract (nausea, abdominal pain, crampy diarrhea, vomiting), and neurologic system (syncope, seizure, dizziness, and a sense of impending doom). The severity of an anaphylactic reaction is often proportionate to the speed of symptom onset.

### LABORATORY AND IMAGING STUDIES

The laboratory evaluation of patients with urticaria and angioedema must be tailored to the clinical situation. Acute urticaria and angioedema do not require specific laboratory evaluation except to document the suspected cause. For patients with chronic urticaria and angioedema, laboratory evaluation should be performed to exclude underlying diseases (Table 81-4). Patients with recurrent angioedema without urticaria should be evaluated for HAE (Table 81-5).

Measurement of the mast cell mediators, histamine and tryptase, may be helpful when the diagnosis of anaphylaxis is in question. A tryptase level is a more useful test because histamine is released quickly, has a short half-life, and is often difficult to detect in the serum. Serum tryptase levels peak 1 to 1.5 hours after anaphylaxis. Elevated levels may be helpful in establishing the diagnosis, but normal tryptase levels do not rule out the diagnosis. It is best to measure a serum tryptase level 1 to 2 hours after the onset of symptoms. It also can be ordered retrospectively on stored serum that is less than 2 days old.

### DIFFERENTIAL DIAGNOSIS

The diagnosis of urticaria and angioedema is straightforward; finding the etiology may be more difficult. Other dermatologic conditions can mimic urticaria. **Erythema multiforme** has target-shaped, erythematous, macular or papular lesions that may look similar to urticaria, but the lesions are fixed and last for several days. Other dermatologic diseases include dermatitis herpetiformis and bullous pemphigoid, which are quite pruritic, and early on, the lesions may resemble urticaria. Mastocytosis is characterized by mast cell infiltration of various organs, including the skin. Some patients have skin lesions similar in appearance to urticaria rather than the classic urticaria pigmentosa. Urticaria pigmentosa appears as hyperpigmented, red-brown macules, which may coalesce.
When these lesions are stroked, they urticate, which is called the Darier sign. A rare disorder that should be included in the differential diagnosis of urticaria is Muckle-Wells syndrome. It is an autosomal dominant disorder characterized by episodic urticaria presenting in infancy, with sensorineural deafness, amyloidosis, arthralgias, and skeletal abnormalities. Another rare syndrome is Schnitzler syndrome, which is characterized by chronic urticaria, macroglobulinemia, bone pain, anemia, fever, fatigue, and weight loss. Urticarial vasculitis is a small vessel vasculitis with histologic features of a leukocytoclastic response. The main distinguishing feature is that the lesions last longer than 24 hours, may be tender, and leave behind skin pigmentation. Skin biopsy is required for definitive diagnosis.

The diagnosis of anaphylaxis is usually apparent from the acute and often dramatic onset of multisystem involvement of the skin, respiratory tract, and cardiovascular system. Sudden cardiovascular collapse in the absence of cutaneous symptoms suggests vasovagal collapse, seizure disorder, aspiration, pulmonary embolism, or myocardial infarction. Laryngeal edema, especially with abdominal pain, suggests HAE. Many patients with anaphylaxis are initially thought to have septic shock (see Chapter 40).

**TREATMENT**

Avoidance of triggering agents is important in the management of urticaria and angioedema. The mainstay of pharmacologic treatment is H1 antihistamines. Second-generation H1 antihistamines, such as cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine, are preferred because they have fewer adverse effects. If a second-generation H1 antihistamine, by itself, does not provide adequate relief, the next step is to add a sedating H1 antihistamine at bedtime or as needed. Additional pharmacologic therapies, such as corticosteroids, antihistamines, H2-receptor antagonists, and bronchodilators, may be given to improve symptoms. Up to 20% of people with anaphylaxis have biphasic or protracted anaphylaxis.

A person with biphasic anaphylaxis has both early- and late-phase reactions. The biphasic reaction is a recurrence of anaphylactic symptoms after an initial remission, occurring within 8 to 72 hours after the initial reaction. A person with protracted anaphylaxis has signs and symptoms that persist for hours or even days despite treatment, although this is rare.

**PREVENTION**

Prevention of urticaria, angioedema, and anaphylaxis focuses on avoidance of known triggers. A referral to an allergy specialist for a thorough history, diagnostic testing, and recommendations for avoidance is suggested for patients following severe reactions or anaphylaxis. Skin testing and serum IgE-specific testing are available for foods, inhalants, insect venoms, drugs (penicillin), vaccines, and latex. Educating the patient and family members about the signs and symptoms of anaphylaxis and using self-administered epinephrine early result in better outcomes. Fatal anaphylaxis has occurred despite timely and appropriate treatment. A MedicAlert bracelet with appropriate information should be worn. Medications such as β-blockers, angiotensin-converting enzyme inhibitors, and monoamine oxidase inhibitors should be discontinued because they may exacerbate anaphylaxis or interfere with its treatment.
Immune complexes were first described after administration of drugs, foreign proteins, or infections. The symptoms of serum sickness typically occur 7 to 21 days after the administration of drugs, foreign proteins, or infections. Symptom onset may be more rapid (within 1 to 4 days) in previously sensitized individuals. The classic clinical manifestations consist of fever, polyarthralgias, lymphadenopathy, and cutaneous symptoms. Cutaneous lesions vary and may include urticaria, angioedema, erythema multiforme, morbilliform rash, and a palpable purpura or serpiginous rash at the interface of the dorsal and palmar or plantar aspects of the hands and feet. Carditis, glomerulonephritis, Guillain-Barre syndrome, encephalomyelitis, and peripheral neuritis are rare complications.

**LABORATORY AND IMAGING STUDIES**

Laboratory tests may show an elevated erythrocyte sedimentation rate, presence of circulating immune complexes, and depressed complement (C3 and C4) levels. Skin biopsy
SPECIMENS show immune deposits of IgM, IgA, IgE, or C3. Hematuria or proteinuria or both may be present. The diagnosis is established by history of exposure to an inciting cause, characteristic clinical manifestations, and laboratory testing showing circulating immune complexes and depressed complement levels.

TREATMENT AND PREVENTION
Serum sickness is self-limited and resolves within 1 to 2 weeks; therefore, treatment is symptomatic relief. Antihistamines may be administered to relieve pruritus. Nonsteroidal anti-inflammatory drugs are given for fever and joint pain, and, if necessary, prednisone (1 to 2 mg/kg orally daily) is administered with a tapering dose. Allergy skin testing does not predict the likelihood of serum sickness development.

The primary means of prevention is to avoid exposure to the implicated cause.

INSECT ALLERGIES

ETIOLOGY
Systemic allergic reactions usually result from stinging insects of the order Hymenoptera, which include apids (honeybee and bumblebee), vespids (yellow jacket, wasp, yellow-face, and white-face hornets), and formicids (fire and harvester ants). Honeybees have a barbed stinger that remains embedded after a sting. Yellow jackets are responsible for most allergic reactions in most parts of the United States, whereas wasps are the most frequent cause of sting reactions in Texas. Fire ants are found in the southeastern and south central United States.

Biting insects rarely cause anaphylaxis. Anaphylaxis has been described, however, after the bites of a kissing bug (Triatoma), bed bug, blackfly, and deerfly. Large local reactions from biting insects, such as mosquitoes, fleas, and flies, are a more common occurrence. The reaction appears urticarial and is caused by the salivary secretions deposited by the biting insect and does not represent an allergic response.

EPIDEMIOLOGY
Insect sting allergy may develop at any age and typically manifests after several uneventful stings. Although children are stung more frequently than adults, systemic allergic reactions occur in only about 1% of children and 3% of adults. Reactions in adults are generally more severe than in children and can result in death. Large local reactions to insect stings are more common in children, with an estimated incidence of 20% for children and 10% for adults.

CLINICAL MANIFESTATIONS
The diagnosis of insect sting allergy is dependent on the history of the reaction and the presence of venom-specific IgE. Normal reactions to insect stings, which are observed in 90% of children, include localized pain, swelling, and erythema at the sting site that usually subside within 24 hours. Large local reactions occur in approximately 10% of patients. They are usually late-phase, IgE-mediated reactions, with large swelling, contiguous to the sting site that develops over 24 to 48 hours and resolves within 2 to 7 days. Virtually all individuals with large local reactions have similar reactions with subsequent stings. Systemic reactions are IgE mediated and occur in 1% of children. They can be mild and nonlife-threatening with cutaneous symptoms only or life-threatening with respiratory, cardiovascular, or neurologic symptoms of anaphylaxis (see Chapter 81). Toxic reactions may result if a person receives a large number of stings (50 to 100). Symptoms include malaise, nausea, and emesis resulting from the toxic effects of the venom. Unusual reactions, such as vasculitis, nephrosis, neuritis, serum sickness, and encephalitis, rarely are associated with insect stings (Table 83-1).

LABORATORY AND IMAGING STUDIES
A positive skin test to Hymenoptera venom extract demonstrates the presence of venom-specific IgE in the context of a positive sting reaction history and helps identify specific insects to which an individual is allergic. Venom-specific IgE antibodies also may be measured by in vitro serum tests. Both testing methods should be considered complementary because neither test alone detects all patients with insect sting allergy. Future reactions correlate more with past individual patterns than the level of sensitivity of venom skin testing or serum specific IgE testing.

DIFFERENTIAL DIAGNOSIS
A history of an immediate systemic reaction is necessary before venom testing and immunotherapy should be considered.
Identification of the offending insect is often unreliable. Honeybee stings may be identified by the stinger that remains in place. Vespid stings are usually unprovoked and occur at summer’s end when the insects are more aggressive.

TREATMENT
Local reactions should be treated by cleaning the site, applying cold compresses, and administering oral antihistamines and analgesics. Occasionally large local reactions may be mistaken for cellulitis. Infection is unlikely if reaction occurs within 24 to 48 hours after a sting. Treatment is with an oral corticosteroid for 4 to 5 days rather than oral antibiotics.

Treatment of systemic reactions is guided by the severity of the reaction, but epinephrine is the cornerstone of therapy and should be administered without delay. Antihistamines may be administered concurrently with epinephrine. Corticosteroids should be given to prevent recurrent or prolonged symptoms. For severe reactions, intravenous fluids and epinephrine, oxygen, and respiratory support in an intensive care unit may be needed. After acute care of a systemic sting reaction, patients should be provided an epinephrine autoinjector, referral to an allergist/immunologist, and instructions on prevention of insect stings.

COMPLICATIONS
At least 50 to 100 fatalities per year in the United States are attributed to insect sting reactions. Most deaths (80%) occur in adults older than 40 years of age, and only 2% occur in individuals younger than 20 years of age. Approximately one half of deaths occur in persons without any history of a prior sting reaction.

PROGNOSIS
Successfully avoiding the stinging insect is the most important prognostic factor. More than 85% of adults who complete 5 years of immunotherapy tolerate challenge stings without systemic reactions for 5 to 10 years after completion.

PREVENTION
Measures to reduce the chance of accidental sting include exterminating infested areas; not eating or drinking outdoors; wearing long pants and shoes; and avoiding brightly colored clothing, fragrances, or hairspray when outdoors. Common insect repellents are not effective against Hymenoptera.

Current recommendations are to administer venom immunotherapy to individuals who have had a systemic life-threatening reaction from an insect sting and have positive venom skin tests or elevated levels of venom-specific IgE. All persons with a history of systemic reactions to insects should be instructed in the use of an epinephrine autoinjector and encouraged to wear a MedicAlert bracelet. Children younger than 16 years of age who have had only a cutaneous reaction generally do not require immunotherapy because their prognosis is benign and can be managed with the availability of epinephrine.

ADVERSE REACTIONS TO FOODS

ETIOLOGY AND EPIDEMIOLOGY
An adverse reaction to food is a generic description of any untoward reaction after food ingestion, including toxic reactions such as food poisoning and nontoxic reactions, which can be subdivided further into nonimmune and immune reactions. Lactose intolerance is a nonimmune reaction. Food allergy or hypersensitivity reactions encompass immune reactions to food and can be divided further into IgE-mediated reactions, which are typically rapid in onset, and non-IgE-mediated reactions.

Oral tolerance is the process of suppression of the immune response to the array of dietary elements ingested daily. Food allergy or hypersensitivity reactions are the result of immune reactions to glycoproteins and develop in genetically predisposed individuals. In children, cow’s milk, eggs, peanuts, soybean, wheat, tree nuts, fish, and shellfish cause 90% of IgE-mediated reactions. In older children and adults, peanuts, tree nuts, fish, and shellfish account for most reactions. Exposure to the allergenic food protein results in cross-linking of the IgE receptor found on the mast cells and basophils, which become activated and degranulate, releasing numerous potent mediators and cytokines. Non-IgE-mediated reactions typically occur hours to days after the allergen ingestion and are manifest as gastrointestinal symptoms. A cell-mediated immune mechanism may be responsible.

Approximately 6% to 8% of children are affected with food allergy. In adults this declines to 1% to 2%.

CLINICAL MANIFESTATIONS
Symptoms of hypersensitivity reactions vary from involvement of the skin, gastrointestinal tract, and respiratory tract to anaphylaxis. Non-IgE-mediated food allergy typically presents during infancy as proctitis/proctocolitis, enteropathy, or enterocolitis (Table 84-1).

LABORATORY AND IMAGING STUDIES
In acute IgE reactions, skin prick allergy testing and serum testing to foods may help confirm the suspected food allergy.

DIAGNOSIS
A careful history focuses on symptoms, the time interval from ingestion to onset of symptoms, the quantity of food necessary to evoke the reaction, the most recent reaction, patterns of reactivity, and associated factors such as exercise and medication use. Skin prick testing can be performed to confirm IgE-mediated food allergies. A negative skin test virtually excludes an IgE-mediated reaction (unless the clinical history suggests a severe reaction after an isolated ingestion of the food). A positive skin test indicates sensitization but does not prove clinical reactivity and must be interpreted, based on the history.
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>AGE GROUP</th>
<th>CHARACTERISTICS</th>
<th>DIAGNOSIS</th>
<th>PROGNOSIS/COURSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgE-MEDIATED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute gastrointestinal hypersensitivity</td>
<td>Any</td>
<td>Onset: minutes to 2 h Nausea, abdominal pain, emesis, diarrhea</td>
<td>History, positive PST, and/or serum food-IgE</td>
<td>Variable, food-dependent Milk, soy, egg, and wheat typically outgrown Peanut, tree nuts, seeds, and shellfish typically persist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Typically in conjunction with cutaneous and/or respiratory symptoms</td>
<td>Confirmatory OFC</td>
<td></td>
</tr>
<tr>
<td>Pollen-food allergy syndrome (oral allergy syndrome)</td>
<td>Any, most common in young adults (50% of birch pollen adults)</td>
<td>Immediate symptoms on contact of raw fruit with oral mucosa Pruritus, tingling, erythema or angioedema of the lips, tongue, oropharynx, throat pruritus/tightness</td>
<td>History, positive PST with raw fruits or vegetables; OFC-positive with raw fruit; negative with cooked</td>
<td>Severity of symptoms may vary with pollen season Symptoms may improve with pollen immunotherapy in subset of patients</td>
</tr>
<tr>
<td><strong>IgE- AND/OR NON-IGE-MEDIATED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic eosinophilic esophagitis</td>
<td>Any, but especially infants, children, adolescents</td>
<td>Children: chronic/intermittent symptoms of gastroesophageal reflux, emesis, dysphagia, abdominal pain, irritability Adults: abdominal pain, dysphagia, food impaction</td>
<td>History, positive PST, and/or food-IgE in 50%, but poor correlation with clinical symptoms Patch testing may be of value Elimination diet and OFC Endoscopy, biopsy provides conclusive diagnosis and response to treatment information</td>
<td>Variable, not well established, improvement with elimination diet within 6–8 wk Elemental diet may be required Often responds to swallowed topical steroids</td>
</tr>
<tr>
<td>Allergic eosinophilic gastroenteritis</td>
<td>Any</td>
<td>Chronic/intermittent abdominal pain, emesis, irritability, poor appetite, failure to thrive, weight loss, anemia, protein-losing gastroenteropathy</td>
<td>History, positive PST, and/or food-IgE in 50%, but poor correlation with clinical symptoms Patch testing may be of value Elimination diet and OFC Endoscopy, biopsy provides conclusive diagnosis and response to treatment information</td>
<td>Variable, not well established, improvement with elimination diet within 6–8 wk Elemental diet may be required</td>
</tr>
<tr>
<td><strong>NON-IgE-MEDIATED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic proctocolitis</td>
<td>Young infants (&lt;6 mo), frequently breastfed</td>
<td>Blood-streaked or heme-positive stools, otherwise healthy-appearing</td>
<td>History, prompt response (resolution of gross blood in 48 h) to allergen elimination Biopsy conclusive but not necessary in vast majority</td>
<td>Majority able to tolerate milk/soy by 1 yr of age</td>
</tr>
<tr>
<td>Food protein-induced enterocolitis syndrome</td>
<td>Young infants</td>
<td>Chronic emesis, diarrhea, failure to thrive on chronic exposure On reexposure following a period of elimination, subacute, repetitive emesis, dehydration (15% shock), diarrhea Breastfeeding protective</td>
<td>History, response to dietary restriction OFC</td>
<td>Most resolve in 1–3 yr</td>
</tr>
<tr>
<td>Dietary protein-induced enteropathy</td>
<td>Young infants</td>
<td>Protracted diarrhea, (steatorrhea), emesis, failure to thrive, anemia in 40%</td>
<td>History, endoscopy, and biopsy Response to dietary restriction</td>
<td>Most resolve in 1–2 yr</td>
</tr>
<tr>
<td>Celiac disease (gluten-sensitive enteropathy)</td>
<td>Any</td>
<td>Chronic diarrhea, malabsorption, abdominal distention, flatulence, failure to thrive or weight loss May be associated with oral ulcers and/or dermatitis herpetiformis</td>
<td>Biopsy diagnostic: villus atrophy Screening with serum IgA antitissue transglutaminase and antigliadin Resolution of symptoms with gluten elimination and relapse on oral challenge</td>
<td>Lifelong</td>
</tr>
</tbody>
</table>

An in vitro serum specific IgE assay can be used to help confirm clinical allergy as well. Many allergists and laboratories regard the ImmunoCAP system as the method of choice. This method uses a quantitative fluorescent immunoassay, which is more sensitive than other assays; this method also has improved specificity and reproducibility compared to other assays. These tests provide supplementary information to skin tests. Researchers have tried to determine concentrations of food-specific IgE at which clinical reactions are highly likely to occur (Table 84-2). Patients with allergen specific IgE levels greater than 95% of the predictive value may be considered allergic, and there is no need for an oral food challenge. Monitoring the allergen specific IgE level may be helpful in predicting whether a child has outgrown the food allergy. Oral food challenges remain the standard of diagnosis and can be performed to determine whether a child can eat the food safely.

### PROGNOSIS AND PREVENTION

Hypersensitivity to egg, milk, wheat, and soy resolves within the first 5 years of life in approximately 80% of children. Sensitivity to certain foods, such as peanuts, tree nuts, fish, and shellfish, tends to be lifelong. However, 20% of children who manifested peanut allergy younger than 2 years of age may outgrow it.

Avoidance of the suspect food is crucial. Careful reading of food labels is a priority. A MedicAlert bracelet with appropriate information should be worn. The Food Allergy Research & Education organization (www.foodallergy.org) is a useful educational resource for families and physicians.

Recommendations for prevention of allergic diseases aimed at the high-risk newborn who has not manifested atopic disease include (1) breastfeeding for the first 4 to 6 months or (2) using a hydrolyzed casein formula (e.g., Alimentum or Nutramigen) or partially hydrolyzed whey formula (e.g., Good Start) (if supplementing) for the first 4 to 6 months and delaying introduction of solid foods until 4 to 6 months of age. Other approaches, such as maternal avoidance diets during pregnancy and during lactation, as well as avoidance of allergenic foods for infants beyond 6 months of age, are unproven.

### ADVERSE REACTIONS TO DRUGS

#### ETIOLOGY

An adverse drug reaction is defined as an unwanted, negative consequence associated with the use of a drug or biologic agent. Drug reactions can be classified as immunologic or nonimmunologic reactions (Table 85-1). Nearly 75% to 80% of adverse drug reactions are caused by a predictable, nonimmunologic mechanism, and between 5% and 10% of all drug reactions are explained by an immune-mediated mechanism. The remaining drug reactions are caused by an unpredictable mechanism, which may or may not be immune-mediated. The Gell and Coombs classification can be used to describe some drug-induced allergic reactions (see Table 77-1). Many drug reactions cannot be classified because the exact immune mechanism has not been defined. Most drugs cannot elicit an immune response because of their small size; rather, the drug or a metabolite acts as a hapten and binds to larger molecules, such as tissue or serum proteins, a process called haptenation. The multivalent hapten-protein complex forms a new immunogenic epitope that elicits T- and B-lymphocyte responses.

#### EPIDEMIOLOGY

Drug reactions to penicillins and cephalosporins are the most common allergic drug reactions encountered in the pediatric population. Approximately 6% to 10% of children are labeled as penicillin allergic. Risk factors for drug reactions include previous drug exposure, increasing age (>20 years of age), parenteral or topical administration, higher dose, intermittent

---

**Table 84-2** Interpretation of Serum IgE Antibody Concentrations

<table>
<thead>
<tr>
<th>FOOD</th>
<th>FOOD-SPECIFIC IgE ANTIBODY CONCENTRATIONS AT OR ABOVE WHICH CLINICAL REACTIONS ARE HIGHLY LIKELY (kUa/L)</th>
<th>POSITIVE PREDICTIVE VALUE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>7</td>
<td>98</td>
</tr>
<tr>
<td>≤2 yr of age</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>Milk</td>
<td>15</td>
<td>95</td>
</tr>
<tr>
<td>≤2 yr of age</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>Peanut</td>
<td>14</td>
<td>95–100</td>
</tr>
<tr>
<td>Fish</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Soybean</td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>74</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>≈15</td>
<td>≈5</td>
</tr>
</tbody>
</table>


**Table 85-1** Concentrations at or above which clinical reactions are highly likely

<table>
<thead>
<tr>
<th>FOOD</th>
<th>Concentration (kUa/L)</th>
<th>Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>7</td>
<td>98</td>
</tr>
<tr>
<td>≤2 yr of age</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>Milk</td>
<td>15</td>
<td>95</td>
</tr>
<tr>
<td>≤2 yr of age</td>
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<td>95</td>
</tr>
<tr>
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<td>14</td>
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</tr>
<tr>
<td>Fish</td>
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<td>100</td>
</tr>
<tr>
<td>Soybean</td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>Wheat</td>
<td>26</td>
<td>74</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>≈15</td>
<td>≈5</td>
</tr>
</tbody>
</table>
repeated exposure, and a genetic predisposition of slow drug metabolism. An atopic background does not predispose an individual to the development of drug reactions but may indicate a greater risk of serious reaction.

**CLINICAL MANIFESTATIONS**

Allergic reactions can be classified as **immediate (anaphylactic) reactions**, which occur within 60 minutes of drug administration; **accelerated reactions**, which begin 1 to 72 hours after drug administration; and **late reactions**, which occur after 72 hours. The most common form of adverse drug reaction is cutaneous. Accelerated reactions are usually dermatologic or serum sickness reactions. Late reactions include desquamating dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and serum sickness.

**LABORATORY AND IMAGING STUDIES**

Skin testing protocols are standardized for penicillin and are well described for other agents, such as local anesthetics, muscle relaxants, vaccines, and insulin. Positive skin testing to such reagents confirms the presence of antigen-specific IgE and supports the diagnosis of a type I hypersensitivity reaction in the appropriate clinical setting.

**DIFFERENTIAL DIAGNOSIS**

The broadest experience with managing adverse drug reactions is with penicillin. Penicillin allergy should be evaluated when the individual is well and not in acute need of treatment. Penicillin skin testing is helpful for IgE-mediated reactions because of its negative predictive value; only 1% to 3% of patients with negative skin tests have a reaction, which is mild, when re-exposed to penicillin. Skin testing for penicillin should be performed using the major determinant, penicilloyl polylysine (available as Pre-Pen), and minor determinants, which include penicillin G, penicilloate, and penilloate.

Skin testing to penicillin does not predict non-IgE-mediated reactions. For patients with a history consistent with serum sickness or desquamative-type reactions, skin testing should not be performed, and penicillin should be avoided indefinitely.

The risk of a child who has reacted positively to penicillin skin testing suffering an allergic reaction to a cephalosporin antibiotic is less than 2%. It is believed that the first-generation cephalosporins (e.g., cephalexin) are more likely than second-generation (e.g., cefuroxime) or third-generation (cefpodoxime) cephalosporins to be cross-reactive. This is due to the chemical similarity of side chains of the β-lactam ring between penicillin and first-generation cephalosporins.

**TREATMENT**

If penicillin skin testing is positive, penicillin should be avoided, and an alternative antibiotic should be used. If there is a definite need for penicillin, desensitization can be accomplished by administration of increasing amounts of drug over a short time in a hospital setting. The exact mechanism of desensitization is unclear; however, it is thought to render
mast cells unresponsive to the drug. To maintain desensitization, the drug must be given at least twice daily. If the drug is stopped for longer than 48 hours, the patient is no longer desensitized, and the same protocol must be repeated before repeated antibiotic use.

For other antibiotics, the relevant allergenic determinants produced by metabolism or degradation are not well defined. Skin testing to the native antibiotic in nonirritating concentrations can be performed. A negative response does not exclude allergy; however, a positive response suggests the presence of IgE-mediated allergy. In the case of a negative skin test response, a graded challenge or test dose may be administered, depending on the clinical history of the reaction. Patients who have experienced Stevens-Johnson syndrome, toxic epidermal necrolysis, or serum sickness should not be challenged.

COMPLICATIONS
Anaphylaxis is the most serious complication of allergic drug reactions and can result in death (see Chapter 81).

PROGNOSIS
Most drug reactions do not seem to be allergic in nature. Repeated, intermittent exposure during childhood or early adulthood contributes to an increased incidence of adverse drug reactions in adults.

PREVENTION
Avoidance of the suspect drug is paramount. A MedicAlert bracelet with appropriate information should be worn. One of the most common concerns in regard to allergic drug reactions is cross-reactivity between penicillin and cephalosporins. In children with a history of penicillin allergy, it is important to determine whether they are truly allergic by skin testing to penicillin, using the major and minor determinants. If the penicillin skin test is negative, there is not an increased risk of an allergic reaction to cephalosporins. A positive penicillin skin test leads to an alternate non-cross-reacting antibiotic, a graded challenge to the required cephalosporin under appropriate monitoring, or desensitization to the required cephalosporin.

For children with a history of a cephalosporin allergy who require another cephalosporin, two approaches may be considered: a graded challenge with a cephalosporin that does not share the same side chain determinant, or skin testing with the same or a different cephalosporin. A positive response suggests the presence of IgE-mediated allergy, and the value of a negative test is unknown. Skin testing with cephalosporins has not been standardized or validated.

Suggested Reading
The rheumatic diseases (collagen vascular or connective tissue diseases) of childhood are characterized by autoimmunity and inflammation, which may be localized or generalized. The classic rheumatic diseases of children include juvenile idiopathic arthritis (JIA), formerly called juvenile rheumatoid arthritis, systemic lupus erythematosus (SLE), and juvenile dermatomyositis (JDM). Vasculitis is a component of many rheumatic diseases. Musculoskeletal pain syndromes are a set of overlapping conditions characterized by poorly localized pain involving the extremities. Scleroderma, Behçet syndrome, and Sjögren syndrome are rare in childhood. The differential diagnosis of rheumatologic disorders typically includes infections, postinfectious processes, and malignancies (Table 86-1).

**HISTORY**

The history can identify symptoms that reflect the source of the inflammation, including whether it is localized or systemic. Symptoms of systemic inflammation tend to be nonspecific. Fever, caused by cytokine release, can take many forms. A hectic fever, without periodicity or pattern, is commonly found in vasculitides such as Kawasaki disease but also occurs in children with underlying infection. Certain illnesses, such as systemic-onset JIA, produce a patterned fever with regular temperature spikes once or twice a day. Other rheumatic illnesses cause low-grade fevers. Charting the child's fever pattern, particularly in the absence of antipyretics, is useful. Rashes occur in many forms (see Table 86-1). Other systemic symptoms (malaise, anorexia, weight loss, and fatigue) can vary from mild to debilitating.

Symptoms of localized inflammation vary depending on the involved site. Arthritis, or inflammation of the synovium (synovitis), leads to joint pain, swelling, and impaired ability to use the affected joint. Morning stiffness or gelling is described. The child may be slow to arise in the morning and may have a limp. Children may refrain from usual activities and athletics. Enthesitis is inflammation at the insertion of a ligament to a bone. Serositis, inflammation of serosal lining such as pleuritis, pericarditis, or peritonitis, gives rise to chest pain, shortness of breath, or abdominal pain. Myositis, inflammation of the muscle, may lead to symptoms of muscle pain, weakness, or difficulty performing tasks of daily living. Vasculitis, inflammation of the blood vessels, leads to non-specific symptoms of rash (petechiae, purpura) and edema when small vessels deep in the papillary dermis are involved; involvement of medium-sized vessels results in a circumscribed tender nodule.

**PHYSICAL EXAMINATION**

A thorough history and physical examination is frequently sufficient to narrow the differential diagnosis and elicit the diagnosis. The child's overall appearance, evidence of growth failure, or failure to thrive may point to a significant underlying inflammatory disorder. The head and neck examination may show evidence of mucosal ulceration, seen in diseases such as SLE. The eye examination may show pupillary irregularity and synchiae from uveitis or the conjunctivitis of Kawasaki disease. Diffuse lymphadenopathy may be found and is nonspecific. The respiratory and cardiac examinations may show pericardial or pleural friction rubs, indicating serositis. Splenomegaly or hepatomegaly raises suspicion of activation of the reticuloendothelial system that occurs in systemic-onset JIA or SLE.

The joint examination is crucial for the diagnosis of arthritis and may identify evidence of joint swelling, effusion, tenderness, and erythema from increased blood flow. Joint contractures may be seen. The joint lining, or synovium, may be thickened from chronic inflammation. Activation of epiphyseal growth plates in an area of arthritis can lead to localized bony proliferation and limb length discrepancies. Conversely inflammation at sites of immature growth centers may lead to maldevelopment of bones, such as the carpals or tarsals, resulting in crowding, or the temporomandibular joints, resulting in micrognathia. A rash or evidence of underlying skin disorders, such as skin thickening from scleroderma or sclerodactyly, may be noted. Chronic Raynaud phenomenon may result in nail-fold capillary changes, ulceration, or digital tuft wasting.

**COMMON MANIFESTATIONS**

The rheumatic diseases of childhood encompass a heterogeneous group of diseases with a shared underlying pathogenesis: disordered functioning of the immune system leading to inflammation directed against native proteins, with secondary increases in numbers of activated lymphocytes, inflammatory
<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>SYSTEMIC LUPUS ERYTHEMATOSUS</th>
<th>JUVENILE IDIOPATHIC ARTHRITIS</th>
<th>RHEUMATIC FEVER</th>
<th>LYME DISEASE</th>
<th>LEUKEMIA</th>
<th>GONOCOCCEMIA</th>
<th>KAWASAKI DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F &gt; M</td>
<td>Type-dependent</td>
<td>M = F</td>
<td>M = F</td>
<td>M = F</td>
<td>F &gt; M</td>
<td>M = F</td>
</tr>
<tr>
<td>Age</td>
<td>10–20 yr</td>
<td>1–16 yr</td>
<td>&gt;5–20 yr</td>
<td>2–10 yr</td>
<td>&gt;12 yr</td>
<td>&lt;5 yr</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>Butterfly; discoid</td>
<td>Salmon-pink macules (systemic onset)</td>
<td>Erythema marginatum</td>
<td>Erythema migrans</td>
<td>No</td>
<td>Palms/soles, papulopustules</td>
<td>Diffuse maculopapular (nonspecific), desquamation</td>
</tr>
<tr>
<td>Monarticular, pauciarticular</td>
<td>Yes</td>
<td>50%</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Polyarticular</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Small joints</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Rare</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Temporomandibular joint</td>
<td>No</td>
<td>Rare</td>
<td>No</td>
<td>Rare</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Eye disease</td>
<td>Uveitis/retinitis</td>
<td>Iridocyclitis (rare in systemic)</td>
<td>No</td>
<td>Conjunctivitis, keratitis</td>
<td>No</td>
<td>No</td>
<td>Conjunctivitis, uveitis</td>
</tr>
<tr>
<td>Total WBC count</td>
<td>Decreased</td>
<td>Increased (decreased in macrophage activation syndrome)</td>
<td>Normal to increased</td>
<td>Normal</td>
<td>Increased or neutropenia ± blasts</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>ANA</td>
<td>Positive (&gt;99%)</td>
<td>Positive (50%)</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>Positive or negative</td>
<td>Positive (10%) (polyarticular)</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Other laboratory results</td>
<td>Complement, antibodies to double-stranded DNA</td>
<td>Anti-CCP antibody + in adult type RA</td>
<td>ASO anti-DNase B</td>
<td>Cryoglobulin, immune complexes</td>
<td>+ Bone marrow</td>
<td>+ Culture for Neisseria gonorrhoeae</td>
<td>Thrombocytosis, immune complexes</td>
</tr>
<tr>
<td>Erosive arthritis</td>
<td>Rare</td>
<td>Yes</td>
<td>Rare</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Other clinical manifestations</td>
<td>Proteinuria, serositis</td>
<td>Fever, serositis (systemic onset)</td>
<td>Carditis, nodules, chorea</td>
<td>Carditis, neuropathy, meningitis</td>
<td>Thrombocytopenia</td>
<td>Sexual activity, menses</td>
<td>Fever, lymphadenopathy, swollen hands/feet, mouth lesions</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Autoimmune</td>
<td>Autoimmune</td>
<td>Group A streptococcus</td>
<td>Barrella burgdorferi</td>
<td>Acute lymphoblastic leukemia</td>
<td>N. gonorrhoeae</td>
<td>Unknown</td>
</tr>
<tr>
<td>Treatment</td>
<td>NSAIDs, corticosteroids, hydroxychloroquine, immunosuppressive agents</td>
<td>NSAIDs, methotrexate, TNF blockers for resistant disease</td>
<td>Penicillin prophylaxis, aspirin, corticosteroids</td>
<td>Penicillin, doxycycline, ceftriaxone</td>
<td>Corticosteroids, chemotherapy</td>
<td>Ceftriaxone</td>
<td>Intravenous immunoglobulin, aspirin</td>
</tr>
</tbody>
</table>

ANA, Antinuclear antibody; ASO, antistreptolysin-O titer; CCP, cyclic citrullinated protein; NSAID, nonsteroidal anti-inflammatory drug; TNF, tumor necrosis factor; WBC, white blood cell.
cytokines, and circulating antibodies. This antibody production can be nonspecific, or it can be targeted against specific native proteins, leading to subsequent disease manifestations (Table 86-2). Although immune system hyperactivity may be self-limited, the hallmark of most rheumatic diseases of childhood is chronicity, or the perpetuation of the inflammatory process, which can lead to long-term disability.

**INITIAL DIAGNOSTIC EVALUATION**

Although rheumatic diseases sometimes present with non-specific symptoms, especially early in the course, over time a characteristic set of symptoms and physical findings can be elicited. In conjunction with carefully chosen confirmatory laboratory tests, an appropriate differential diagnosis is made, and eventually the correct diagnosis and treatment plan is developed.

**LABORATORY TESTING**

Evidence of an underlying systemic inflammation may be indicated by elevated acute phase reactants, especially the erythrocyte sedimentation rate, but also the white blood cell count, platelet count, and C-reactive protein. The complete blood count may demonstrate a normochromic, normocytic anemia of chronic disease. These laboratory findings are non-specific for any particular rheumatologic diagnosis. Certain laboratory tests may help confirm a diagnosis, such as autoantibody production in SLE or muscle enzyme elevation in JDM, or identify increased risk for complications, such as uveitis in a patient with JIA with a positive antinuclear antibody.

**DIAGNOSTIC IMAGING**

Radiologic studies should focus on areas of concern identified by history or physical examination. Radiography of joints in patients with arthritis on examination may be beneficial, but radiographic abnormalities may lag far behind the clinical examination. Tests with greater sensitivity, such as bone scan, computed tomography scan, and magnetic resonance imaging, may be useful when trying to differentiate between synovitis and traumatic soft tissue injury. Magnetic resonance imaging may also be useful to identify evidence of central nervous system involvement with SLE or for evidence of myositis with JDM.

---

**Table 86-2** Manifestations of Autoantibodies

| Coombs-positive hemolytic anemia  |
| Immune neutropenia               |
| Immune thrombocytopenia          |
| Thrombosis (anticardiolipin, antiphospholipid, lupus anticoagulant) |
| Immune lymphopenia               |
| Antimitochondrial (primary biliary cirrhosis, SLE) |
| Antimicrosomal (chronic active hepatitis, SLE) |
| Antithyroid (thyroiditis, SLE)   |
| Antineutrophil cytoplasmic antibody (ANCA-cytoplasmic) (granulomatosis with polyangiitis) |
| ANCA-perinuclear (microscopic polyangiitis) |
| Anti-CCP (rheumatoid positive JIA) |

**ANTINUCLEAR ANTIBODIES TO SPECIFIC NUCLEAR ANTIGENS AND ASSOCIATED MANIFESTATIONS**

- Single-stranded DNA (nonspecific, indicates inflammation)
- Double-stranded DNA (SLE, renal disease)
- DNA-histone (drug-induced SLE)
- Sm (Smith) (SLE, renal, CNS)
- RNP (ribonucleoprotein) (SLE, Sjögren syndrome, scleroderma, polymyositis, MCTD)
- Ro (Robert: SSA) (SLE, neonatal lupus-congenital heart block, Sjögren syndrome)
- La (Lane: SSB) (SLE, neonatal lupus [congenital heart block], Sjögren syndrome)
- Jo-1 (polymyositis, dermatomyositis)
- Scl-70 (systemic sclerosis)
- Centromere (CREST; limited scleroderma)
- PM-ScI (scleroderma, UCTD)


ANCA, Antineutrophil cytoplasmic antibody; CCP, cyclic citrullinated protein; CNS, central nervous system; CREST syndrome, calcinosis, Raynaud phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia; MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; SSA, Sjögren syndrome antigen A; SSB, Sjögren syndrome antigen B; UCTD, undifferentiated connective tissue disease.

Most rheumatologic diagnoses are established by clinical findings and fulfillment of classification criteria. Laboratory testing should be judicious and based on a differential diagnosis rather than random screening in search of a diagnosis. Laboratory tests confirm clinical diagnoses rather than develop them.

**HENOCH-SCHÖNLEIN PURPURA**

**ETIOLOGY**

Henoch-Schönlein purpura (HSP) is a vasculitis of unknown etiology characterized by inflammation of small blood vessels with leukocytic infiltration of tissue, hemorrhage, and ischemia. The immune complexes associated with HSP are predominantly composed of IgA.

**EPIDEMIOLOGY**

HSP is the most common systemic vasculitis of childhood and cause of nonthrombocytopenic purpura, with an incidence of 13 per 100,000 children. It occurs primarily in children 3 to 15 years of age, although it has been described in adults. HSP is slightly more common in boys than girls and occurs more frequently in the winter than in the summer months.
HSP is characterized by rash, arthritis, and, less frequently, gastrointestinal or renal vasculitis. The hallmark of HSP is palpable purpura, caused by small vessel inflammation in the skin leading to extravasation of blood into the surrounding tissues, frequently with IgA deposition. The rash is classically found in dependent areas: below the waist, on the buttocks, and lower extremities. The rash can begin as small macules or urticarial lesions but rapidly progresses to purpura with areas of ecchymosis. The rash also can be accompanied by edema, particularly of the calves and dorsum of the feet, scalp, and scrotum or labia. HSP occasionally is associated with encephalopathy, pancreatitis, and orchitis.

Arthritis occurs in 80% of patients with HSP and is most common in the lower extremities, particularly the ankles and knees. The arthritis is acute and very painful with refusal to bear weight. Joint swelling can be confused with peripheral edema seen with the rash of HSP.

Gastrointestinal involvement occurs in about one half of affected children and most typically presents as mild to moderate crampy abdominal pain, thought to be due to small vessel involvement of the gastrointestinal tract leading to ischemia. Less commonly, significant abdominal distention, bloody diarrhea, intussusception, or abdominal perforation occurs and requires emergent intervention. Gastrointestinal involvement is typically seen during the acute phase of the illness. It may precede the onset of rash.

One third of children with HSP develop renal involvement, which can be acute or chronic. Although renal involvement is mild in most cases, acute glomerulonephritis manifested by hematuria, hypertension, or acute renal failure can occur. Most cases of glomerulonephritis occur within the first few months of presentation, but rarely patients develop late renal disease, which ultimately can lead to chronic renal disease, including renal failure.

**CLINICAL MANIFESTATIONS**

HSP is characterized by rash, arthritis, and, less frequently, gastrointestinal or renal vasculitis. The hallmark of HSP is palpable purpura, caused by small vessel inflammation in the skin leading to extravasation of blood into the surrounding tissues, frequently with IgA deposition. The rash is classically found in dependent areas: below the waist, on the buttocks, and lower extremities. The rash can begin as small macules or urticarial lesions but rapidly progresses to purpura with areas of ecchymosis. The rash also can be accompanied by edema, particularly of the calves and dorsum of the feet, scalp, and scrotum or labia. HSP occasionally is associated with encephalopathy, pancreatitis, and orchitis.

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**LABORATORY AND IMAGING STUDIES**

Erythrocyte sedimentation rate, C-reactive protein, and white blood cell count are elevated in patients with HSP. The platelet count is the most important test, because HSP is characterized by nonthrombocytopenic purpura with a normal, or even high, platelet count, differentiating HSP from other causes of purpura that are associated with thrombocytopenia such as autoimmune thrombocytopenia, systemic lupus erythematosus, or leukemia. A urinalysis screens for evidence of hematuria. A serum blood urea nitrogen and creatinine should be obtained to evaluate renal function. Testing the stool for blood may identify evidence of gut ischemia. Any question of gut perforation requires radiologic investigation.

**DIFFERENTIAL DIAGNOSIS**

The diagnosis of HSP is based on the presence of two of four criteria (Table 87-1), which provides 87.1% sensitivity and 87.7% specificity for the disease. The differential diagnosis includes other systemic vasculitides (Table 87-2) and diseases associated with thrombocytopenic purpura, such as idiopathic thrombocytopenic purpura and leukemia.

**TREATMENT**

Therapy for HSP is supportive. A short-term course of nonsteroidal anti-inflammatory drugs can be administered for the acute arthritis. Systemic corticosteroids usually are reserved for children with gastrointestinal disease and provide significant relief of abdominal pain. A typical dosing regimen is prednisone, 1 mg/kg/day for 1 to 2 weeks, followed by a taper schedule. Recurrence of abdominal pain as corticosteroids are weaned may necessitate a longer course of treatment. Acute nephritis typically is treated with corticosteroids but may require more aggressive immunosuppressive therapy.

**COMPLICATIONS**

Most cases of HSP are monophasic, lasting 3 to 4 weeks and resolving completely. The rash can wax and wane, however, for 1 year after HSP. Parents should be warned regarding possible recurrences. The arthritis of HSP does not leave any permanent joint damage; it does not typically recur. Gastrointestinal involvement can lead to temporary abnormal peristalsis that poses a risk of intussusception, which may be followed by complete obstruction or infarction with bowel perforation. Any child

**Table 87-1**

Criteria for Diagnosis of Henoch-Schönlein Purpura

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable purpura</td>
<td>Raised, palpable hemorrhagic skin lesions in the absence of thrombocytopenia</td>
</tr>
<tr>
<td>Bowel angina</td>
<td>Diffuse abdominal pain or the diagnosis of bowel ischemia</td>
</tr>
<tr>
<td>Diagnostic biopsy</td>
<td>Histologic changes showing granulocytes in the walls of arterioles or venules; IgA deposits in vessel wall</td>
</tr>
<tr>
<td>Pediatric age group</td>
<td>Age &lt;20 years at onset of symptoms</td>
</tr>
</tbody>
</table>

*The diagnosis of Henoch-Schönlein purpura is based on the presence of two of four criteria.
KAWASAKI DISEASE

ETIOLOGY
Kawasaki disease (KD) is a vasculitis of unknown etiology that is characterized by multisystem involvement and inflammation of small to medium-sized arteries with resulting aneurysm formation.

EPIDEMIOLOGY
KD is the second most common vasculitis of childhood. It is more common in children of Asian descent. It has been described in variable frequency in all parts of the world; the highest frequency is in Japan. KD most commonly occurs in children younger than 5 years of age, with a peak between 2 to 3 years, and is rare in children older than 7 years. The incidence in the United States is approximately 6 per 100,000 children who are younger than 5 years of age. A seasonal variability has been described with a peak between February and May, but the disease occurs throughout the year.

CLINICAL MANIFESTATIONS
The clinical course of KD can be divided into three phases, each with its own unique manifestations. Aneurysmal involvement of the coronary arteries is the most important manifestation of KD.

Acute Phase
The acute phase of KD, which lasts 1 to 2 weeks, is marked by sudden onset of a high, hectic fever (>40 °C) without an apparent source. The onset of fever is followed by conjunctival erythema; mucosal changes, including dry, cracked lips and a strawberry tongue; cervical lymphadenopathy; and swelling of the hands and feet (Fig. 88-1). Conjunctivitis is bilateral, bulbar, and nonsuppurative. Cervical lymphadenopathy is found in 70% of children and should be greater than 1.5 cm in diameter for the purposes of diagnosis. A rash, which can vary in appearance, occurs in 80% of children with KD and may be particularly accentuated in the inguinal area and on the chest. Extreme irritability is prominent, especially in infants. Abdominal pain and hydrops of the gallbladder, cerebrospinal fluid pleocytosis, sterile pyuria, and arthritis, particularly of medium-sized to large joints, may occur. Carditis in the acute phase may be manifested by tachycardia, shortness of breath, or overt congestive heart failure. Giant coronary artery aneurysms, which are rare but occur most commonly in very young children, can appear during this phase.

Subacute Phase
The subacute phase, which lasts until about the fourth week, is characterized by gradual resolution of fever (if untreated) and other symptoms. Desquamation of the skin, particularly of the fingers and toes, appears at this point. The platelet count, previously normal or slightly depressed, increases to a significant degree (often >1 million/mm³). This phase heralds the onset of coronary artery aneurysms, which may also appear in the convalescent phase and pose the highest risk of morbidity and mortality. Risk factors for development of coronary artery aneurysms include prolonged fever, prolonged elevation of inflammatory parameters such as the erythrocyte

with a recent history of HSP who presents with acute abdominal pain, obstipation, or diarrhea should be evaluated for intussusception. Renal involvement rarely may lead to renal failure.

PROGNOSIS
The prognosis of HSP is excellent. Most children have complete resolution of the illness without any significant sequelae. Patients with HSP renal disease (elevated blood urea nitrogen, persistent high-grade proteinuria) are at highest risk for long-term complications, such as hypertension or renal insufficiency, particularly if the initial course was marked by significant nephritis. There is a long-term risk of progression to end-stage renal disease in less than 1% of children with HSP. The rare patients who develop end-stage renal disease may require renal transplantation. HSP may recur in the transplanted kidney.

Decision-Making Algorithms
Available @ StudentConsult.com

Lymphadenopathy
Fever Without a Source
Fever of Unknown Origin

Table 87-2 Classification of Vasculitides

<table>
<thead>
<tr>
<th>ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCUITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis)</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
</tr>
<tr>
<td>HYPERSENSITIVITY SYNDROMES</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>Serum sickness (e.g., drug-related)</td>
</tr>
<tr>
<td>Vasculitis associated with infections</td>
</tr>
<tr>
<td>CONNECTIVE TISSUE DISEASES</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Dermatomyositis</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>GIANT CELL ARTERITIS</td>
</tr>
<tr>
<td>Temporal arteritis</td>
</tr>
<tr>
<td>Takayasu arteritis</td>
</tr>
<tr>
<td>OTHERS</td>
</tr>
<tr>
<td>Behçet syndrome</td>
</tr>
<tr>
<td>Kawasaki disease</td>
</tr>
<tr>
<td>Hypocomplementemic urticarial vasculitis</td>
</tr>
</tbody>
</table>
sedimentation rate (ESR), age younger than 1 year or older than 6 years, and male gender.

**Convalescent Phase**
The convalescent phase begins with the disappearance of clinical symptoms and continues until the ESR returns to normal, usually 6 to 8 weeks after the onset of illness. Beau lines of the fingernails may appear during this phase.

**LABORATORY AND IMAGING STUDIES**
It is particularly important to exclude other causes of fever, notably infection. It is appropriate to obtain blood and urine cultures and to perform a chest x-ray. In the acute phase, inflammatory parameters are elevated, including white blood cell count, C-reactive protein, and the ESR, which can be profoundly elevated (often >80 mm/hr). Platelet counts may be inappropriately low or normal. A lumbar puncture, if performed to exclude infection, may reveal pleocytosis. Tests of hepatobiliary function may be abnormal. Greatly elevated platelet counts develop during the subacute phase. The development of coronary artery aneurysms is monitored by performing two-dimensional echocardiograms, usually during the acute phase, at 2 to 3 weeks, and again at 6 to 8 weeks. More frequent echocardiograms and, potentially, coronary angiography are indicated for patients who develop coronary artery abnormalities.

**DIFFERENTIAL DIAGNOSIS**
The diagnosis of KD is based on the presence of fever for more than 5 days without an identifiable source and the presence of four of five other clinical criteria (Table 88-1). The diagnosis of incomplete (atypical) KD, which occurs more commonly in infants, is made when fever is present for at least 5 days even if only two or three clinical criteria are present, particularly in the presence of coronary artery aneurysms. The diagnosis of KD should be considered in infants younger than 6 months of age with fever for at least 7 days even if no other criteria are present. Because many of the manifestations of KD are found in other illnesses, many diagnoses must be considered and excluded before the diagnosis of KD can be established (Table 88-2).

**TREATMENT**
Intravenous immunoglobulin (IVIG) is the mainstay of therapy for KD, although the mechanism of action is unknown.
A single dose of IVIG (2 g/kg over 12 hours) results in rapid defervescence and resolution of clinical illness in most patients and, more important, reduces the incidence of coronary artery aneurysms. Aspirin is initially given in anti-inflammatory doses (80 to 100 mg/kg/day divided every 6 hours) in the acute phase. Once the fever resolves, aspirin is reduced to antithrombotic doses (3 to 5 mg/kg/day as a single dose) and given through the subacute and convalescent phases, usually for 6 to 8 weeks, until follow-up echocardiography documents the absence or resolution of coronary artery aneurysms.

Up to 10% of children with KD initially fail to respond satisfactorily to IVIG therapy. Most of these patients respond to retreatment with IVIG, but an alternative preparation of IVIG may be required. Corticosteroids or infliximab are rarely used in KD, as opposed to other vasculitides, but may have a role during the acute phase if active carditis is apparent or for children with persistent fever after two doses of IVIG.

**COMPLICATIONS**

Most cases resolve without sequelae. Myocardial infarction has been documented, most likely caused by stenosis of a coronary artery at the site of an aneurysm. Coronary artery aneurysms found on autopsy in older children following sudden cardiac death may have been due to past KD. Other complications are listed in Table 88-3.

**PROGNOSIS**

IVIG reduces the prevalence of coronary artery disease from 20% to 25% in children treated with aspirin alone to 2% to 4% in children treated with IVIG and aspirin. Other than the risk of persistent coronary artery aneurysms, KD has an excellent prognosis.

**ETIOLOGY**

The chronic arthritides of childhood include several types, the most common of which is juvenile idiopathic arthritis (JIA), formerly called juvenile rheumatoid arthritis (JRA). The classification of JIA includes several other types of juvenile arthritis, such as enthesitis-related arthritis and psoriatic arthritis. The etiology of this autoimmune disease is unknown. The common underlying manifestation of this group of illnesses is the presence of chronic synovitis, or inflammation of the joint synovium. The synovium becomes thickened and hypervascular with infiltration by lymphocytes, which also can be found in the synovial fluid along with inflammatory cytokines. The inflammation leads to production and release of tissue proteases and collagenases. If left untreated, the inflammation can lead to tissue destruction, particularly of the articular cartilage and, eventually, the underlying bony structures.

**EPIDEMIOLOGY**

JIA is the most common chronic rheumatologic disease of childhood, with a prevalence of 1:1000 children. The disease has two peaks, one at 1 to 3 years and one at 8 to 12 years, but it can occur at any age. Girls are affected more commonly than boys, particularly with the oligoarticular form of the illness.

**CLINICAL PRESENTATION**

JIA can be divided into several subtypes, depending on the number of joints involved (less than five versus five or more), the presence of sacroiliac involvement, and the presence of systemic features, each with particular disease characteristics (Table 89-1). Although the onset of the arthritis is slow, the actual joint swelling is often noticed acutely by the child or parent, such as after an accident or fall, and can be confused with trauma (even though traumatic effusions are rare in children). The child may develop pain and stiffness in the joint that limit use, but rarely refuses to use the joint at all. Morning stiffness and gelling also can occur in the joint and, if present, can be followed in response to therapy.

On physical examination, signs of inflammation are present, including joint tenderness, erythema, and effusion (Fig. 89-1). Joint range of motion may be limited because of pain, swelling, or contractures from lack of use. In children, because of the
presence of an active growth plate, it may be possible to find bony abnormalities of the surrounding bone, causing bony proliferation and localized growth disturbance. In a lower extremity joint, a leg length discrepancy may be appreciable if the arthritis is asymmetric.

All children with chronic arthritis are at risk for chronic iridocyclitis or uveitis. There is an association between human leukocyte antigens (HLAs) (HLA-DR5, HLA-DR6, and HLA-DR8) and uveitis. The presence of a positive antinuclear antibody identifies children with arthritis who are at higher risk for chronic uveitis. Although all children with JIA are at increased risk, the subgroup of children, particularly young girls, with oligoarticular (less than five affected joints) JIA and a positive antinuclear antibody are at highest risk, with an incidence of uveitis of 80%. The uveitis associated with JIA can be asymptomatic until the point of visual loss, making it a primary treatable cause of blindness in children. It is crucial for children with JIA to undergo regular ophthalmologic screening with a slit-lamp examination to identify anterior chamber inflammation and to initiate prompt treatment of any active disease.

### Table 89-1 Features of Juvenile Idiopathic Arthritis Subgroups

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>OLIGOARTICULAR</th>
<th>POLYARTICULAR</th>
<th>SYSTEMIC ONSET</th>
<th>SPONDDYLOARTHROPATHIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. joints</td>
<td>&lt;5</td>
<td>≥5</td>
<td>Varies, usually ≥5</td>
<td>Varies</td>
</tr>
<tr>
<td>Types of joints</td>
<td>Medium to large (also small in extended oligoarthritis)</td>
<td>Small to medium</td>
<td>Small to medium</td>
<td>Medium to large, including sacroiliac joints</td>
</tr>
<tr>
<td>Gender predominance</td>
<td>F &gt; M (especially in younger children)</td>
<td>F &gt; M</td>
<td>F = M</td>
<td>M &gt; F</td>
</tr>
<tr>
<td>Systemic features</td>
<td>None</td>
<td>Some constitutional</td>
<td>Prominent</td>
<td>Some constitutional</td>
</tr>
<tr>
<td>Eye disease</td>
<td>+++ (uveitis)</td>
<td>++ (uveitis)</td>
<td>+ (uveitis)</td>
<td>++ (iritis)</td>
</tr>
<tr>
<td>Extra-articular manifestations</td>
<td>None</td>
<td>None</td>
<td>Systemic features</td>
<td>Enthesopathy, psoriasis, bowel disease</td>
</tr>
<tr>
<td>ANA positivity</td>
<td>++</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RF positivity</td>
<td></td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Excellent, &gt;90% complete remission</td>
<td>Good, &gt;50% complete remission, some risk of disability</td>
<td>Variable, depends on extent of arthritis</td>
<td>Variable</td>
</tr>
</tbody>
</table>

ANA, Antinuclear antibody; RA, rheumatoid arthritis; RF, rheumatoid factor.

Oligoarticular Juvenile Idiopathic Arthritis

Oligoarticular JIA is defined as the presence of arthritis in fewer than five joints within 6 months of diagnosis. This is the most common form of JIA, accounting for approximately 50% of cases.

Oligoarticular JIA presents in young children, with a peak at 1 to 3 years and another peak at 8 to 12 years. The arthritis is found in medium-sized to large joints; the knee is the most common joint involved, followed by the ankle and the wrist. It is unusual for small joints, such as the fingers or toes, to be involved, although this may occur. Neck and hip involvement also is uncommon. Children with oligoarticular JIA may be otherwise well without any evidence of systemic inflammation (fever, weight loss, or failure to thrive) or any laboratory evidence of systemic inflammation (elevated white blood cell count or erythrocyte sedimentation rate). A subset of these children later develops polyarticular disease (called extended oligoarthritis).

Polyarticular Juvenile Idiopathic Arthritis

Polyarticular JIA describes children with arthritis in five or more joints within the first 6 months of diagnosis and accounts for about 40% of cases. Children with polyarticular JIA tend to have symmetric arthritis, which can affect any joint but typically involves the small joints of the hands, feet, ankles, wrists, and knees. The cervical spine can be involved, leading
to fusion of the spine over time. In contrast to oligoarticular JIA, children with polyarticular disease can present with evidence of systemic inflammation, including malaise, low-grade fever, growth retardation, anemia of chronic disease, and elevated markers of inflammation. Polyarticular JIA can present at any age, although there is a peak in early childhood. There is a second peak in adolescence, but these children differ by the presence of a positive rheumatoid factor (and anti-CCP antibody) and most likely represent a subgroup with true adult rheumatoid arthritis; the clinical course and prognosis are similar to the adult entity.

**Systemic-Onset Juvenile Idiopathic Arthritis**
A small subgroup of patients (approximately 10%) with juvenile arthritis does not present with onset of arthritis but rather with preceding systemic inflammation. This form of JIA, thought to be an autoinflammatory disease, manifests with a typical recurring, spiking fever, usually once or twice per day, which can occur for several weeks to months. This is accompanied by a rash, typically morbilliform and salmon-colored. The rash may be evanescent and occur at times of high fever only. Rarely the rash can be urticarial in nature. Internal organ involvement also occurs. Serositis, such as pleuritis and pericarditis, occurs in 50% of children. Pericardial tamponade rarely may occur. Hepatosplenomegaly occurs in 70% of children. Children with systemic-onset JIA appear sick; they have significant constitutional symptoms, including malaise and failure to thrive. Laboratory findings show the inflammation, with elevated erythrocyte sedimentation rate, C-reactive protein, white blood cell count, and platelet counts and anemia. The arthritis of JIA follows the systemic inflammation by 6 weeks to 6 months. The arthritis is typically polyarticular in nature and can be extensive and resistant to treatment, placing these children at highest risk for long-term disability.

**Spondyloarthropathies**
The spondyloarthropathies describe a group of arthritides that include inflammation of the axial skeleton and sacroiliac joints and enthesitis, or inflammation of tendinous insertions. These include juvenile ankylosing spondylitis, psoriatic arthritis, and the arthritis of inflammatory bowel disease. This group of diseases can also present with peripheral arthritis and can be initially classified in other subgroups. It is only later, when the patient develops evidence of sacroiliac arthritis, psoriasis, or gastrointestinal disease, that the diagnosis becomes clear (Table 89-2). Other important features of this group include the frequent presence of HLA-B27 and the need for earlier treatment with tumor necrosis factor (TNF) blockers.

**LABORATORY AND IMAGING STUDIES**
Most children with oligoarticular JIA have no laboratory abnormalities. Children with polyarticular and systemic-onset disease commonly show elevated acute phase reactants and anemia of chronic disease. In all pediatric patients with joint or bone pain, a complete blood count should be performed to exclude leukemia, which also can present with limb pain (see Chapter 155). All patients with oligoarticular JIA should have an antinuclear antibody test to help identify those at higher risk for uveitis. Older children and adolescents with polyarticular disease should have a rheumatoid factor performed to identify children with early onset adult rheumatoid arthritis.

Diagnostic arthrocentesis may be necessary to exclude suppurative arthritis in children who present with acute onset of monarticular symptoms. The synovial fluid white blood cell count is typically less than 50,000 to 100,000/mm³ and should be predominantly lymphocytes, rather than neutrophils seen with suppurative arthritis. Gram stain and culture should be negative (see Chapter 118).

The most common radiologic finding in the early stages of JIA is a normal bone x-ray. Over time, periarticular osteopenia, resulting from decreased mineralization, is most commonly found. Growth centers may be slow to develop, whereas there may be accelerated maturation of growth plates or evidence of bony proliferation. Erosions of bony articular surfaces may be a late finding. If the cervical spine is involved, fusion of C1–4 may occur, and atlantoaxial subluxation may be demonstrable.

**DIFFERENTIAL DIAGNOSIS**
The diagnosis of JIA is established by the presence of arthritis, the duration of the disease for at least 6 weeks, and exclusion of other possible diagnoses. Although a presumptive diagnosis

<p>| Table 89-2 | Comparison of Juvenile Idiopathic Arthritis and Spondyloarthropathies |</p>
<table>
<thead>
<tr>
<th>CLINICAL MANIFESTATIONS</th>
<th>JIA</th>
<th>JAS</th>
<th>PSA</th>
<th>IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender predominance</td>
<td>F</td>
<td>M</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Back symptoms</td>
<td>–</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Family history</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>ANA positivity</td>
<td>++</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HLA-B27 positivity</td>
<td>–</td>
<td>++</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RF positivity</td>
<td>+ (in late-onset JIA)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Extra-articular manifestations</td>
<td>Systemic symptoms (systemic-onset JRA)</td>
<td>Enthesopathy</td>
<td>Psoriasis, nail changes</td>
<td>Bowel symptoms</td>
</tr>
<tr>
<td>Eye disease</td>
<td>Anterior uveitis</td>
<td>Posterior uveitis</td>
<td>Anterior uveitis</td>
<td></td>
</tr>
</tbody>
</table>

ANA, Antinuclear antibody; IBD, inflammatory bowel disease; JAS, juvenile ankylosing spondylitis; JIA, juvenile idiopathic arthritis; PSA, poststreptococcal arthritis; RF, rheumatoid factor.
of systemic-onset JIA can be established for a child during the systemic phase, a definitive diagnosis is not possible until arthritis develops. Children must be younger than 16 years of age at time of onset of disease; the diagnosis of JIA does not change when the child becomes an adult. Because there are so many other causes of arthritis, these disorders need to be excluded before providing a definitive diagnosis of JIA (Table 89-3). The acute arthritides can affect the same joints as JIA but have a shorter time course.

**TREATMENT**

The treatment of JIA focuses on suppressing inflammation, preserving and maximizing function, preventing deformity, and preventing blindness. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first choice in the treatment of JIA. Naproxen, sulindac, ibuprofen, indomethacin, and others have been used successfully. Systemic corticosteroid medications, such as prednisone and prednisolone, should be avoided in all but the most extreme circumstances, such as for severe systemic-onset JIA with internal organ involvement or for significant active arthritis leading to the inability to ambulate. In this circumstance, the corticosteroids are used as bridging therapy until other medications take effect. For patients with a few isolated inflamed joints, intra-articular corticosteroids may be helpful.

Second-line medications, such as hydroxychloroquine and sulfasalazine, have been used in patients whose arthritis is not completely controlled with NSAIDs alone. **Methotrexate**, given either orally or subcutaneously, has become the drug of choice for polyarticular and systemic-onset JIA, which may not respond to baseline agents alone. Methotrexate can cause bone marrow suppression and hepatotoxicity; regular monitoring can minimize these risks. Leflunomide, with a similar adverse effect profile to methotrexate, has also been used. Biologic agents that inhibit TNF-α and block the inflammatory cascade, including **etanercept, infliximab**, and **adalimumab**, are effective in the treatment of JIA. The risks of these agents are greater, however, and include serious infection and, possibly, increased risk of malignancy. Anakinra, an interleukin-1 receptor antagonist, is very beneficial in the treatment of the systemic features of systemic-onset JIA.

**COMPLICATIONS**

Complications with JIA result primarily from the loss of function of an involved joint secondary to contractures, bony fusion, or loss of joint space. Physical and occupational therapies, professionally and through home programs, are crucial to preserve and maximize function. More serious complications stem from associated uveitis; if left untreated, it can lead to serious visual loss or blindness.

**PROGNOSIS**

The prognosis of JIA is excellent, with an overall 85% complete remission rate. Children with oligoarticular JIA uniformly tend to do well, whereas children with polyarticular disease and systemic-onset disease constitute most children with functional disability. Systemic-onset disease, a positive rheumatoid factor, poor response to therapy, and the presence of erosions on x-ray all connote a poorer prognosis. The importance of physical and occupational therapy cannot be overstated because when the disease remits, the physical limitations remain with the patient into adulthood.
Chapter 90

SYSTEMIC LUPUS ERYTHEMATOSUS

ETIOLOGY
Systemic lupus erythematosus (SLE) is a multisystem disorder of unknown etiology characterized by a production of large amounts of circulating autoantibodies. This antibody production may be due to loss of T-lymphocyte control on B-lymphocyte activity, leading to hyperactivity of B lymphocytes, which leads to nonspecific and specific antibody and autoantibody production. These antibodies form immune complexes that become trapped in the microvasculature, leading to inflammation and ischemia.

EPIDEMIOLOGY
Although SLE affects primarily women of childbearing age, approximately 5% of cases present in childhood, mainly around puberty. SLE is rare in children younger than 9 years of age. Although there is a female predominance of this disease in adolescence and adulthood, there is an equal gender distribution in children. The overall prevalence of SLE in the pediatric population is 10 to 25 cases per 100,000 children.

CLINICAL MANIFESTATIONS
Patients with SLE can present either in an abrupt fashion with fulminant disease or in an indolent manner (Tables 90-1 and 90-2). Nonspecific symptoms are common but can be quite profound and may include significant fatigue and malaise, low-grade fever, and weight loss. Skin disease can be a prominent finding, occurring in up to 95% of patients. A raised, erythematous rash on the cheeks, called a malar butterfly rash, is common (Fig. 90-1). This rash also can occur across the bridge of the nose, on the forehead, and on the chin. Photosensitivity can be problematic, particularly during the summer months. Both of these rashes improve with appropriate therapy. The rash of discoid lupus, by contrast, is an inflammatory process that leads to disruption of the dermal-epidermal junction, resulting in permanent scarring and loss of pigmentation in the affected area. If discoid lupus occurs in the scalp, permanent alopecia ensues because of loss of hair follicles. Raynaud phenomenon, although not specific for SLE, and livedo reticularis also can occur.

Mouth and nasal sores resulting from mucosal ulceration are a common complaint in patients with SLE and can lead to ulceration and perforation of the nasal septum. Because of reticuloendothelial system stimulation, lymphadenopathy and splenomegaly are common findings in SLE. In particular, axillary lymphadenopathy can be a sensitive indicator of disease activity. Serositis can be seen, with chest pain and pleural or pericardial friction rubs or frank effusion.

Renal involvement is one of the most serious manifestations of SLE and is common in pediatric SLE, occurring in 50% to 70% of children. Renal disease may range from microscopic proteinuria or hematuria to gross hematuria, nephrotic syndrome, and renal failure. Hypertension or the presence of edema suggests lupus renal disease.

Arthralgias and arthritis are common. The arthritis is rarely deforming and typically involves the small joints of the hands; any joint may be involved. Myalgias or frank myositis, with muscle weakness and muscle fatigability, may occur. SLE can affect the central nervous system (CNS), leading to a myriad of symptoms ranging from poor school performance and difficulty concentrating, to seizures, psychosis, and stroke.

LABORATORY AND IMAGING STUDIES
Testing for SLE is performed to establish the diagnosis, determine prognosis, and monitor response to therapy. Although nonspecific, a positive antinuclear antibody is found in more than 97% of patients with SLE, usually at high titers. Because of its high sensitivity, a negative antinuclear antibody has a high negative predictive value for SLE. The presence of

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<table>
<thead>
<tr>
<th>Table 90-1</th>
<th>Criteria for Diagnosis of Systemic Lupus Erythematosus*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHYSICAL SIGNS</td>
<td></td>
</tr>
<tr>
<td>Malar butterfly rash</td>
<td></td>
</tr>
<tr>
<td>Discoid lupus</td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td></td>
</tr>
<tr>
<td>Oral and nasopharyngeal ulcers</td>
<td></td>
</tr>
<tr>
<td>Nonerosive arthritis (more than two joints with effusion and tenderness)</td>
<td></td>
</tr>
<tr>
<td>Pleuritis or pericarditis (serositis)</td>
<td></td>
</tr>
<tr>
<td>Seizures or psychosis in absence of metabolic toxins or drugs</td>
<td></td>
</tr>
<tr>
<td>RENAL DISEASE (NEPHRITIS)</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (&gt;500 mg/24 h)</td>
<td></td>
</tr>
<tr>
<td>Cellular casts (RBC, granular, or tubular)</td>
<td></td>
</tr>
<tr>
<td>HEMATOLOGIC DISEASE</td>
<td></td>
</tr>
<tr>
<td>Hemolytic anemia with reticulocytosis or</td>
<td></td>
</tr>
<tr>
<td>Leukopenia (&lt;4000 on two occasions) or</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia (&lt;1500 on two occasions) or</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100,000/mm³)</td>
<td></td>
</tr>
<tr>
<td>SEROLOGIC DATA</td>
<td></td>
</tr>
<tr>
<td>Positive anti-dsDNA or</td>
<td></td>
</tr>
<tr>
<td>Positive anti-Sm or</td>
<td></td>
</tr>
<tr>
<td>Evidence of presence of antiphospholipid antibodies</td>
<td></td>
</tr>
<tr>
<td>IgG or IgM anticardiolipin antibodies or</td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant or</td>
<td></td>
</tr>
<tr>
<td>False-positive VDRL for &gt;6 mo</td>
<td></td>
</tr>
<tr>
<td>Positive ANA in absence of drugs known to induce lupus</td>
<td></td>
</tr>
</tbody>
</table>

*ANA, Antinuclear antibody; RBC, red blood cell; VDRL, Venereal Disease Research Laboratory. These are the 1997 revised criteria for diagnosing systemic lupus erythematosus (SLE). A patient must have 4 of the 11 criteria to establish the diagnosis of SLE. These criteria may be present at the same or at different times during the patient's illness. Additional, less specific diagnostic manifestations are noted in Table 90-2.
antibodies to double-stranded DNA should raise suspicion for SLE because these antibodies are present in most patients with SLE and are found almost exclusively in the disease. Titers of anti-double-stranded DNA antibodies are quantifiable and vary with disease activity. Antibodies directed against Sm (Smith) are specific to SLE but are found in only approximately 30% of persons with SLE, limiting its clinical utility. Antibodies to Ro (SSA) and La (SSB) also can be found in patients with SLE, but they also occur in patients with Sjögren syndrome. Likewise patients with SLE can have antibodies directed against phospholipids, which also can be seen in other rheumatologic diseases and in primary antiphospholipid syndrome.

Hematologic abnormalities also are prevalent in patients with SLE. Leukopenia, primarily manifest as lymphopenia, is common. Thrombocytopenia and anemia of chronic disease may be found. Rarely patients with SLE develop Coombs-positive autoimmune hemolytic anemia. Excessive antibody production can lead to polyclonal hypergammopathy with an elevated globulin fraction in the serum. Excessive circulating antibodies and immune complexes also lead to the consumption of complement proteins, with low levels of C3 and C4 and decreased complement function as measured by CH50. Effective therapy returns the low complement levels to normal. This is one way to monitor therapy except in patients with familial deficiency in complement components, which, itself, predisposes to SLE.
Urinalysis may show hematuria and proteinuria, identifying patients with lupus nephritis. Serum blood urea nitrogen and creatinine evaluate renal function. Hypoalbuminemia and hypoproteinemia may be present. Elevation of muscle enzymes may be a clue for the presence of myositis. Elevated cerebrospinal fluid (CSF) protein and an elevated IgG-to-albumin ratio when comparing CSF with serum (IgG index) can indicate antibody production in the CSF and help diagnose SLE affecting the CNS. CNS lupus has a specific pattern on gadolinium-enhanced magnetic resonance imaging.

DIFFERENTIAL DIAGNOSIS
Because SLE is a multisystem disease, it can be difficult to diagnosis early in the disease course. Suspicion must be high in patients who present with diffuse symptoms, particularly adolescent girls. Many of the clinical manifestations of SLE are found in other inflammatory illnesses and during acute or chronic infection. Criteria have been developed for the diagnosis of SLE (see Table 90-1). The presence of 4 of 11 of these criteria has 98% sensitivity and 97% specificity for SLE.

TREATMENT
Corticosteroids have been the mainstay of treatment for SLE for decades. Initial use of pulse methylprednisolone and high-dose oral prednisone (up to 2 mg/kg) frequently is required, followed by cautious tapering to minimize recurrence of symptoms. Nonsteroidal anti-inflammatory drugs have been used to treat the arthralgias and arthritis associated with SLE. Hydroxychloroquine is used not only for the treatment of lupus skin disease, such as discoid lupus, but as maintenance therapy. Hydroxychloroquine treatment results in longer periods of wellness between flares of disease as well as decreased numbers of flares.

Corticosteroids and hydroxychloroquine frequently are not sufficient therapies for lupus nephritis or cerebritis. Cyclophosphamide is effective for the worst forms of lupus nephritis, with significant improvements in outcome and decreased rates of progression to renal failure. CNS lupus responds to cyclophosphamide. For patients who are not able to tolerate the tapering of corticosteroids, the use of steroid-sparing agents, such as azathioprine, methotrexate, or mycophenolate mofetil, may be indicated.

Patients with SLE should be counseled to wear sun block and avoid sun exposure because exposure to the sun precipitates flares of the disease. Because of this prohibition, patients benefit from calcium and vitamin D supplementation to reduce the risk of osteoporosis that may result from prolonged corticosteroid use. Early treatment of hyperlipidemia to decrease long-term cardiovascular complications is also indicated.

COMPLICATIONS
Long-term complications include avascular necrosis secondary to corticosteroid use, infections, and myocardial infarction. Adult patients with SLE develop accelerated atherosclerosis, not only because of prolonged corticosteroid use but also due to the underlying disease. All patients with SLE should be counseled regarding their weight and maintaining an active lifestyle to reduce other cardiac risk factors.

PROGNOSIS
Outcomes for SLE have improved significantly over the past several decades and depend largely on the organ systems that are involved. Worse prognoses are seen in patients with severe lupus nephritis or cerebritis, with the risk of chronic disability or progression to renal failure. With current therapy for the disease and the success of renal transplantation, however, most patients live well into adulthood.

JUVENILE DERMATOMYOSITIS
ETIOLOGY
The etiology of juvenile dermatomyositis (JDM) is unknown. It is characterized by activation of T and B lymphocytes, leading to vasculitis affecting small vessels of skeletal muscle, with immune complex deposition and subsequent inflammation of blood vessels and muscle. JDM may follow infections, allergic reactions, or sun exposure, but no causal relationship has been shown.

EPIDEMIOLOGY
JDM is a rare disease, with an incidence of less than 0.1:100,000 children. JDM can occur in all age groups with a peak incidence between 4 to 10 years. The disease is slightly more common in girls than boys.

CLINICAL MANIFESTATIONS
Dermatomyositis tends to present in a slow, progressive fashion, with insidious onset of fatigue, malaise, and progressive muscle weakness, accompanied by low-grade fevers and rash. Some children present in an acute fashion, however, with rapid onset of severe disease.

The muscle disease of JDM primarily affects the proximal muscles, particularly the hip and shoulder girdles, and the abdominal and neck muscles. Children have difficulty climbing steps, getting out of chairs, and getting off the floor. The patient may have a positive Gower sign. In severe cases, the patient is not able to sit up from a supine position or even lift the head off the examination table (see Chapter 182). If muscles of the upper airway and pharynx are involved, the patient’s voice will sound nasal and the patient may have difficulty swallowing.

A classic JDM rash occurs on the face and across the cheeks but also can be found on the shoulders and back (shawl sign). Patients may have heliotrope discoloration of the eyelids. Scaly, red plaques (Gottron papules) classically are found across the knuckles but can be found on the extensor surfaces of any joint. Patients may have periungual erythema and dilated nail-fold capillaries. Less commonly, patients develop cutaneous vasculitis, with inflammation, erythema, and skin breakdown.
exposure. Accordingly supplementation with calcium and be advised to wear sun block and refrain from prolonged sun the muscle disease; sunlight may lead to flare. Patients should sun worsens the cutaneous manifestations and exacerbates do not significantly affect the muscle disease. Exposure to the sone has been used for the skin manifestations. These drugs is useful as adjunctive therapy. Hydroxychloroquine or dap- sporine or cyclophosphamide. Intravenous immunoglobulin showing muscle inflammation.

At some point, 15% of patients with JDM develop arthri- tis, commonly affecting small joints, but any joint may be involved. Raynaud phenomenon, hepatomegaly, and spleno- megaly may also occur.

LABORATORY AND IMAGING STUDIES
Many patients with JDM have no evidence of systemic inflam- mation (normal blood count and erythrocyte sedimentation rate). Evidence of myositis can be identified in 98% of children with active JDM by elevated serum muscle enzymes, including aspartate aminotransferase, alanine aminotransferase, creatine phosphokinase, aldolase, and lactate dehydrogenase. Electromyography and muscle biopsy can document the myo- sitis. Magnetic resonance imaging is a noninvasive means of showing muscle inflammation.

DIFFERENTIAL DIAGNOSIS
Diagnosis of JDM is based on the presence of documented muscle inflammation in the setting of classic rash (Table 91-1). A small percentage of children have muscle disease without skin manifestations, but polymyositis is sufficiently rare in children that they should have a muscle biopsy to exclude other causes of muscle weakness, such as muscular dystrophy (particularly boys). The differential diagnosis also includes postinfectious myositis and other myopathies (see Chapter 182).

TREATMENT
Methotrexate, supplemented by short-term use of systemic corticosteroids, is the cornerstone of therapy for JDM. Initial treatment with pulse intravenous methylprednisolone is fol- lowed by several months of tapering doses of oral prednisone. Early institution of methotrexate significantly decreases the duration of corticosteroid use and its associated toxicities. In severe or refractory cases, it may be necessary to use cyclo- sporine or cyclophosphamide. Intravenous immunoglobulin is useful as adjunctive therapy. Hydroxychloroquine or dap- sone has been used for the skin manifestations. These drugs do not significantly affect the muscle disease. Exposure to the sun worsens the cutaneous manifestations and exacerbates the muscle disease; sunlight may lead to flare. Patients should be advised to wear sun block and refrain from prolonged sun exposure. Accordingly supplementation with calcium and active forms of vitamin D is also indicated.

Table 91-1 Criteria for Diagnosis of Juvenile Dermatomyositis*
| Rash typical of dermatomyositis |
| Symmetric proximal muscle weakness |
| Elevated muscle enzymes (ALT, AST, LDH, CPK, and aldolase) |
| EMG abnormalities typical of dermatomyositis (fasciculations, needle insertion irritability, and high-frequency discharges) |
| Positive muscle biopsy specimen with chronic inflammation |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CPK: Creatine phosphokinase; EMG: Electromyography; LDH: Lactate dehydrogenase.

*To make a definitive diagnosis of dermatomyositis, four of five criteria are required.

COMPLICATIONS
The most serious complication of JDM is the development of calcinosis. Dystrophic calcification can occur in the skin and soft tissues in any area of the body; it ranges from mild to extensive (calcinosis universalis). Although it is difficult to predict who will develop calcinosis, it occurs more commonly in children with cutaneous vasculitis; prolonged disease activity, or delays in onset of therapy. Patients with JDM who develop vasculitis also are at risk for gastrointestinal perfora- tion and gastrointestinal bleeding. JDM has been associated with lipatrophy and insulin resistance, which can progress to type 2 diabetes. Control of insulin resistance frequently leads to improvement in muscle disease in these patients.

PROGNOSIS
The outcome of JDM depends greatly on the extent of muscle disease and the time between disease onset and initiation of therapy. JDM follows one of three clinical courses: a monopa- sic course, in which patients are treated and improve without significant sequelae; a chronic recurrent course; and a chronic progressive course marked by poor response to therapy and resulting loss of function. Patients who ultimately develop cal- cinosis are at risk for chronic loss of mobility, depending on the extent of calcium deposition. The association of derma- tomyositis with malignancy seen in adults does not occur in children.

MUSCULOSKELETAL PAIN SYNDROMES

GROWING PAINS
Growing pains, or benign musculoskeletal pain syndrome, occur in 10% to 20% of school-age children. The peak age range is 3 to 7 years; the syndrome seems to be more common in boys than girls. There is no known etiology, although there seems to be a familial predisposition.

Children with growing pains complain of deep, crampy pain in the calves and thighs. It most typically occurs in the evening or as nocturnal pain that occasionally can waken the child from sleep. Growing pains tend to be more common in children who are extremely active; bouts are exacerbated by increased physical activity. The physical examination is unre- markable, with no evidence of arthritis or muscular tender- ness or weakness. Laboratory studies or x-rays, if performed, are normal.

The diagnosis of growing pains is based on a typical history and a normal physical examination. Hypermobility excludes the diagnosis. It is important to consider leukemia as a cause of nocturnal leg pain in children of this age group, so it is pru- dent to document a normal complete blood count.

The treatment of growing pains consists of reassurance and a regular bedtime ritual of stretching and relaxation. The pain can be relieved by massage. Some patients may benefit from
a nighttime dose of acetaminophen or an analgesic dose of a nonsteroidal anti-inflammatory drug (NSAID). Occasionally nocturnal awakening has been of long duration, leading to disruptive behavior patterns. In these cases, intervention must be aimed at decreasing the secondary gain associated with nighttime parental attention and should focus on sleep hygiene. Other than the negative behavioral patterns that can occur, there are no significant complications. Growing pains are not associated with other illnesses and resolve over time.

BENIGN HYPERMOBILITY

Hypermobility syndromes are disorders of unknown etiology that cause musculoskeletal pain secondary to excessive mobility of joints. These disorders most commonly present in children 3 to 10 years of age. Girls are more commonly affected than boys. There is a familial predisposition to hypermobility syndromes.

Hypermobility can be isolated to a specific joint group or can present as a generalized disorder. Symptoms vary depending on the joints involved. The most consistent symptom is pain, which may occur during the day or night. The discomfort may increase after exertion but rarely interferes with regular physical activity. Children with hypermobility of the ankles or feet may complain of chronic leg or back pain.

Joint hypermobility may be quite marked. Range of motion may be exaggerated with excessive flexion or extension at the metacarpophalangeal joints, wrists, elbows, or knees (genu recurvatum) (Fig. 92-1). There may be excessive pronation of the ankles. Hypermobility of the foot (flat foot; pes planus) is shown by the presence of a longitudinal arch of the foot that disappears with weight bearing and may be associated with a shortened Achilles tendon (see Chapter 200). These findings are rarely associated with tenderness on examination. No laboratory test abnormalities are apparent, and radiographs of affected joints are normal.

The diagnosis of isolated hypermobility is made on the basis of physical examination with demonstration of exaggerated mobility of a joint. Generalized hypermobility is diagnosed by the presence of sufficient criteria (Table 92-1) and the absence of evidence of other underlying disorders. Excessive skin elasticity, easy bruising, or mitral valve prolapse suggests Ehlers-Danlos syndrome or Marfan syndrome rather than benign hypermobility.

The treatment of hypermobility consists of reassurance and regular stretching, similar to treatment for other benign musculoskeletal disorders. NSAIDs can be administered as needed but do not need to be prescribed on a regular basis. Arch supports can be helpful in children with symptomatic pes planus but are not indicated in the absence of symptoms. Benign hypermobility tends to improve with increasing age and is not associated with long-term complications.

<table>
<thead>
<tr>
<th>Table 92-1 Criteria for Diagnosis of Benign Hypermobility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Touch thumb to flexor aspect of the forearm</strong></td>
</tr>
<tr>
<td>1 point each for right and left</td>
</tr>
<tr>
<td><strong>Extend fifth metacarpophalangeal joint to 90 degrees</strong></td>
</tr>
<tr>
<td>1 point each for right and left</td>
</tr>
<tr>
<td>&gt;10 degrees hyperextension of elbow</td>
</tr>
<tr>
<td>1 point each for right and left</td>
</tr>
<tr>
<td>&gt;10 degrees hyperextension of knee</td>
</tr>
<tr>
<td>1 point each for right and left</td>
</tr>
<tr>
<td><strong>Touch palms to floor with knees straight</strong></td>
</tr>
<tr>
<td>1 point</td>
</tr>
</tbody>
</table>

* >6 points defines hypermobility.

MYOFASCIAL PAIN SYNDROMES AND FIBROMYALGIA

The myofascial pain syndromes are a group of noninflammatory disorders characterized by diffuse musculoskeletal pain, the presence of multiple tender points, fatigue, malaise, and poor sleep patterns. The etiology of these disorders is unknown, although there seems to be a familial predisposition. Although these disorders sometimes follow viral infection or trauma, no causal relationship has been shown. The myofascial pain syndromes are most common in adults but can occur in children (particularly >12 years of age). The syndromes are more common in girls than in boys. The prevalence of fibromyalgia in children has been reported to be 6%.

Patients with myofascial pain syndromes complain of long-standing diffuse pain in muscles and in the soft tissues around joints that can occur at any time of day, awaken the patient from sleep, and interfere with regular activities. There is frequently a high degree of school absenteeism, despite maintaining adequate school performance. A significant percentage of patients with myofascial pain syndromes exhibit symptoms consistent with depression. An increased incidence of sexual abuse has been reported in children presenting with fibromyalgia.

Physical examination is typically unremarkable with the exception of the presence of specific points that are
painful—not just tender—to digital palpation. These points often are located on the neck, back, lateral epicondyles, greater trochanter, and knees. There is no evidence of arthritis or muscular weakness.

Patients with myofascial pain syndromes frequently undergo extensive medical testing because of the concern for underlying inflammatory disease. These tests are invariably normal. Children may have a false-positive antinuclear antibody, which is found in 20% of the normal pediatric population.

The diagnosis of myofascial pain syndrome is based on the presence of multiple tender points in the absence of other illness. To fulfill strict criteria for a diagnosis of fibromyalgia, the patient must have a history of diffuse pain for at least 3 months and the presence of 11 of 18 specific tender points on examination. It is important to exclude underlying inflammatory diseases, such as systemic lupus erythematosus, or the post-infectious fatigue that characteristically follows Epstein-Barr virus and influenza virus infection. Mood and conversion disorders also should be considered.

Treatment consists of pain control, usually using NSAIDs, physical therapy, relaxation techniques, and education regarding sleep hygiene. Patients may require low doses of medications, such as amitriptyline to regulate sleep or gabapentin to reduce pain sensitivity. Education and reassurance are crucial.

Because of the disability associated with myofascial pain syndromes, patients and parents frequently believe that the child has a serious underlying condition and may be resistant to reassurance. It should be emphasized that there is no simple cure, and time and perseverance are required.

The long-term outcomes in the myofascial pain syndromes vary. Patients and families who focus on therapy and are positive in their approach tend to have better outcomes. Patients who demand prolonged evaluations, especially from multiple health care providers, may do more poorly. Overall children with fibromyalgia and myofascial pain syndromes have better prognoses than their adult counterparts.

**Suggested Reading**


Overlapping clinical symptoms caused by infectious and noninfectious illnesses make the diagnosis of some diseases difficult. Clinicians are concerned that an untreated minor infection may progress to a life-threatening illness, if appropriate treatment is not given. However unnecessary treatment with antimicrobial agents may lead to a serious problem—emergence of antimicrobial resistant organisms. Accurate diagnosis of infectious and noninfectious diseases and providing specific treatment only as indicated reduce the unnecessary use of antibiotics.

A thorough assessment of the patient, including a detailed history, complete physical examination, and appropriate diagnostic testing is the cornerstone of optimal care.

INITIAL DIAGNOSTIC EVALUATION

The ability to diagnose specific infections accurately begins with an understanding of the epidemiology; risk factors, including exposures to sick contacts or environmental risks (e.g., zoonosis); and age-related susceptibility reflecting the maturity of the immune system. Obtaining a thorough history and physical examination identifies most of these elements (Tables 93-1 and 93-2) and guides appropriate use of other diagnostic tests.

Unique questions that help identify whether an infection is causing the patient’s symptoms include a detailed environmental history (including sick contacts, travel, and animal exposure) (see Table 93-1). Certain infections are more common in specific geographic areas. For instance parasitic infections are more common in tropical climates. Diarrhea may be bacterial, viral, or parasitic in the tropics, but in temperate climates parasitic causes of diarrhea, other than giardiasis, are much less likely. Certain fungal infections have specific geographic distribution (coccidioidomycosis in the southwestern United States, blastomycosis in the upper Midwest, and histoplasmosis in central United States). In other areas, fungal pneumonias are rare except in immunocompromised persons.

An immunization history is critical for determining susceptibility to vaccine preventable diseases. Family history, especially of unexpected deaths of male infants, may suggest familial immunodeficiency (see Chapters 73 through 76). Localization of symptoms to a specific site may narrow diagnostic possibilities (see Table 93-2).

A complete physical examination is essential to identify signs of infection, which may be systemic, such as fever and shock, or focal, including swelling, erythema, tenderness, and limitation of function. Many infectious diseases are associated with characteristic cutaneous signs (see Table 97-1). Accurate otolaryngologic examination is critical for diagnosing upper respiratory tract infections and otitis media, the most common childhood infectious diseases in the United States.

DIFFERENTIAL DIAGNOSIS

Fever does not always represent infection. Rheumatologic disease, inflammatory bowel disease, Kawasaki disease, poisoning, and malignancy also may present with fever. Particularly, children with overwhelming infection may be afebrile or hypothermic. Common symptoms, such as bone pain or lymphadenopathy that suggest infection, may also be due to leukemia, lymphoma, juvenile idiopathic arthritis, or Kawasaki disease (see Chapters 88, 89, and 153). Acute mental status changes or focal neurologic impairment could be manifestations of infections (encephalitis, meningitis, or brain abscess) or noninfectious causes (brain or spinal tumors, inflammatory conditions, postinfectious sequelae, or impairment from toxic ingestions or inhalants). Many manifestations of mucosal allergy (rhinitis, diarrhea) may mimic common infectious diseases (see Chapter 77).

Some infections are prone to recurrence, especially if treatment is suboptimal (inadequate antimicrobial or shorter duration). Recurrent, severe, or unusual (opportunistic) infections suggest the possibility of immunodeficiency (see Chapters 72 and 125).

SCREENING TESTS

Laboratory diagnosis of infection includes examination of bacterial morphology using Gram stain, various culture techniques,
molecular microbiologic methods such as polymerase chain reaction, and assessment of the immune response with antibody titers or skin testing. The **acute phase response** is a nonspecific metabolic and inflammatory response to infection, trauma, autoimmune disease, and some malignancies. **Acute phase reactants** such as erythrocyte sedimentation rate and C-reactive protein are commonly elevated during an infection but are not specific for infection and do not identify any specific infection. These tests are often used to monitor response to therapy.

A **complete blood count** is frequently obtained for evidence of infection. The initial response to infection, especially in children, is usually a **leukocytosis** (increased number of circulating leukocytes) with an initial neutrophilic response to both bacterial and viral infections. With most viral infections, this response is transient and is followed quickly by a characteristic mononuclear response. In general, bacterial infections are associated with greater neutrophil counts than viral infections (Table 93-3). A **shift-to-the-left** is an increase in the numbers of circulating immature cells of the neutrophil series, including band forms, metamyelocytes, and myelocytes and indicates the rapid release of cells from the bone marrow. It is characteristic of the early stages of infection and, if sustained, bacterial infections. Transient lymphopenia at the beginning of illness and lasting 24 to 48 hours has been described with many viral infections. **Atypical lymphocytes** are mature T lymphocytes with larger, eccentrically placed, and indented nuclei classically seen with infectious mononucleosis caused by Epstein-Barr virus. Other infections associated with atypical lymphocytosis include cytomegalovirus infection, toxoplasmosis, viral hepatitis, rubella, roseola, mumps, and some drug reactions. **Eosinophilia** is characteristic of allergic diseases but may be seen with tissue-invasive multicellular parasites, such as the migration of the larval stages of parasites through skin, connective tissue, and viscera. High-grade eosinophilia (>30% eosinophils, or a total eosinophil count >3000/μL) frequently occurs during the muscle invasion phase of illness.

### Table 93-1  Clues from the History for Risk of Infection

| Season of year | Age | General health | Weight change | Fever—presence, duration, and pattern | Previous similar symptoms | Previous infections and other illnesses | Previous surgeries, dental procedures | Preceding trauma | Presence of outbreaks or epidemics in the community | Exposures to infected individuals | Exposures to farm or feral animals and pets | Exposures to ticks and mosquitoes | Sexual history, including possibility of sexual abuse | Illicit drug use | Transfusion of blood or blood products | Travel history | Daycare or school attendance | Sources of water and food (e.g., undercooked meat, unpasteurized dairy products) | Home sanitary facilities and hygiene | Pica | Exposure to soil-borne and waterborne organisms (e.g., swimming in brackish water) | Presence of foreign bodies (e.g., indwelling catheters, shunt, grafts) | Immunization history | Immunodeficiency (chemotherapy, acquired, congenital) | Current medications |

### Table 93-2  Localizing Manifestations of Infection

<table>
<thead>
<tr>
<th>SITE</th>
<th>LOCALIZING SYMPTOMS</th>
<th>LOCALIZING SIGNS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye</td>
<td>Eye pain, double vision, photophobia, conjunctival discharge</td>
<td>Periorbital edema, periorbital erythema, drainage, chemoisis, limitation of extraocular movements</td>
</tr>
<tr>
<td>Ear</td>
<td>Ear pain, drainage</td>
<td>Red bulging tympanic membrane, drainage from ear canal</td>
</tr>
<tr>
<td>Upper respiratory tract</td>
<td>Rhinorrhea, sore throat, cough, drooling, stridor, trismus, sinus pain, tooth pain, hoarse voice</td>
<td>Nasal congestion, pharyngeal erythema, enlarged tonsils with exudate, swollen red epiglottis, regional lymphadenopathy</td>
</tr>
<tr>
<td>Lower respiratory tract</td>
<td>Cough, chest pain, dyspnea, sputum production, cyanosis</td>
<td>Tachypnea, crackles, wheezing, localized diminished breath sounds, intercostal retractions</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Nausea, vomiting, diarrhea, abdominal pain (focal or diffuse), anorexia, weight loss</td>
<td>Hypoactive or hyperactive bowel sounds, abdominal tenderness (focal or generalized), hematochezia</td>
</tr>
<tr>
<td>Liver</td>
<td>Anorexia, vomiting, dark urine, light stools</td>
<td>Jaundice, hepatomegaly, hepatic tenderness, bleeding diatheses, coma</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>Dysuria, frequency, urgency, flank or suprapubic pain, vaginal discharge</td>
<td>Costovertebral angle or suprapubic tenderness, cervical motion and adnexal tenderness</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Lethargy, irritability, headache, neck stiffness, seizures</td>
<td>Nuchal rigidity, Kernig sign, Brudzinski sign, bulging fontanelle, focal neurologic deficits, altered mental status, coma</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Dyspnea, palpitations, fatigue, exercise intolerance, chest pain</td>
<td>Tachycardia, hypotension, cardiomegaly, hepatomegaly, splenomegaly, crackles, petechiae, Osler nodes, Janeway lesions, Roth spots, new or change in murmur, distended neck veins, pericardial friction rub, muffled heart sounds</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Limp, bone pain, limited function (pseudoparalysis)</td>
<td>Local swelling, erythema, warmth, limited range of motion, point bone tenderness, joint line tenderness</td>
</tr>
</tbody>
</table>

*Fever usually accompanies infection as a systemic manifestation.
of trichinellosis, the pulmonary phases of ascariasis and hookworm infection (eosinophilic pneumonia), and the hepatic and central nervous system phases of visceral larva migrans.

Other common screening tests include urinalysis for urinary tract infections, transaminases for liver function, and lumbar puncture for evaluation of the cerebrospinal fluid if there is concern for meningitis or encephalitis (see Chapters 100 and 101). Various tests may help distinguish viral versus bacterial infection, but definitive diagnosis requires identifying the agent by culture or another test, such as polymerase chain reaction.

**Cultures** are the mainstay of diagnosis of many infections. Blood cultures are sensitive and specific for bacteremia, which may be primary or secondary to a focal infection (osteomyelitis, gastroenteritis, urinary tract, and endocarditis). Urine cultures are important to confirm urinary tract infection, which may be occult in young infants. Cultures should be obtained with every lumbar puncture, aspiration, or biopsy of other fluid collections or masses. Specific types of cultures (bacterial, fungal, viral, or mycobacterial) are guided by the clinical problem. Tissue culture techniques are used to identify viruses and intracellular bacterial pathogens.

Antibiotics often are begun before a definitive diagnosis is established, complicating the ability to rely on subsequent cultures for microbiologic diagnosis (see Chapter 95). Although persistent or progressive symptoms, despite antibiotic treatment, may indicate the need to change the regimen, more frequently this indicates the need to stop all antibiotics to facilitate definitive diagnosis by obtaining appropriate cultures. Antibiotics should not be given before obtaining appropriate cultures unless there is a life-threatening situation (e.g., septic shock).

**Rapid tests**, such as antigen tests, are useful for preliminary diagnosis and are included in numerous bacterial, viral, fungal, and parasitic antigen detection tests. **SeroLogic tests**, using enzyme-linked immunosorbent assay or Western blotting, showing an IgM response, high IgG titer, or seroconversion between acute and convalescent sera, can be used for diagnosis. **Molecular tests**, such as polymerase chain reaction for DNA or RNA, offer the specificity of culture, high sensitivity, and rapid results. When an unusual infection is suspected, a microbiologist should be consulted before samples are obtained.

### Table 93-3: Differentiating Viral from Bacterial Infections

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>VIRAL</th>
<th>BACTERIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechiae</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Purpura</td>
<td>Rare</td>
<td>If severe</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>Uncommon*</td>
<td>Common</td>
</tr>
<tr>
<td>Shift-to-the-left (Ibands)</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Possible</td>
<td>Suggests overwhelming infection</td>
</tr>
<tr>
<td>1 ESR</td>
<td>Unusual*</td>
<td>Common</td>
</tr>
<tr>
<td>1 CRP</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>1 TNF, IL-1, PAF</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Meningitis (pleocytosis)</td>
<td>Lymphocytic†</td>
<td>Neutrophilic</td>
</tr>
<tr>
<td>Meningeal signs positive†</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

**CRP**, C-reactive protein; **ESR**, erythrocyte sedimentation rate; **IL**, interleukin; **PAF**, platelet-activating factor; **TNF**, tumor necrosis factor.

*Adenovirus and herpes simplex may cause leukocytosis and increased ESR; Epstein-Barr virus may cause petechiae and increased ESR.

†Early viral (enterovirus, arbovirus) meningitis initially may have a neutrophilic pleocytosis.

‡Nuchal rigidity, bulging fontanelle, Kernig sign, Brudzinski sign.

### Diagnostic Imaging

The choice of diagnostic imaging mode should be based on the location of the findings. In the absence of localizing signs and during an acute infection, imaging of the entire body is less productive. **Plain x-rays** are useful initial tests for respiratory tract infections. **Ultrasonography** is a noninvasive, nonirradiating technique well suited to infants and children for imaging solid organs. It also is useful to identify soft tissue abscesses with lymphadenitis and to diagnose supplicative arthritis of the hip. **Computed tomography (CT)** (with contrast enhancement) and magnetic resonance imaging (MRI) (with gadolinium enhancement) allow characterization of lesions and precise anatomic localization and are the modalities of choice for the brain. CT shows greater bone detail, and MRI shows greater tissue detail. MRI is especially useful for diagnosis of osteomyelitis, myositis, and necrotizing fasciitis. High-resolution CT is useful for complicated chest infections. Judicious use of CT scans is important because of the long-term effects of radiation on children’s health. Contrast studies (upper gastrointestinal series, barium enema) are used to identify mucosal lesions of the gastrointestinal tract, whereas CT or MRI is preferred for evaluation of appendicitis and intra-abdominal masses. A voiding cystourethrogram may be used to evaluate for vesicoureteral reflux, a predisposing factor for upper urinary tract infections. **Radionuclide scans**, such as technetium-99m for osteomyelitis and dimercaptosuccinic acid for acute pyelonephritis, are often informative.

### Chapter 94: Immunization and Prophylaxis

#### Immunization

Childhood immunization has markedly reduced the impact of major infectious diseases. **Active immunization** induces immunity through the administration of a **vaccine** or toxoid (inactivated toxin). **Passive immunization** includes transplacental transfer of maternal antibodies and the administration of antibody, either as immunoglobulin or monoclonal antibody.

Vaccinations may be with live attenuated viruses (measles, mumps, rubella [MMR], varicella, nasal influenza), inactivated or killed viruses (polio, hepatitis A, intramuscular influenza), recombinant products (hepatitis B, human papillomavirus), reassortants (rotavirus), or immunogenic components of
bacteria (pertussis, *Haemophilus influenzae* type b, *Neisseria meningitidis*, and *Streptococcus pneumoniae*), including toxins (diphtheria, tetanus). Many purified polysaccharides are T-independent antigens that initiate B-cell proliferation without involvement of CD4+ T lymphocytes and are poor immunogens in children younger than 2 years of age. Conjugation of a polysaccharide to a protein carrier induces a T-dependent response in infants and creates immunogenic vaccines for *H. influenzae* type b, *S. pneumoniae*, and *N. meningitidis*.

Childhood immunization standards and recommendations in the United States (Figs. 94-1 and 94-2) are formulated by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians. In the United States, due to state laws requiring immunization for school entry, approximately 95% of children entering kindergarten are vaccinated for the common infectious diseases. The ACIP recommends that children in the United States routinely receive vaccines against 16 diseases (see Fig. 94-1). This schedule includes up to 21 injections in four to five visits by 18 months of age. Children and adolescents who are at increased risk for pneumococcal infections should receive the pneumococcal polysaccharide vaccine, as well. Children who are behind in immunization should receive catch-up immunizations as rapidly as feasible. Infants born prematurely, regardless of birth weight, should be vaccinated at the same chronologic age and according to the same schedule as full-term infants and children (see Fig. 94-2). The single exception to this practice is providing hepatitis B vaccine for infants weighing less than 2000 g if the mother is hepatitis B virus surface antigen (HBsAg)-negative at 1 month instead of at birth. Vaccines for adolescents should be given at 11 to 12 years of age (see Fig. 94-1), with completion of any vaccine series at 13 to 18 years of age and a booster for *N. meningitidis* at 16 years of age.

Vaccines should be administered after obtaining informed consent. The National Childhood Vaccine Injury Act requires that all health care providers provide parents or patients with copies of Vaccine Information Statements prepared by the Centers for Disease Control and Prevention (http://www.cdc.gov/vaccines/pubs/vis/default.htm) before administering each vaccine dose.

Most vaccines are administered by intramuscular or subcutaneous injection. The preferred sites for administration are the anterolateral aspect of the thigh in infants and the deltoid region in children and adults. Multiple vaccines can be administered simultaneously at anatomically separate sites (different limbs, or separated by >1 in.) without diminishing the immune response. MMR and varicella vaccines should be administered simultaneously or more than 30 days apart. Administration of blood products and immunoglobulin can diminish response to live virus vaccines if administered before the recommended interval.

General contraindications to vaccination include serious allergic reaction (anaphylaxis) after a previous vaccine dose or to a vaccine component, immunocompromised states or pregnancy (live virus vaccines), and moderate or severe acute illness with or without fever. History of anaphylactic-like reactions to eggs is a contraindication to influenza and yellow fever vaccines, which are produced in embryonated chicken eggs. Current preparations of measles and mumps vaccines, which are produced in chick embryo fibroblast tissue culture, do not contain significant amounts of egg proteins and may be administered without testing children with history of egg allergy. Mild acute illness, with or without fever, convalescent phase of illness, recent exposure to infectious diseases, current antimicrobial therapy, breastfeeding, mild to moderate local reaction or low-grade to moderate fever after previous vaccination, and history of penicillin or other nonvaccine allergy or receiving allergen extract immunotherapy are not contraindications to immunization.

Severe immunosuppression resulting from congenital immunodeficiency, human immunodeficiency virus (HIV) infection, leukemia, lymphoma, cancer therapy, or a prolonged course of high-dose corticosteroids (>2 mg/kg/day for >2 weeks) predisposes to complications and is a contraindication for live virus vaccines. For HIV-infected children who do not have evidence of severe immunosuppression, MMR vaccination is recommended at 12 months of age with a second dose 1 month later rather than waiting until 4 to 6 years of age. Varicella vaccine is contraindicated for persons with cellular immunodeficiency but is recommended for persons with impaired humoral immunity (hypogammaglobulinemia or dysgammaglobulinemia) and at 12 months of age for HIV-infected children without evidence of severe immunosuppression, given as two doses 3 months apart.

The National Childhood Vaccine Injury Act requires that clinically significant adverse events after vaccination be reported to the Vaccine Adverse Event Reporting System (VAERS) (http://www.vaers.hhs.gov or (800) 822-7967). Suspected cases of vaccine-preventable diseases should be reported to state or local health departments. The act also established the National Vaccine Injury Compensation Program, a no-fault system in which persons thought to have suffered an injury or death as a result of administration of a covered vaccine can seek compensation.

**PROPHYLAXIS**

Prophylaxis may include antibiotics, immunoglobulin or monoclonal antibody, vaccine, alone or in combination; they may be used postexposure, for perinatal exposure, and pre-exposure for persons at increased risk for infection. Primary prophylaxis is used to prevent infection before a first occurrence. Secondary prophylaxis is used to prevent recurrence after a first episode.

**Meningococcus**

Primary prophylaxis to all contacts of index cases of *N. meningitidis* infection should be administered as soon as possible (see Chapter 100). Prophylaxis is recommended for all household contacts, especially young children; child care or nursery school contacts in the previous 7 days; for direct exposure to the index patient’s secretions through kissing or sharing of toothbrushes or eating utensils; and for mouth-to-mouth resuscitation or unprotected contact during endotracheal intubation within 7 days before onset of illness. Prophylaxis is also recommended for contacts who frequently sleep or eat in the same dwelling as the index patient or passengers seated directly next to the index case during airline flights lasting longer than 8 hours. Chemoprophylaxis is not recommended for casual contacts with no history of direct exposure to the patient’s oral secretions (school or work mate), indirect
**Recommended immunization schedule for persons aged 0 through 18 years – 2013.**
*(FOR THOSE WHO FALL BEHIND OR START LATE, SEE THE CATCH-UP SCHEDULE [FIGURE 94-2]).*

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars in Figure 94-1. To determine minimum intervals between doses, see the catch-up schedule (Fig. 94-2). School entry and adolescent vaccine age groups are in bold.

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Birth</th>
<th>1 mo</th>
<th>2 mos</th>
<th>4 mos</th>
<th>6 mos</th>
<th>9 mos</th>
<th>12 mos</th>
<th>15 mos</th>
<th>18 mos</th>
<th>19-23 mos</th>
<th>2-3 yrs</th>
<th>4-6 yrs</th>
<th>7-10 yrs</th>
<th>11-12 yrs</th>
<th>13-15 yrs</th>
<th>16-18 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B <em>(HepB)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1 dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus <em>(RV)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2 doses)</td>
<td></td>
<td>(1 dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, tetanus, &amp; acellular pertussis <em>(DTaP)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4 doses)</td>
<td></td>
<td>(3 doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetanus, diphtheria, &amp; acellular pertussis <em>(Tdap)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4 doses)</td>
<td></td>
<td>(2 doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae type B <em>(Hib)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2 doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal conjugate <em>(PCV13)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4 doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal polysaccharide <em>(PPSV23)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3 doses)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated Poliovirus <em>(IPV)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3 doses)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Varicella <em>(VAR)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2 doses)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles, mumps, rubella <em>(MMR)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(2 doses)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human papillomavirus <em>(HPV)</em></td>
<td></td>
<td>(3 doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(3 doses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal <em>(MenACWY)</em></td>
<td></td>
<td>1 dos</td>
<td></td>
<td></td>
<td></td>
<td>(2 doses)</td>
<td></td>
<td></td>
<td>(2 doses)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Annual vaccination *(ILV only)*

Annual vaccination *(ILV or LAIV)*

**Figure 94-1** Recommended immunization schedules for persons ages 0 through 18 years—United States, 2013. (Approved by the Advisory Committee on Immunization Practices; American Academy of Pediatrics; American Academy of Family Physicians; and American College of Obstetricians and Gynecologists. (Courtesy of the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html](http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html).)
Vaccination of persons with high-risk conditions:

- Administer a single dose of PCV13 for children aged 12 through 23 months who have received all prior doses of PCV or PCV13 vaccine.
- Administer the second dose 1 to 2 months after the first dose.

6. Pneumococcal polysaccharide vaccine (PPSV23) (Minimum age: 2 years)

Vaccination of persons with high-risk conditions:

- If any dose in series was RV-5 or vaccine product is unknown for any dose in the series, for children aged 2 through 4 years, at least 6 months after the previous dose.
- If RV-1(Rotarix) is administered for the first and second doses, a third dose is not indicated.

Catch-up vaccination:

- For children aged 2 through 4 years who had wheezing in the past 12 months, or children who are receiving influenza vaccine for the first time.
- For the 2013-14 season, follow dosing guidelines in the 2013-14 ACIP influenza vaccine recommendations.

9. Measles, mumps, and rubella (MMR) vaccine (Minimum age: 12 months for routine vaccination)

Vaccination of persons with high-risk conditions:

- Administer the first dose of MMR vaccine at ages 12 through 15 months, and the second dose 4 to 6 years after the first dose.
- For booster doses among persons high-risk conditions refer to vaccine manufacturers' publications/vaccines/publications/mm1307r1.html.

Additional information

- For contraindications and precautions to use of a vaccine and one for additional information regarding that vaccine, vaccine providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/sta..html.

- For the purposes of calculating intervals between doses, 4 weeks = 28 days. Ten intervals of 4 months or longer = 3 years. Ten intervals of 8 months or longer = 1 year. Ten intervals of 6 months or longer = 1.5 years. Ten intervals of 4 months or longer = 2 years. Ten intervals of 3 months or longer = 2.5 years. Ten intervals of 2 months or longer = 3 years. Ten intervals of 1 month or longer = 4 years. Ten intervals of 0.5 months or longer = 5 years. Ten intervals of 0.25 months or longer = 6 years. Ten intervals of 0.125 months or longer = 7 years. Ten intervals of 0.0625 months or longer = 8 years. Ten intervals of 0.03125 months or longer = 9 years. Ten intervals of 0.015625 months or longer = 10 years. Ten intervals of 0.0078125 months or longer = 11 years. Ten intervals of 0.00390625 months or longer = 12 years. Ten intervals of 0.001953125 months or longer = 13 years. Ten intervals of 0.0009765625 months or longer = 14 years. Ten intervals of 0.00048828125 months or longer = 15 years. Ten intervals of 0.000244140625 months or longer = 16 years. Ten intervals of 0.0001220703125 months or longer = 17 years. Ten intervals of 0.00006103515625 months or longer = 18 years. Ten intervals of 0.000030517578125 months or longer = 19 years. Ten intervals of 0.0000152587890625 months or longer = 20 years. Ten intervals of 0.00000762939453125 months or longer = 21 years. Ten intervals of 0.000003814697265625 months or longer = 22 years. Ten intervals of 0.0000019073486328125 months or longer = 23 years. Ten intervals of 0.00000095367431640625 months or longer = 24 years. Ten intervals of 0.000000476837158203125 months or longer = 25 years. Ten intervals of 0.0000002384185791015625 months or longer = 26 years. Ten intervals of 0.00000011920928955078125 months or longer = 27 years. Ten intervals of 0.000000059604644775390625 months or longer = 28 years. Ten intervals of 0.000000029802322387695312 months or longer = 29 years. Ten intervals of 0.000000014901161193847656 months or longer = 30 years. Ten intervals of 0.000000007450580596923828 months or longer = 31 years. Ten intervals of 0.000000003725290298461914 months or longer = 32 years. Ten intervals of 0.000000001862645149230957 months or longer = 33 years. Ten intervals of 0.000000000931322574615478 months or longer = 34 years. Ten intervals of 0.000000000465661287307739 months or longer = 35 years. Ten intervals of 0.000000000232830643653869 months or longer = 36 years. Ten intervals of 0.000000000116415321826935 months or longer = 37 years. Ten intervals of 0.000000000058207660913467 months or longer = 38 years. Ten intervals of 0.000000000029103830456733 months or longer = 39 years. Ten intervals of 0.000000000014551915228367 months or longer = 40 years. Ten intervals of 0.000000000007275957614184 months or longer = 41 years. Ten intervals of 0.000000000003637978807091 months or longer = 42 years. Ten intervals of 0.000000000001818989403546 months or longer = 43 years. Ten intervals of 0.000000000000909494701773 months or longer = 44 years. Ten intervals of 0.000000000000454747350887 months or longer = 45 years. Ten intervals of 0.000000000000227373675443 months or longer = 46 years. Ten intervals of 0.000000000000113686837722 months or longer = 47 years. Ten intervals of 0.000000000000056843418861 months or longer = 48 years. Ten intervals of 0.000000000000028421709430 months or longer = 49 years. Ten intervals of 0.000000000000014210854715 months or longer = 50 years.

10. Varicella (VAR) vaccine (Minimum age: 12 months)

Vaccination of persons with high-risk conditions:

- Administer the first dose of VAR vaccine at age 12 through 15 months, and the second dose 4 to 6 years after the first dose.
- For booster doses among persons high-risk conditions refer to vaccine manufacturers' publications/vaccines/publications/mm1307r1.html.
The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child’s age. Always use this table in conjunction with Figure 94-1 and the footnotes that follow.

### Persons aged 4 months through 6 years

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum Age for Dose 1</th>
<th>Minimum Interval Between Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 1 to dose 2</td>
<td>Dose 2 to dose 3</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Birth</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>6 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Diphtheria, tetanus, pertussis</td>
<td>6 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Haemophilus influenza type b</td>
<td>6 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>6 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Inactivated poliovirus</td>
<td>6 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>6 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>12 months</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Varicella</td>
<td>12 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>12 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

### Persons aged 7 through 18 years

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Minimum Age for Dose 1</th>
<th>Minimum Interval Between Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose 1 to dose 2</td>
<td>Dose 2 to dose 3</td>
</tr>
<tr>
<td>Tetanus, diphtheria, tetanus, diphtheria, pertussis</td>
<td>7 years</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>9 years</td>
<td>Routine dosing intervals are recommended²⁴</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>12 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Birth</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Inactivated poliovirus</td>
<td>6 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>6 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Measles, mumps, rubella</td>
<td>12 months</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Varicella</td>
<td>12 months</td>
<td>3 months</td>
</tr>
</tbody>
</table>

**Figure 94-2** Catch-up immunization schedule for persons ages 4 months through 18 years who start late or who are more than 1 month behind—United States, 2013. This figure provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child’s age. Always use this table in conjunction with the Recommended Immunization Schedule for 2013 and the footnotes that follow. (Approved by the Advisory Committee on Immunization Practices; American Academy of Pediatrics; American Academy of Family Physicians; and American College of Obstetricians and Gynecologists.) (Courtesy of the U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html](http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html).)
For further guidance on the use of the vaccines mentioned below, see:

4. Hepatitis B (HBV) vaccine. (Minimum age: birth)

Routine vaccination:
- Administer monovalent HBV vaccine to all newborns before hospital discharge.
- For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer Hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and anti-HB surface antibody at 6 months of age.
- If mother’s HBsAg status is unknown, within 12 hours of birth administer HBV vaccine to all infants weighing ≥ 2000 grams (no later than age 1 week).
- If HBsAg-positive, also administer HBIG for infants weighing ≥ 2000 grams (no later than age 1 week).

Doses following the birth dose
- The second dose should be administered at age 1 to 2 months.
- Monovalent HBV vaccine should be used for all doses after April 26, 2006.
- Infants who did not receive a birth dose should receive 3 doses of a HBV-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months as starting as soon as feasible. See Figure 3.
- The minimum interval between dose 1 and dose 2 is 4 weeks and between dose 2 and 3 is 6 weeks. See Figure 2.
- Administration of a total of 4 doses of HepB vaccine is recommended when a combination vaccine containing HepB is administered after the birth dose.

Catch-up vaccination:
- Unvaccinated infants should complete a 3-dose series.
- A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
- For other catch-up issues, see Figure 2.

5. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: infancy)

Routine vaccination:
- Administer 2-dose series of DTaP vaccine at ages 2, 4, 15–18 months, and 4 through 6 months. The fourth dose may be administered as the adolescent Tdap dose, provided at least 5 months have elapsed since the first dose.

Catch-up vaccination:
- If the fourth dose (DTaP) of DTaP vaccine is not necessary if the fourth dose is at least 6 months after the third dose.
- For other catch-up issues, see Figure 2.

6. Polio and tetanus toxoids and acellular pertussis (Tdap) vaccine. (Minimum: 10 years for Boostrix, 11 years for Adacel)

Routine vaccination:
- Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
- Tdap can be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
- Administer Tdap vaccine to pregnant adolescents during each pregnancy (preferably during 27 through 36 weeks gestation) regardless of number of doses received to date, but not too close to the date of delivery.
- An accelerated dose of Tdap vaccine administered to children aged 7 through 10 years can count as part of the catch-up series. This dose can count as the third dose if the child had fewer than 3 doses of Tdap vaccine, or the child can later receive a Tdap booster dose at age 11–12 years.

3. Haemophilus influenzae type b (Hib) conjugate vaccine. (Minimum age: 6 weeks)

Routine vaccination:
- Administer a Hib vaccine primary series and a booster dose to all infants.
- The primary series should be administered at 2, 4, and 6 months of age. A Hib (HI) antibody level of ≥ 0.15 μg/mL is used as a criterion for clinical trials.
- If the first 2 doses were PRP-OMP (PedvaxHIB or Comvax), and were administered at 2 and 4 months of age, the dose at 6 months should not be administered. Use Td vaccine for this age group.
- For children aged 10 years and older, who have not been immunized with the childhood Hib vaccine series, one dose of Hib (HI) vaccine is recommended.
- For other catch-up issues, see Figure 2.

3. Haemophilus influenzae type b (Hib) conjugate vaccine. (Minimum age: 6 weeks)

Routine vaccination:
- Administer a Hib vaccine primary series and a booster dose to all infants.
- The primary series should be administered at 2, 4, and 6 months of age. However, a dose of Hib (HI) vaccine should be administered at 2 and 4 months of age, if the dose at 6 months is not administered. One booster dose at age 12 through 15 months.
- Hib (PRP-T) should only be used for the booster (final) dose in children aged 12 through 15 months.
- If the first 2 doses were PRP-OMP (PedvaxHIB or Comvax), and were administered at 2 and 4 months of age, the dose at 6 months should not be administered. Use Td vaccine for this age group.
- For unvaccinated children aged 15 months or older, administer only 1 booster dose.
- For other catch-up issues, see Figure 2.

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- For unvaccinated children aged 15 months or older, administer only 1 booster dose.
- For other catch-up issues, see Figure 2.

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- The primary series should be administered at 2, 4, and 6 months of age. However, a dose of Hib vaccine should be administered at 2 and 4 months of age, if the dose at 6 months is not administered. One booster dose at age 12 through 15 months.
- Hib (PRP-T) should only be used for the booster (final) dose in children aged 12 through 15 months.
Contact with the index patient, or medical personnel without direct exposure to the patient’s oral secretions. Rifampin twice daily for 2 days, ceftriaxone once, and ciprofloxacin once (>18 years of age) are the recommended regimens. Azithromycin may be used in the case of resistant organisms.

**Tetanus**

All postexposure wound treatment begins with immediate, thorough cleansing using soap and water, removal of foreign bodies, and debridement of devitalized tissue. Tetanus prophylaxis after wounds and injuries includes vaccination of persons with incomplete immunization and tetanus immunoglobulin for contaminated wounds (soil, feces, saliva), puncture wounds, avulsions, and wounds resulting from missiles, crushing, burns, and frostbite (Table 94-1).

**Rabies**

Rabies immunoglobulin (RIG) and rabies vaccine are extremely effective for prophylaxis after exposure to rabies but are of no known benefit after symptoms appear. Because rabies is one of the deadliest infections, recognition of potential exposure and prophylaxis are crucial. Any healthy-appearing domestic animal responsible for an apparently unprovoked bite should be observed for 10 days for signs of rabies, without immediate treatment of the victim. Prophylaxis should be administered if the animal is rabid or suspected to be rabid, or if the animal develops signs of rabies while under observation. A captured wild animal should be euthanized (by animal control officials) without a period of observation and its brain examined for evidence of rabies. If the biting animal is not captured, particularly if it is a wild animal of a species known to harbor the virus in the region, rabies should be presumed and prophylaxis administered to the victim. Skunks, raccoons, foxes, woodchucks, most other carnivores, and bats are regarded as rabid unless proved negative by testing. Prophylaxis also should be provided following exposure to a bat for persons who might be unaware or unable to relate that a bite or direct contact has occurred, such as a mentally disabled person, a sleeping child, or an unattended infant.

All rabies postexposure management begins with immediate thorough cleansing of the bite using soap and water and, if available, irrigation with a virucidal agent such as povidone-iodine. RIG at a dose of 20 U/kg should be administered, with the full dose of RIG infiltrated subcutaneously into the area around the wound, if possible. Any remaining RIG that cannot be infiltrated into the wound should be administered as an intramuscular injection. Inactivated rabies vaccine should be administered simultaneously as soon as possible, with additional vaccine doses at 3, 7, and 14 days.

<table>
<thead>
<tr>
<th>Previous Tetanus Immunization (Doses)</th>
<th>DTap, Tdap, or Td†</th>
<th>TIG†,‡</th>
<th>DTap, Tdap, or Td</th>
<th>TIG‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncertain or &lt;3 doses</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>≥3 doses</td>
<td>Yes if ≥10 yr since the last tetanus toxoid-containing vaccine dose</td>
<td>No</td>
<td>Yes if ≥5 yr since the last tetanus toxoid-containing vaccine dose</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 94-1 Guide to Tetanus Prophylaxis in Routine Wound Management

The selection of anti-infective therapy depends on a number of factors: the site of infection and clinical syndrome, host immunity, probable causative agents, the pathogen’s susceptibility to antimicrobial agents and the local epidemiology of resistance, the pharmacokinetics of the selected agents, and their pharmacodynamics in specific patient populations.

**Empirical or presumptive anti-infective therapy** is based on a clinical diagnosis combined with published evidence and experience of the probable causative pathogens. **Definitive therapy** relies on microbiologic diagnosis by isolation or other direct evidence of a pathogen. Microbiologic diagnosis permits characterization of the pathogen’s anti-infective drug susceptibilities and delivery of the appropriate anti-infective agent to the site of infection in concentrations sufficient to kill or alter the pathogen and facilitate an effective immune response. Antiviral therapy must include consideration of the intracellular nature of viral replication and, to avoid toxicity to host cells, must be targeted to viral-specific proteins, such as the thymidine kinase of herpesviruses or the reverse transcriptase of human immunodeficiency virus.

Empirical antimicrobial therapy is best initiated after obtaining appropriate cultures of fluids or tissues. In high-risk circumstances, such as neonatal sepsis or bacteremia in immunocompromised persons, empirical therapy includes broad-spectrum antimicrobials (see Chapters 96 and 120).
Empirical antimicrobial therapy may be tailored to specific pathogens based on the clinical diagnosis (e.g., streptococcal pharyngitis) or defined risks (e.g., close exposure to tuberculosis). Definitive therapy can additionally minimize drug toxicity, development of resistant microorganisms, and cost.

Antimicrobial agents are an adjunct to the normal host immune response. Infections associated with foreign bodies, such as an intravascular catheter, are difficult to eradicate with antimicrobials alone because of organism-produced biofilms that impair phagocytosis. Similarly it is difficult for phagocytic cells to eradicate bacteria amid vegetations of fibrin and platelets on infected heart valves. Prolonged, bactericidal therapy is required with these infections, and outcomes are not always satisfactory. Foreign body devices may have to be removed if sterilization does not occur promptly. Infections in closed spaces with limited perfusion (such as abscesses or chronic osteomyelitis with poorly perfused bone) are difficult to cure without surgical drainage, debridement of the infected tissue, and reestablishment of a good vascular supply.

Optimal antimicrobial therapy requires an understanding of both the pharmacokinetics (e.g., bioavailability and tissue penetration) of the administered drugs and their pharmacodynamics (e.g., metabolism and excretion by the body) in specific patient populations. The bioavailability of orally administered antibiotics varies, depending on the acid stability of the drug; degree of gastric acidity; and whether it is taken with food, antacids, H2 blockers, or other medications. An ileus or diffuse diarrhea may alter intestinal transit time and result in unpredictable absorption.

The site and nature of the infection may affect the choice of antimicrobials. Aminoglycosides, active against aerobic organisms only, have significantly reduced activity in abscesses with low pH and oxygen tension. Infections of the central nervous system or the eye necessitate treatment with antimicrobials that penetrate and achieve therapeutic levels in these sites.

Limited renal function (as in premature infants or those with renal failure) requires increasing dosing intervals to allow time for excretion of certain drugs. The larger volume of distribution of certain hydrophilic antimicrobials and increased renal clearance (e.g., in cystic fibrosis) requires higher doses to achieve therapeutic levels. Weight-based dosage regimens may result in overdoses in obese children due to significantly smaller volumes of distribution for hydrophilic drugs. Determining serum drug levels for antibiotics with narrow safety margins (e.g., aminoglycosides and vancomycin) minimizes adverse effects of treatment.

Drug-drug interactions must be considered when multiple antimicrobial agents are used to treat infection. Use of two or more antimicrobial agents may be justified before organism identification or for the benefit of two drugs with different mechanisms of action. Several antimicrobials are administered routinely in combination (e.g., trimethoprim-sulfamethoxazole, amoxicillin-clavulanate) because of synergism (significantly greater bacterial killing or spectrum of activity than when either is used alone). The use of a bacteriostatic drug, such as a tetracycline, along with a β-lactam agent, effective against growing organisms only, may result in antibiotic antagonism, or less bacterial killing in the presence of both drugs than if either is used alone.

Core body temperature is normally maintained within 1 °C to 1.5 °C in a range of 37° C to 38° C. Normal body temperature is generally considered to be 37° C (98.6° F; range, 97° F to 99.6° F). There is a normal diurnal variation, with maximum temperature in the late afternoon. Rectal temperatures higher than 38° C (>100.4° F) generally are considered abnormal, especially if associated with symptoms.

Normal body temperature is maintained by a complex regulatory system in the anterior hypothalamus. Development of fever begins with release of endogenous pyrogens into the circulation as the result of infection, inflammatory processes, or malignancy. Microbes and microbial toxins act as exogenous pyrogens by stimulating release of endogenous pyrogens, including cytokines such as interleukin-1, interleukin-6, tumor necrosis factor, and interferons. These cytokines reach the anterior hypothalamus, liberating arachidonic acid, which is metabolized to prostaglandin E2. Elevation of the hypothalamic thermostat occurs via a complex interaction of complement and prostaglandin-E2 production. Antiinfectives (acetaminophen, ibuprofen, aspirin) inhibit hypothalamic cyclooxygenase, decreasing production of prostaglandin E2. Aspirin is associated with Reye syndrome in children and is not recommended as an antipyretic. The response to antiinfectives does not distinguish bacterial from viral infections.

The pattern of fever in children may vary, depending on age and the nature of the illness. Neonates may not have a febrile response and may be hypothermic, despite significant infection, whereas older infants and children younger than 5 years of age may have an exaggerated febrile response with temperatures of up to 105° F (40.6° C) in response to either a serious bacterial infection or an otherwise benign viral infection. Fever to this degree is unusual in older children and adolescents and suggests a serious process. The fever pattern does not reliably distinguish bacterial from viral infections.

Children with fever without a focus present a diagnostic challenge that includes identifying bacteremia and sepsis. Bacteremia, the presence of bacteria in the bloodstream, may be primary or secondary to a focal infection. Sepsis is the systemic response to infection that is manifested by hyperthermia or hypothermia, tachycardia, tachypnea, and shock (see Chapter 40). Children with septicemia and signs of central nervous system dysfunction (irritability, lethargy), cardiovascular impairment (cyanosis, poor perfusion), and disseminated intravascular coagulation (petechiae, ecchymosis) are...
readily recognized as toxic appearing or septic. Most febrile illnesses in children may be categorized as follows:

- **Fever of short duration** accompanied by localizing signs and symptoms, in which a diagnosis can often be established by clinical history and physical examination
- **Fever without localizing signs (fever without a focus)**, frequently occurring in children younger than 3 years of age, in which a history and physical examination fail to establish a cause
- **Fever of unknown origin (FUO)**, defined as fever for >14 days without an identified etiology despite history, physical examination, and routine laboratory tests or after 1 week of hospitalization and evaluation

**FEVER IN INFANTS YOUNGER THAN 3 MONTHS OF AGE**

Fever or temperature instability in infants younger than 3 months of age is associated with a higher risk of serious bacterial infections than in older infants. These younger infants usually exhibit only fever and poor feeding, without localizing signs of infection. Most febrile illnesses in this age group are caused by common viral pathogens, but serious bacterial infections include *bacteremia* (caused by group B streptococcus [GBS], *Escherichia coli*, and *Listeria monocytogenes* in neonates; and *Streptococcus pneumoniae, Haemophilus influenzae*, nontypoidal *Salmonella*, and *Neisseria meningitidis* in 1- to 3-month-old infants), urinary tract infection (UTI) (*E. coli*), pneumonia (*S. pneumoniae*, GBS, or *Staphylococcus aureus*), meningitis (*S. pneumoniae, H. influenzae* type b, GBS, *N. meningitidis*, herpes simplex virus [HSV], enteroviruses), *bacterial diarrhea* (*Salmonella, Shigella, E. coli*), and *osteomyelitis* or septic arthritis (*S. aureus* or GBS).

Differential between viral and bacterial infections in young infants is difficult. Febrile infants <3 months of age who appear ill, especially if follow-up is uncertain, and all febrile infants <4 weeks of age should be admitted to the hospital for empirical antibiotics pending culture results. After blood, urine, and cerebrospinal fluid cultures are obtained, broad-spectrum parenteral antibiotics (typically ampicillin with cefotaxime or gentamicin) are administered. The choice of antibiotics depends on the pathogens suggested by localizing findings. The possibility of neonatal HSV should also be considered in febrile children <4 weeks old, and abnormal acyclovir begun in those in whom neonatal HSV is a concern. Well-appearing febrile infants ≥4 weeks of age without an identifiable focus and with certainty of follow-up are at a low risk of developing a serious bacterial infection (0.8% develop bacteremia, and 2% develop a serious localized bacterial infection). Specific criteria identifying these low-risk infants include age older than 1 month, well-appearing without a focus of infection, no history of prematurity or prior antimicrobial therapy, a white blood cell (WBC) count of 5000 to 15,000/µL, and urine with less than 10 WBCs/high-power field. Fecal leukocyte testing and chest radiograph can be considered in infants with diarrhea or respiratory signs. Low-risk infants may be followed as outpatients without empirical antibiotic treatment, or, alternatively, may be treated with intramuscular ceftriaxone. Regardless of antibiotic treatment, close follow-up for at least 72 hours, including re-evaluation in 24 hours or immediately with any clinical change, is essential.

**FEVER IN CHILDREN 3 MONTHS TO 3 YEARS OF AGE**

A common problem is the evaluation of a febrile but well-appearing child younger than 3 years of age without localizing signs of infection. Although most of these children have self-limited viral infections, some have occult bacteremia (bacteremia without identifiable focus) or UTIs, and a few have severe and potentially life-threatening illnesses. It is difficult, even for experienced clinicians, to differentiate patients with bacteremia from those with benign illnesses.

**Observational assessment** is a key part of the evaluation. Descriptions of normal appearance and alertness include child looking at the observer and looking around the room, with eyes that are shiny or bright. Descriptions that indicate severe impairment include glassy eyes and stares vacantly into space. Observations such as sitting, moving arms and legs on table or lap, and sits without support reflect normal motor ability, whereas no movement in mother’s arms and lies limply on table indicate severe impairment. Normal behaviors, such as vocalizing spontaneously, playing with objects, reaching for objects, smiling, and crying with anxious stimuli, reflect playfulness; abnormal behaviors reflect irritability. Normally, crying children are consolable and stop crying when held by the parent, whereas severe impairment is indicated by continual cry despite being held and comforted.

Children between 2 months and 3 years of age are at increased risk for infection with organisms with polysaccharide capsules, including *S. pneumoniae, H. influenzae, N. meningitidis*, and nontypoidal *Salmonella*. Effective phagocytosis of these organisms requires opsonic antibody. Transplacental maternal IgG initially provides immunity to these organisms, but as the IgG gradually dissipates, risk of infection increases. In the United States, use of conjugate *H. influenzae* type b and *S. pneumoniae* vaccines has dramatically reduced the incidence of these infections. Determining the child’s immunization status is essential to evaluate risk of these infections. An approach to evaluation of these children is outlined in Figure 96-1.

Most episodes of fever in children younger than 3 years of age have a demonstrable source of infection elicited by history, physical examination, or a simple laboratory test. In this age group, the most commonly identified serious bacterial infection is a UTI. A blood culture to evaluate for occult bacteremia, and urinalysis and urine culture to evaluate for a UTI, should be considered for all children younger than 3 years of age with fever without localizing signs. Stool culture should be obtained in those with diarrhea marked by blood or mucus. Ill-appearing children should be admitted to the hospital and treated with empirical antibiotics.

Approximately 0.2% of well-appearing febrile children 3 to 36 months of age vaccinated against *S. pneumoniae* and *H. influenzae* and without localizing signs have occult bacteremia. Risk factors for occult bacteremia include temperature of 102.2°F (39°C) or greater, WBC count of 15,000/mm³ or more, and elevated absolute neutrophil count, band count, erythrocyte sedimentation rate, or C-reactive protein. No combination of demographic factors (socioeconomic status, race, gender, and age), clinical parameters, or laboratory tests in these children reliably predicts occult bacteremia. Occult bacteremia in otherwise healthy children is usually transient and self-limited but may progress to serious localizing infections. Well-appearing children usually are followed as...
Figure 96-1 Approach to a child younger than 36 months of age with fever without localizing signs. The specific management varies, depending on the age and clinical status of the child.

Important historical elements include the impact the fever has on the child’s health and activity; weight loss; the use of drugs, medications, or immunosuppressive therapy; history of unusual, severe, or chronic infection suggesting immunodeficiency (see Chapter 72); immunizations; exposure to unprocessed or raw foods; history of pica and exposure to soil-borne or waterborne organisms; exposure to industrial or hobby-related chemicals; blood transfusions; domestic or foreign travel; exposure to animals; exposure to ticks or mosquitoes; ethnic background; recent surgical procedures or dental work; tattooing and body piercing; and sexual activity.

The etiology of most occult infections causing FUO is an unusual presentation of a common disease. Sinusitis, endocarditis, intra-abdominal abscesses (perinephric, intrahepatic, subdiaphragmatic), and central nervous system lesions (tuberculoma, cystercerosis, abscess, toxoplasmosis) may be relatively asymptomatic. Infections are the most common cause of FUO in children, followed by inflammatory diseases, malignancy, and other etiologies (Table 96-1). Inflammatory diseases account for approximately 20% of episodes. Malignancies are a less common cause of FUO in children than in adults, accounting for about 10% of all episodes. Approximately 15% of children with FUO have no diagnosis. Fever eventually resolves in many of these cases, usually without sequelae, although some may develop definable signs of rheumatic disease over time. Common infections causing FUO in patients with known or newly diagnosed immunodeficiency include viral hepatitis, Epstein-Barr virus, cytomegalovirus, Bartonella henselae, ehrlichiosis, Salmonella, and tuberculosis.

Factitious fever or fever produced or feigned intentionally by the patient (Munchausen syndrome) or the parent of a child (Munchausen syndrome by proxy) is an important consideration, particularly if family members are familiar with health care practices (see Chapter 22). Fever should be recorded in the hospital by a reliable individual who remains with the patient when the temperature is taken. Continuous observation over a long period and repetitive evaluation are essential.

Screening tests for FUO include complete blood count with WBC and differential count, platelet count, erythrocyte
Figure 96-2 Approach to the evaluation of fever of unknown origin (FUO) in children. Screening laboratory tests include a complete blood count and differential white blood cell count, platelet count, erythrocyte sedimentation rate, hepatic transaminase levels, urinalysis, bacterial cultures of urine and blood, chest radiograph, and evaluation for rheumatic disease with antinuclear antibody, rheumatoid factor, and serum complement (C3, C4, CH50). PCR, polymerase chain reaction.

Table 96-1 Causes of Fever of Unknown Origin in Children

<table>
<thead>
<tr>
<th>INFECTIONS</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOCALIZED INFECTIONS</strong></td>
<td>Mycoplasma pneumoniae</td>
</tr>
<tr>
<td>Abscesses: abdominal, brain, dental, hepatic, pelvic, perinephric, rectal, subphrenic, splenic, periappendiceal, psoas</td>
<td>Relapsing fever (Borrelia recurrentis, other Borrelia)</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>Salmonellosis</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>Spiroillum minus (rat-bite fever)</td>
</tr>
<tr>
<td>Mastoiditis</td>
<td>Streptobacillus moniliformis (rat-bite fever)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Whipple disease</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Yersiniosis</td>
</tr>
<tr>
<td><strong>BACTERIAL DISEASES</strong></td>
<td>VIRAL DISEASES</td>
</tr>
<tr>
<td>Actinomycosis</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Bartonella henselae (cat-scratch disease)</td>
<td>HIV (and associated opportunistic infections)</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>Infectious mononucleosis (Epstein-Barr virus)</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>CHLAMYDIAL DISEASES</td>
</tr>
<tr>
<td>Francisella tularensis (tularemia)</td>
<td>Lymphogranuloma venereum</td>
</tr>
<tr>
<td>Gonococcemia (chronic)</td>
<td>Psittacosis</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>RICKETTSIAL DISEASES</td>
</tr>
<tr>
<td>Listeria monocytogenes (listeriosis)</td>
<td>Ehrlichiosis</td>
</tr>
<tr>
<td>Lyme disease (Borrelia burgdorferi)</td>
<td>Q fever (Coxiella burnetii)</td>
</tr>
<tr>
<td>Meningococcemia (chronic)</td>
<td></td>
</tr>
</tbody>
</table>
sedimentation rate, C-reactive protein, hepatic transaminase levels, urinalysis, cultures of urine and blood, chest radiograph, and evaluation for rheumatic disease with antinuclear antibody, rheumatoid factor, and serum complement (C3, C4, CH50). Additional tests for FUO may include throat culture, stool culture, tuberculin skin test or interferon-gamma release assay, HIV antibody, Epstein-Barr virus antibody profile, and \( B. henselae \) antibody. Consultation with infectious disease, immunology, rheumatic disease, or oncology specialists should be considered. Further tests may include lumbar puncture for cerebrospinal fluid analysis and culture; computed tomography or magnetic resonance imaging of the chest, abdomen, and head; radionuclide scans; and bone marrow biopsy for cytology and culture.

<table>
<thead>
<tr>
<th>Causes of Fever of Unknown Origin in Children—cont’d</th>
</tr>
</thead>
</table>

**INFECTIONS**
- Rocky Mountain spotted fever
- Tick-borne typhus

**Fungal Diseases**
- Blastomycosis (extrapulmonary)
- Coccidioidomycosis (disseminated)
- Histoplasmosis (disseminated)

**Parasitic Diseases**
- Extraintestinal amebiasis
- Babesiosis
- Giardiasis
- Malaria
- Toxoplasmosis
- Trichinosis
- Trypanosomiasis
- Visceral larva migrans (Toxocara)

**Inflammatory Diseases**
- Behçet syndrome
- Crohn’s disease
- Drug fever
- Hypersensitivity pneumonitis
- Juvenile dermatomyositis
- Juvenile idiopathic arthritis (systemic onset, Still disease)
- Inflammatory bowel disease (Crohn’s disease, ulcerative colitis)
- Kawasaki disease
- Polyarteritis nodosa
- Rheumatic fever
- Sarcoidosis
- Serum sickness
- Systemic lupus erythematosus
- Weber-Christian disease

**Malignancies**
- Atrial myxoma
- Cholesterol granuloma
- Ewing sarcoma
- Hepatoma

**Miscellaneous**
- Addison disease
- Anhidrotic ectodermal dysplasia
- Castleman disease
- Chronic active hepatitis
- Cyclic neutropenia
- Deafness, urticaria, amyloidosis syndrome
- Diabetes insipidus (central and nephrogenic)
- Fabry disease
- Factitious fever
- Familial dysautonomia
- Familial Mediterranean fever and other autoinflammatory disorders
- Granulomatous hepatitis
- Hemophagocytic syndromes
- Hypertriglyceridemia
- Hypothalamic-central fever
- Ichthyosis
- Infantile cortical hyperostosis
- Inflammatory bowel disease
- Factitious fever
- Kikuchi-Fujimoto disease
- Metal fume fever
- Pancreatitis
- Periodic fever syndromes
- Poissoning
- Postoperative (pericardiectomy, craniectomy)
- Pulmonary embolism
- Thrombophlebitis
- Thyrotoxicosis
- Tumor necrosis factor-\( \alpha \) receptor-associated periodic fever syndrome (TRAPS)

Rashes are a common manifestation of many infections; this chapter describes five common childhood viral exanthems characterized by fever and rash. Rash distribution and appearance provide important clues to the differential diagnosis, including other infectious agents (Table 97-1).

### MEASLES (RUBEOLA)

**Etiology**

Measles (rubeola) is highly contagious and is caused by a single-stranded RNA paramyxovirus with one antigenic type. Humans are the only natural host. Measles virus infects the upper respiratory tract and regional lymph nodes and is spread systemically during a brief, low-titer primary viremia. A secondary viremia occurs within 5 to 7 days as virus-infected monocytes spread the virus to the respiratory tract, skin, and other organs. Virus is present in respiratory secretions, blood, and the urine of infected individuals. Measles virus is transmitted by droplets or the airborne route and is highly contagious. Infected persons are contagious from 1 to 2 days before onset of symptoms—from about 5 days before to 4 days after the appearance of rash—and immunocompromised persons can have prolonged excretion of contagious virus.

**Epidemiology**

Measles remains endemic in regions of the world where measles vaccination is not available and is responsible for about 1 million deaths annually. Since 2000 there typically have been fewer than 100 cases reported annually in the United States, although outbreaks resulting from imported virus after international travel occur. Infections of nonimmigrant children during outbreaks may occur among those too young to be vaccinated or in communities with low immunization rates. Most young infants are protected by transplacental maternal antibody until the end of their first year.

**Clinical Manifestations**

Measles infection is divided into four phases: incubation, prodromal (catarrhal), exanthematous (rash), and recovery. The incubation period is 8 to 12 days from exposure to symptom onset and a mean of 14 days (range, 7 to 21) from exposure to rash onset. The manifestations of the 3-day prodromal period
Table 97-1  Differential Diagnosis of Fever and Rash—cont’d

<table>
<thead>
<tr>
<th>LESION PATHOGEN OR DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macular or Maculopapular Rash</td>
</tr>
<tr>
<td>Coxsackievirus</td>
</tr>
<tr>
<td>Bacteria Staphylococcal scalded skin syndrome</td>
</tr>
<tr>
<td>Staphylococcal bullous impetigo</td>
</tr>
<tr>
<td>Group A streptococcal crusted impetigo</td>
</tr>
<tr>
<td>Rickettsiae Rickettsialpox</td>
</tr>
<tr>
<td>Other Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Erythema multiforme (Stevens-Johnson syndrome)</td>
</tr>
<tr>
<td>Petechial-Purpuric</td>
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<tr>
<td>Viruses Adenovirus</td>
</tr>
<tr>
<td>Atypical measles</td>
</tr>
<tr>
<td>Congenital rubella</td>
</tr>
<tr>
<td>Congenital cytomegalovirus</td>
</tr>
<tr>
<td>Enterovirus</td>
</tr>
<tr>
<td>Papular-purpuric gloves and socks (parvovirus B19)</td>
</tr>
<tr>
<td>HIV</td>
</tr>
<tr>
<td>Hemorrhagic fever viruses</td>
</tr>
<tr>
<td>Bacteria Sepsis (meningococcal, gonococcal, pneumococcal, <em>Haemophilus influenzae</em> type b)</td>
</tr>
<tr>
<td>Infective endocarditis</td>
</tr>
<tr>
<td><em>Ecthyma gangrenosum (Pseudomonas aeruginosa)</em></td>
</tr>
<tr>
<td><em>Vibrio vulnificus</em></td>
</tr>
<tr>
<td>Rickettsiae Rocky Mountain spotted fever</td>
</tr>
<tr>
<td>Epidemic typhus</td>
</tr>
<tr>
<td>Ehrlichiosis</td>
</tr>
<tr>
<td>Fungi Necrotic eschar (<em>Aspergillus, Mucor</em>)</td>
</tr>
<tr>
<td>Other Vasculitis</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>Malaria</td>
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<tr>
<td>Erythema Nodosum</td>
</tr>
<tr>
<td>Viruses Epstein-Barr virus</td>
</tr>
<tr>
<td>HBV</td>
</tr>
<tr>
<td>Bacteria Group A streptococcus</td>
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<td><em>Mycobacterium tuberculosis</em></td>
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<td><em>Yersinia</em></td>
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<td>Cat-scratch disease (<em>Bartonella henselae</em>)</td>
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<td>Fungi Coccidioidomycosis</td>
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<td>Histoplasmosis</td>
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<td>Other Sarcoidosis</td>
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<td>Inflammatory bowel disease</td>
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<td>Estrogen-containing oral contraceptives</td>
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are cough, coryza, conjunctivitis, and the pathognomonic Koplik spots (gray-white, sand grain-sized dots on the buccal mucosa opposite the lower molars) that last 12 to 24 hours. The conjunctiva may reveal a characteristic transverse line of inflammation along the eyelid margin (Stimson line). The classic symptoms of cough, coryza, and conjunctivitis occur during the secondary viremia of the exanthematous phase, which often is accompanied by high fever (40° C to 40.5° C [104° F to 105° F]). The macular rash begins on the head (often above the hairline) and spreads over most of the body in a cephalad to caudal pattern over 24 hours. Areas of the rash often are confluent. The rash fades in the same pattern, and illness severity is related to the extent of the rash. It may be petechial or hemorrhagic (black measles). As the rash fades, it undergoes brownish discoloration and desquamation.

Cervical lymphadenitis, splenomegaly, and mesenteric lymphadenopathy with abdominal pain may be noted with the rash. Otitis media, pneumonia, and diarrhea are more common in infants. Liver involvement is more common in adults.

The term modified measles describes mild cases of measles occurring in persons with partial protection against measles. Modified measles occurs in persons vaccinated before 12 months of age or with coadministration of immune serum globulin, in infants with disease modified by transplacental antibody, or in persons receiving immunoglobulin.

**Laboratory and Imaging Studies**
Routine laboratory findings are nonspecific and do not aid in diagnosis. Leukopenia is characteristic. In patients with acute encephalitis, the cerebrospinal fluid reveals an increased protein, a lymphocytic pleocytosis, and normal glucose levels. Measles virus culture is not generally available, though identification of measles RNA via reverse transcriptase-polymerase chain reaction (PCR) may be available through state public health departments or the Centers for Disease Control and Prevention (CDC). Serologic testing for IgM antibodies that appear within 1 to 2 days of the rash and persist for 1 to 2 months in unimmunized persons confirms the clinical diagnosis, though IgM antibodies may be present only transiently in immunized people. Suspected cases should be reported immediately to the local or state health department.

**Differential Diagnosis**
The constellation of fever, rash, cough, and conjunctivitis is diagnostic for measles. Koplik spots are pathognomonic but are not always present at the time the rash is most pronounced. Confirmation is by diagnostic antibody increases in acute and convalescent sera. The rash must be differentiated from rubella, roseola, enteroviral or adenoviral infection, infectious mononucleosis, toxoplasmosis, meningococcemia, scarlet fever, rickettsial disease, Kawasaki disease, Kawasaki disease, serum sickness, and drug rash.

**Treatment**
Routine supportive care includes maintaining adequate hydration and antipyretics. High-dose vitamin A supplementation has been shown to improve the outcome of infants with measles in developing countries. The World Health Organization recommends routine administration of vitamin A for 2 days to all children with acute measles.

*HBV*, Hepatitis B virus; *HHV*, human herpesvirus.
Complications and Prognosis

Otitis media is the most common complication of measles infection. Interstitial (measles) pneumonia can occur, or pneumonia may result from secondary bacterial infection with *Streptococcus pneumoniae*, *Staphylococcus aureus*, or group A streptococcus. Persons with impaired cell-mediated immunity may develop giant cell (Hecht) pneumonia, which is usually fatal. Myocarditis and mesenteric lymphadenitis are infrequent complications.

Encephalomyelitis occurs in 1 to 2 per 1000 cases and usually occurs 2 to 5 days after the onset of the rash. Early encephalitis probably is caused by direct viral infection of brain tissue, whereas later onset encephalitis is a demyelinating and probably an immunopathologic phenomenon. Subacute sclerosing panencephalitis is a late neurologic complication of slow measles infection that is characterized by progressive behavioral and intellectual deterioration and eventual death. It occurs in approximately 1 in every 1 million cases of measles, an average of 8 to 10 years after measles. There is no effective treatment.

Deaths most frequently result from bronchopneumonia or encephalitis, with much higher risk in persons with malignancy, severe malnutrition, age under 5 years, or immunocompromise (such as HIV infection). Late deaths in adolescents and adults usually result from subacute sclerosing panencephalitis. Other forms of measles encephalitis in immunocompetent persons are associated with a mortality rate of approximately 15%, with 20% to 30% of survivors having serious neurologic sequelae.

Prevention

Live measles vaccine prevents infection and is recommended as measles, mumps, and rubella (MMR) for children at 12 to 15 months and 4 to 6 years of age. The MMRV (MMR combined with varicella vaccine) is an alternative vaccine for children 12 months to 12 years of age, provided there are no contraindications, but is associated with a higher rate of febrile seizures following administration. The second dose of MMR is not a booster dose but significantly reduces the primary vaccine failure rate, from <5% to <1%. Contraindications to measles vaccine include immunocompromised states or an immunosuppressive course of corticosteroids (>2 mg/kg/day for >14 days); pregnancy; or recent administration of immunoglobulin (3 to 11 months, depending on dose). MMR vaccination is recommended for all HIV-infected persons without evidence of severe immunosuppression (low age-specific total CD4 T-lymphocyte count or a low CD4 T-lymphocyte count as a percentage of total lymphocytes), children with cancer in remission who have not received chemotherapy in the previous 3 months, and children who have not received immunosuppressive corticosteroids in the previous month. Susceptible household contacts with a chronic disease or who are immunocompromised should receive postexposure prophylaxis with measles vaccine within 72 hours of measles exposure or immunoglobulin within 6 days of exposure.

RUBELLA (GERMAN OR 3-DAY MEASLES)

Etiology

Rubella, also known as German measles or 3-day measles, is caused by a single-stranded RNA virus with a glycolipid envelope and is a member of the togavirus family. Humans are the only natural host. Rubella virus invades the respiratory epithelium and disseminates via a primary viremia. After replication in the reticuloendothelial system, a secondary viremia ensues, and the virus can be isolated from peripheral blood monocytes, cerebrospinal fluid, and urine. Rubella virus is most contagious through direct or droplet contact with nasopharyngeal secretions from 2 days before until 5 to 7 days after rash onset, although virus may be present in nasopharyngeal secretions from 7 days before until 14 days after the rash.

Infection in utero results in significant morbidity from congenital rubella syndrome (CRS) with associated ophthalmologic, cardiac, and neurologic manifestations (see Chapter 66). Maternal infection during the first trimester results in fetal infection with generalized vasculitis in more than 90% of cases. Infants with congenital rubella may shed the virus in nasopharyngeal secretions and urine for longer than 12 months after birth and may transmit the virus to susceptible contacts.

Epidemiology

In unvaccinated populations, rubella usually occurs in the spring, with epidemics occurring in cycles of every 6 to 9 years. Approximately 25% to 50% of cases are subclinical. Fewer than 20 cases of rubella now occur annually in the United States. Outbreaks of rubella occasionally occur in nonvaccinated groups from internationally imported cases. Transplacental antibody is protective during the first 6 months of life.

Clinical Manifestations

The incubation period for postnatal rubella is typically 16 to 18 days (range, 14 to 21 days). The mild cattarchal symptoms of the prodromal phase of rubella may go unnoticed. The characteristic signs of rubella are retroauricular, posterior cervical, and posterior occipital lymphadenopathy accompanied by an erythematous, maculopapular, discrete rash. The rash begins on the face and spreads to the body, lasting for 3 days and less prominent than that of measles. Rose-colored spots on the soft palate, known as Forchheimer spots, develop in 20% of patients and may appear before the rash. Other manifestations of rubella include mild pharyngitis, conjunctivitis, anorexia, headache, malaise, and low-grade fever. Polyarthritis, usually of the hands, may occur, especially among adult females, but usually resolves without sequelae. Paresthesias and tendinitis may occur.

Laboratory and Imaging Studies

Routine laboratory findings are nonspecific and generally do not aid in diagnosis. The white blood cell count usually is normal or low, and thrombocytopenia rarely occurs. Diagnosis is confirmed by serologic testing for IgM antibodies (typically positive 5 days after symptom onset) or by a fourfold or greater increase in specific IgG antibodies in paired acute and convalescent sera. CRS cases can have detectable IgM until
3 months of age, and stable or rising IgG titers over the first 7 to 11 months of age. False-positive IgM results can occur. Cases of suspected congenital rubella syndrome and postnatal rubella infection should be reported to the local and state health department.

**Differential Diagnosis**
The rash must be differentiated from measles, roseola, enteroviral or adenoviral infection, infectious mononucleosis, toxoplasmosis, scarlet fever, rickettsial disease, Kawasaki disease, serum sickness, and drug rash.

**Complications and Prognosis**
Other than congenital rubella syndrome (see Chapter 66) arising from rubella infection during pregnancy, complications are rare. Deaths rarely occur with rubella encephalitis.

**Prevention**
Live rubella vaccine prevents infection and is recommended as MMR for children at 12 to 15 months and at 4 to 6 years of age. After vaccination, rubella virus is shed from the nasopharynx for several weeks, but it is not communicable. In children, rubella vaccine rarely is associated with adverse effects, but in postpubertal females, it causes arthralgias in 25% of vaccinated individuals and acute arthritis-like symptoms in 10% of vaccinated individuals. These symptoms typically develop 1 to 3 weeks after vaccination and last 1 to 3 days.

**Contraindications** to rubella vaccine include immunocompromised states or an immunosuppressive course of corticosteroids (>2 mg/kg/day for >14 days); pregnancy; or recent administration of immunoglobulin (3 to 11 months, depending on dose). Vaccine virus has been recovered from fetal tissues, although no cases of CRS have been identified among infants born to women inadvertently vaccinated against rubella during pregnancy. Nevertheless women are cautioned to avoid pregnancy after receipt of rubella-containing vaccine for 28 days. All pregnant women should have prenatal serologic testing to determine their immune status to rubella, and susceptible mothers should be vaccinated after delivery and before hospital discharge.

Susceptible, nonpregnant persons exposed to rubella should receive rubella vaccination. Immunoglobulin is not recommended for postexposure prophylaxis of susceptible, pregnant women exposed to rubella.

**ROSEOLA INFANTUM (EXANTHEM SUBITUM)**

**Etiology**
Roseola infantum (exanthem subitum, sixth disease) is caused primarily by human herpesvirus type 6 (HHV-6), and by HHV-7 in 10% to 30% of cases. HHV-6 and HHV-7 are large, enveloped double-stranded DNA viruses that are members of the herpesvirus family. They infect mature mononuclear cells and cause a relatively prolonged (3 to 5 day) viremia during primary infection. They can be detected in the saliva of healthy adults, which suggests, as with other herpesviruses, the development of lifelong latent infection and intermittent viral shedding.

**Epidemiology**
Transplacental antibody protects most infants until 6 months of age. The incidence of infection increases as maternally derived antibody levels decline. By 12 months of age, approximately 60% to 90% of children have antibodies to HHV-6, and essentially all children are seropositive by 2 to 3 years of age. The virus is likely acquired from asymptomatic adults who periodically shed these viruses. HHV-6 is a major cause of acute febrile illnesses in infants and may be responsible for 20% of visits to the emergency department for children 6 to 18 months of age.

**Clinical Manifestations**
Roseola is characterized by high fever (often >40° C) with an abrupt onset that lasts 3 to 5 days. A maculopapular, rose-colored rash erupts coincidentally with defervescence, although it may be present earlier. The rash usually lasts 1 to 3 days but may fade rapidly and is not present in all infants with HHV-6 infection. Upper respiratory symptoms, nasal congestion, erythematous tympanic membranes, and cough may occur. Gastrointestinal symptoms are described. Most children with roseola are irritable and appear toxic. Roseola is associated with approximately one third of febrile seizures. Roseola caused by HHV-6 and HHV-7 is clinically indistinguishable, although HHV-6-associated roseola typically occurs in younger infants. Reactivation of HHV-6 following bone marrow transplantation may result in bone marrow suppression, hepatitis, rash, and encephalitis.

**Laboratory and Imaging Studies**
Routine laboratory findings are nonspecific and do not aid in diagnosis. Encephalitis with roseola is characterized by pleocytosis (30 to 200 cells/mm³) with mononuclear cell predominance, elevated protein concentration, and normal glucose concentration. Serologic testing showing a fourfold rise in acute and convalescent sera or documentation of HHV-6 DNA by PCR in the cerebrospinal fluid is diagnostic.

**Differential Diagnosis**
The pattern of high fever for 3 to 5 days without significant physical findings followed by onset of rash with defervescence of fever is characteristic. Many febrile illnesses may be easily confused with roseola during the preeruptive stage. Serious infections must be excluded, although most children are alert, behave normally, and continue with their usual daily activities.

**Treatment**
There is no specific therapy for roseola. Routine supportive care includes maintaining adequate hydration and antipyretics. In immunocompromised hosts, use of ganciclovir or foscarin can be considered.
Complications and Prognosis

The prognosis for roseola is excellent. A few deaths have been attributed to HHV-6, usually in cases complicated by encephalitis or virus-associated hemophagocytosis syndrome.

Prevention

There are no guidelines for prevention of roseola.

ERYTHEMA INFECTIOSUM (FIFTH DISEASE)

Etiology

Erythema infectiosum (fifth disease) is caused by the human parvovirus B19, a single-stranded DNA virus producing a benign viral exanthem in healthy children. The viral affinity for red blood cell progenitor cells makes it an important cause of aplastic crisis in patients with hemolytic anemias, including sickle cell disease, spherocytosis, and thalassemia. Parvovirus B19 also causes fetal anemia and hydrops fetalis after primary infection during pregnancy. The cell receptor for parvovirus B19 is the erythrocyte P antigen, a glycolipid present on erythroid cells. The virus replicates in actively dividing erythroid stem cells, leading to cell death that results in erythroid aplasia and anemia.

Epidemiology

Erythema infectiosum is common. Parvovirus B19 seroprevalence is only 2% to 9% in children younger than 5 years of age but increases to 15% to 35% in children 5 to 18 years and 30% to 60% in adults. Community epidemics usually occur in the spring. The virus is transmitted by respiratory secretions and by blood product transfusions.

Clinical Manifestations

The incubation period is typically 4 to 14 days and rarely may last 21 days. Parvovirus B19 infections usually begin with a mild, nonspecific illness characterized by fever, malaise, myalgias, and headache. In some cases, the characteristic rash appears 7 to 10 days later. Erythema infectiosum is manifested by rash, low-grade or no fever, and occasionally pharyngitis and mild conjunctivitis. The rash appears in three stages. The initial stage is typically a “slapped cheek” rash with circumoral pallor. An erythematous symmetric, maculopapular, truncal rash appears 1 to 4 days later, then fades as central clearing takes place, giving a distinctive lacy, reticulated rash that lasts 2 to 40 days (mean, 11 days). This rash may be pruritic, does not desquamate, and may recur with exercise, bathing, rubbing, or stress. Adolescents and adults may experience myalgia, significant arthralgias or arthritis, headache, pharyngitis, coriza, and gastrointestinal upset.

Children with shortened erythrocyte life span (e.g., sickle cell disease) may develop a transient aplastic crisis characterized by ineffective erythroid production typically lasting 7 to 10 days (see Chapter 150). Most children with parvovirus B19-induced transient aplastic crisis have multiple symptoms, including fever, lethargy, malaise, pallor, headache, gastrointestinal symptoms, and respiratory symptoms. The reticulocyte count is extremely low, and the hemoglobin level is lower than usual for the patient. Transient neutropenia and thrombocytopenia also commonly occur.

Persistent parvovirus B19 infection may develop in children with immunodeficiency, causing severe anemia resulting from pure red blood cell aplasia. These children do not display the typical manifestations of erythema infectiosum.

Laboratory and Imaging Studies

Hematologic abnormalities occur with parvovirus infection, including reticulocytopenia lasting 7 to 10 days, mild anemia, thrombocytopenia, lymphopenia, and neutropenia. Parvovirus B19 can be detected by PCR and by electron microscopy of erythroid precursors in the bone marrow. Serologic tests showing specific IgM antibody to parvovirus are diagnostic, demonstrating infection that probably occurred in the prior 2 to 4 months.

Differential Diagnosis

The diagnosis of erythema infectiosum in children is established on the basis of the clinical findings of typical facial rash with absent or mild prodromal symptoms, followed by a reticulated rash over the body that waxes and wanes. The differential diagnosis includes measles, rubella, scarlet fever, enteroviral or adenoviral infection, infectious mononucleosis, scarlet fever, Kawasaki disease, systemic lupus erythematosus, serum sickness, and drug reaction.

Treatment

There is no specific therapy. Routine supportive care includes maintaining adequate hydration and antipyretics. Transfusions may be required for transient aplastic crisis. Intrauterine transfusion has been performed for hydrops fetalis associated with fetal parvovirus B19 infection. Intravenous immunoglobulin may be used for immunocompromised persons with severe anemia or chronic infection.

Complications and Prognosis

The prognosis for erythema infectiosum is excellent. Fatalities associated with transient aplastic crisis are rare. Parvovirus B19 is not teratogenic, but in utero infection of fetal erythroid cells may result in fetal heart failure, hydrops fetalis, and fetal death. Of the approximately 50% of women of childbearing age susceptible to parvovirus B19 infection, 30% of exposed women develop infection, with 25% of exposed fetuses becoming infected and 10% of these culminating in fetal death.

Prevention

The greatest risk is to pregnant women. Effective control measures are limited. Exclusion of affected children from school is not recommended, because children generally are not infectious by the time the rash is present. Good handwashing and hygiene are practical measures that should help reduce transmission.

VARICELLA-ZOSTER VIRUS INFECTION (CHICKENPOX AND ZOSTER)

Etiology

Chickenpox and zoster are caused by varicella-zoster virus (VZV), an enveloped, icosahedral, double-stranded DNA
The only natural host. **Chickenpox (varicella)** is the manifestation of primary infection. VZV infects susceptible individuals via the conjunctivae or respiratory tract and replicates in the nasopharynx and upper respiratory tract. It disseminates by a primary viremia and infects regional lymph nodes, the liver, the spleen, and other organs. A secondary viremia follows, resulting in a cutaneous infection with the typical vesicular rash. After resolution of chickenpox, the virus persists in latent infection in the dorsal root ganglia cells. **Zoster (shingles)** is the manifestation of reactivated latent infection of endogenous VZV. Chickenpox is highly communicable in susceptible individuals, with a secondary attack rate of more than 90%. The period of communicability ranges from 2 days before to 7 days after the onset of the rash, when all lesions are crusted.

### Clinical Manifestations

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<tr>
<th>Decision-Making Algorithms</th>
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<tr>
<td>Ataxia</td>
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<td>Alopecia</td>
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<td>Fever and Rash</td>
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<td>Petechiae/Purpura</td>
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The incubation period of varicella is generally 14 to 16 days, with a range of 10 to 21 days after exposure. Prodromal symptoms of fever, malaise, and anorexia may precede the rash by 1 day. The characteristic rash appears initially as small red papules that rapidly progress to nonumbilicated, oval, “teardrop” vesicles on an erythematous base. The fluid progresses from clear to cloudy, and the vesicles ulcerate, crust, and heal. New crops appear for 3 to 4 days, usually beginning on the trunk followed by the head, the face, and, less commonly, the extremities. There may be a total of 100 to 500 lesions, with all forms of lesions being present at the same time. Pruritus is universal and marked. Lesions may be present on mucous membranes. Lymphadenopathy may be generalized. The severity of the rash varies, as do systemic signs and fever, which generally abate after 3 to 4 days.

The preeruption phase of varicella is generally 14 to 16 days, with a range of 10 to 21 days after exposure. Prodromal symptoms of fever, malaise, and anorexia may precede the rash by 1 day. The characteristic rash appears initially as small red papules that rapidly progress to nonumbilicated, oval, “teardrop” vesicles on an erythematous base. The fluid progresses from clear to cloudy, and the vesicles ulcerate, crust, and heal. New crops appear for 3 to 4 days, usually beginning on the trunk followed by the head, the face, and, less commonly, the extremities. There may be a total of 100 to 500 lesions, with all forms of lesions being present at the same time. Pruritus is universal and marked. Lesions may be present on mucous membranes. Lymphadenopathy may be generalized. The severity of the rash varies, as do systemic signs and fever, which generally abate after 3 to 4 days.

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Epidemiology

In the prevaccine era, the peak age of occurrence was 5 to 10 years, with peak seasonal infection in late winter and spring. In the postvaccine era, the incidence of varicella has declined in all age groups, with the peak incidence now in 10 to 14 year olds. Transmission is by direct contact, droplet, and air. Zoster is a recurrence of latent VZV and is transmitted by direct contact. Only 5% of cases of zoster occur in children younger than 15 years of age. The overall incidence of zoster (215 cases per 100,000 person-years) results in a cumulative lifetime incidence of approximately 10% to 20%, with 75% of cases occurring after 45 years of age. The incidence of zoster is increased in immunocompromised persons.

### Laboratory and Imaging Studies

Laboratory testing confirmation for diagnosis is usually unnecessary. PCR is the current diagnostic method of choice, and genotyping to distinguish vaccine and wild-type strains is available through the CDC. Detection of varicella-specific antigen in vesicular fluid by immunofluorescence using monoclonal antibodies or demonstration of a fourfold antibody increase of acute and convalescent sera is also diagnostic but not as sensitive as PCR.

### Differential Diagnosis

The diagnosis of varicella and zoster is based on the distinctive characteristics of the rash. **Eczema herpeticum**, or **Kaposi varicelliform eruption**, is a localized, vesicular eruption caused by HSV that develops on skin affected by underlying eczema or trauma. The differentiation between zoster and HSV infection may be difficult because HSV may cause eruption that appears to be in a dermatomal distribution. Coxsackievirus A infection has a vesiculopustular appearance, but lesions are usually localized to the extremities and oropharynx. A previously healthy patient with more than one recurrence probably has HSV infection, which can be confirmed by viral culture.

### Treatment

Symptomatic therapy of varicella includes nonaspirin antipyretics, cool baths, and careful hygiene. Routine oral administration of acyclovir is not recommended in otherwise healthy children with varicella. The decision to use antiviral medications, the route, and duration of treatment depend on host factors and the risk for severe infection or complications. Early therapy with antivirals (especially within 24 hours of rash onset) in immunocompromised persons is effective in preventing severe complications, including pneumonia, encephalitis, and death from varicella. Acyclovir or valacyclovir may be considered in those at risk of severe varicella, such as unvaccinated persons older than 12 years; those with chronic cutaneous or pulmonary disease; receiving short-course, intermittent, or aerosolized corticosteroids; or receiving long-term salicylate therapy. The dose of acyclovir used for VZV infections is much higher than that for HSV.

Antiviral treatment of zoster accelerates cutaneous healing, hastens the resolution of acute neuritis, and reduces the risk of postherpetic neuralgia. Oral famciclovir and valacyclovir have much greater oral bioavailability than acyclovir and are...
recommended for treatment of zoster in adults. Acyclovir is recommended for children and is an alternative therapy for adults. The necessity of concomitant oral corticosteroids for zoster is controversial.

**Complications and Prognosis**

Secondary infection of skin lesions by streptococci or staphylococci is the most common complication. These infections may be mild, resembling impetigo, or life-threatening with toxic shock syndrome or necrotizing fasciitis. Pneumonia is uncommon in healthy children but occurs in 15% to 20% of healthy adults and immunocompromised persons. Myocarditis, pericarditis, orchitis, hepatitis, ulcerative gastritis, glomerulonephritis, and arthritis may complicate varicella. Reye syndrome may follow varicella; thus, salicylate use is contraindicated during varicella infection.

Neurologic complications frequently include postinfectious encephalitis, cerebellar ataxia, nystagmus, and tremor. Less common neurologic complications include Guillain-Barre syndrome, transverse myelitis, cranial nerve palsies, optic neuritis, and hypothalamic syndrome.

Primary varicella can be a fatal disease in immunocompromised persons as a result of visceral dissemination, encephalitis, hepatitis, and pneumonitis. The mortality rate approaches 15% in children with leukemia who do not receive prophylaxis or therapy for varicella (see Chapter 66).

A severe form of neonatal varicella may develop in newborns of mothers with varicella (but not shingles) occurring 5 days before to 2 days after delivery. The fetus is exposed to a large inoculum of virus but is born before the maternal antibody response develops and can cross the placenta. These infants should be treated as soon as possible with varicella-zoster immunoglobulin (VZIG) or intravenous immunoglobulin if VZIG is unavailable, to attempt to prevent or ameliorate the infection.

Primary varicella usually resolves spontaneously. The mortality rate is much higher for persons older than 20 years of age and for immunocompromised persons. Zoster usually is self-limited, especially in children. Advanced age and severity of pain at presentation and at 1 month are predictors of prolonged pain. Scarring is more common with zoster because of involvement of the deeper layers of the skin.

**Prevention**

Children with chickenpox should not return to school until all vesicles have crusted. A hospitalized child with chickenpox should be isolated in a negative-pressure room to prevent transmission.

A live attenuated varicella vaccine—two doses for all children—is recommended. The first dose should be administered at age 12 to 15 months and the second dose at 4 to 6 years. Varicella vaccine is 85% effective in preventing any disease and 97% effective in preventing moderately severe and severe disease. Transmission of vaccine virus from a healthy vaccinated individual is rare but possible.

Passive immunity can be provided by VZIG, which is indicated within 96 hours of exposure for susceptible individuals at increased risk for severe illness. Administration of VZIG does not eliminate the possibility of disease in recipients and prolongs the incubation period up to 28 days.

**CUTANEOUS INFECTIONS**

**SUPERFICIAL BACTERIAL INFECTIONS**

**Impetigo**

Nonbullous or crusted impetigo is caused most often by *Staphylococcus aureus* and occasionally by group A streptococcus. It begins as a single erythematous papulovesicle that progresses to one or many honey-colored, crusted lesions weeping serous drainage. Bullous impetigo accounts for approximately 10% of all impetigo. The skin lesions are thin-walled (0.5 to 3 cm) bullae with erythematous margins resembling second-degree burns and are associated with *S. aureus* phage type 71. Impetigo most frequently occurs on the face, around the nares and mouth, and on the extremities. Fever is uncommon. The diagnosis usually is established by the clinical appearance alone.

Recommended treatment for nonbullous impetigo is topical 2% mupirocin or oral antistaphylococcal antibiotics. Extensive or disseminated lesions, bullous impetigo, lesions around the eyes, or lesions otherwise not amenable to topical therapy are best treated with oral antibiotics. Streptococcal impetigo is associated with increased risk of postinfectious glomerulonephritis but not acute rheumatic fever (see Chapter 163). Antibiotic treatment does not decrease the risk of postinfectious glomerulonephritis but decreases possible spread of nephritogenic strains to close contacts. Children with impetigo should remain out of school or day care until 24 hours of antibiotic therapy have been completed.

**Cellulitis**

Cellulitis is infection involving the subcutaneous tissues and the dermis and is usually caused by *S. aureus* or group A streptococci. Cellulitis typically presents with indurated, warm, and erythematous macules with indistinct borders that expand rapidly. Additional manifestations commonly include fever, lymphangitis, and regional lymphadenitis. Erysipelas is a superficial variant of cellulitis usually caused by group A streptococcus that involves the dermis only. The rapidly advancing lesions are tender, bright red in appearance, and have sharp margins. The patients may appear toxic. Blood
cultures are recommended for erysipelas. Empirical antibiotic treatment for cellulitis is recommended with a first-generation cephalosporin unless the local S. aureus methicillin-resistance rate is high, in which case alternatives include clindamycin or trimethoprim-sulfamethoxazole (although this agent has poor group A streptococcal activity). Many patients may be managed with oral antibiotics and close follow-up; hospitalization and intravenous antibiotics are recommended for erysipelas and cellulitis of the face, hands, feet, or perineum; those with lymphangitis; and those not responding to outpatient therapy.

Ecthyma usually is caused by group A streptococcus and may complicate impetigo. Initially it is characterized by a lesion with a rim of erythematous induration surrounding an eschar, which, if removed, reveals a shallow ulcer. Ecthyma gangrenosum is a serious skin infection occurring in immunocompromised persons due to hematogenous spread of septic emboli to the skin, classically caused by Pseudomonas aeruginosa, other gram-negative organisms, or occasionally Aspergillus. The lesions begin as purple macules that undergo central necrosis to become exquisitely tender, deep, punched-out ulcers 2 to 3 cm in diameter with a dark necrotic base, raised red edges, and sometimes a yellowish green exudate. Fever usually is present.

Necrotizing fasciitis is the most extensive form of cellulitis and involves deeper subcutaneous tissues and fascial planes. It may progress to myonecrosis of the underlying muscle. Common causes include S. aureus and group A streptococcus alone or in combination with anaerobic organisms, such as Clostridium perfringens. Risk factors include underlying immunodeficiency, recent surgery or trauma, and varicella infection. Lesions progress rapidly with raised or sharply demarcated margins, although disease typically extends on a deeper plane beyond superficially evident lesions. Warning signs of necrotizing fasciitis include pain out of proportion to evident skin lesions, shock or toxic appearance, or crepitus due to subcutaneous gas formation by anaerobes. Necrotizing fasciitis is a surgical emergency, and early consultation with an experienced surgeon is recommended. Adjunctive tests such as magnetic resonance imaging can confirm the presence of gas in tissues, but obtaining imaging should not delay surgical consultation. Treatment includes rapid surgical debridement of all necrotic tissues and broad-spectrum intravenous antibiotics, such as clindamycin plus cefotaxime or ceftriaxone, with or without an aminoglycoside or vancomycin.

P. aeruginosa folliculitis (hot tub folliculitis) presents as pruritic papules; pustules; or deeper, purple-red nodules predominantly on skin areas covered by a swimsuit after bathing in hot tubs. Folliculitis develops 8 to 48 hours after exposure, usually without associated systemic symptoms, and resolves in 1 to 2 weeks without treatment.

Perianal Dermatitis
Perianal dermatitis (perianal streptococcal disease) is caused by group A streptococcus and is characterized by well-demarcated, tender, marked perianal erythema extending 2 cm from the anus. Manifestations include anal pruritus and painful defecation, sometimes with blood-streaked stools. The differential diagnosis includes diaper dermatitis, candidiasis, pinworm infection, and anal fissures. Treatment is oral penicillin or cefuroxime.

SUPERFICIAL FUNGAL INFECTIONS

Cutaneous fungal infections are common in children (Table 98-1). The estimated lifetime risk of developing a dermatophytosis is 10% to 20%. Diagnosis is usually established by visual inspection and may be confirmed by potassium hydroxide (KOH) examination or fungal culture of skin scrapings from the margins of the lesion. Recommended tinea treatment is usually for 4 to 6 weeks and 2 weeks after resolution; topical antifungal creams (e.g., miconazole, clotrimazole, ketoconazole, tolnaftate) are appropriate for tinea corporis, tinea pedis, and tinea cruris, whereas tinea capitis requires oral treatment. The diagnosis of onychomycosis should be confirmed by KOH examination and fungal culture. Recommended treatment is terbinafine or itraconazole for at least 12 weeks.

SUPERFICIAL VIRAL INFECTIONS

Herpes Simplex Virus

Primary herpetic infections can occur after inoculation of the virus at any mucocutaneous site. Herpes simplex virus type 1 (HSV-1) is common in children and classically causes gingivostomatitis, whereas HSV-2 classically infects the genitalia as a sexually transmitted infection (see Chapter 116), though HSV-1 may cause approximately 30% of genital herpes, and
Table 98-1  Superficial Fungal Infections

<table>
<thead>
<tr>
<th>NAME</th>
<th>ETIOLOGY</th>
<th>MANIFESTATIONS</th>
<th>DIAGNOSIS</th>
<th>THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea capitis (ringworm)</td>
<td>Microsporum audouiniai, Trichophyton tonsurans, Microsporum canis</td>
<td>Prepubertal infection of scalp, hair-shafts; black dot alopecia; T. tonsurans common in African Americans</td>
<td>M. audouiniai fluorescence: blue-green with Wood lamp*; +KOH, culture</td>
<td>Griseofulvin; terbinafine, itraconazole</td>
</tr>
<tr>
<td>Kerion</td>
<td>Inflammatory reaction to tinea capitis</td>
<td>Swollen, boggy, crusty, purulent, tender mass with lymphadenopathy; secondary distal id reaction common</td>
<td>As above</td>
<td>As above, plus steroids for id reactions</td>
</tr>
<tr>
<td>Tinea corporis (ringworm)</td>
<td>M. canis, Trichophyton rubrum, others</td>
<td>Slightly pruritic ringlike, erythematous papules, plaques with scaling and slow outward expansion of the border; check cat or dog for M. canis</td>
<td>+KOH, culture; M. canis fluorescence: blue-green with Wood lamp; differential diagnosis: granuloma annulare, pityriasis rosea, nummular eczema, psoriasis</td>
<td>Topical miconazole, clotrimazole, terbinafine, tolnaftate, ciclopirox, oxiconazole, or butenafine</td>
</tr>
<tr>
<td>Tinea cruris (jock itch)</td>
<td>Epidermophyton floccosum, Trichophyton mentaghrophytes, T. rubrum</td>
<td>Symmetric, pruritic, scrotal sparing, scaling plaques</td>
<td>+KOH, culture; differential diagnosis: erythrasma (Corynebacterium minutissimum)</td>
<td>See Tinea corporis, Therapy; wear loose cotton underwear</td>
</tr>
<tr>
<td>Tinea pedis (athlete’s foot)</td>
<td>T. rubrum, T. mentagrophytes</td>
<td>Moccasin or interdigital distribution, dry scales, interdigital maceration with secondary bacterial infection</td>
<td>+KOH, culture; differential diagnosis: C. minutissimum erythrasma</td>
<td>Medications as above; wear cotton socks</td>
</tr>
<tr>
<td>Tinea unguium (onychomycosis)</td>
<td>T. mentagrophytes, T. rubrum, Candida albicans</td>
<td>Uncommon before puberty; peeling of distal nail plate; thickening, splitting of nails</td>
<td>+KOH, culture</td>
<td>Oral terbinafine or itraconazole</td>
</tr>
<tr>
<td>Tinea versicolor</td>
<td>Malassezia furfur</td>
<td>Tropical climates, steroids or immunosuppressive drugs; uncommon before puberty; chest, back, arms; oral hypopigmented or hyperpigmented in African Americans, red-brown in Caucasians; scaling patches</td>
<td>+KOH; orange-gold fluorescence with Wood lamp; differential diagnosis: pityriasis alba</td>
<td>Topical selenium sulfide, oral ketoconazole</td>
</tr>
</tbody>
</table>

YEAST

| Candidiasis | Candida albicans | Diaper area, intense erythematous plaques or pustules, isolated or confluent | +KOH, culture | Topical nystatin; oral nystatin treats concomitant oral thrush |

KOH, Potassium hydroxide.
*Wood lamp examination uses an ultraviolet source in a completely darkened room. Trichophyton usually has no fluorescence.

HSV-2 can cause gingivostomatitis. For the cutaneous manifestations of neonatal HSV infection, see Chapter 65.

**Herpes gingivostomatitis** involves the gingivae and the vermilion border of the lips. Herpes labialis (cold sores or fever blisters) is limited to the vermilion border involving skin and mucous membranes. Clinical manifestations of primary HSV gingivostomatitis include typical oropharyngeal vesicular lesions with high fever, malaise, stingind mouth pain, drooling, fetid breath, and cervical lymphadenopathy.

Herpetic skin lesions are quite painful and characteristically begin as erythematous papules that quickly progress to the characteristically grouped, 2- to 4-mm, fluid-filled vesicles on an erythematous base. Removal of the vesicle roof reveals a small, sharply demarcated ulcer with a punched-out appearance. The characteristic grouped vesicles distinguish HSV from chickenpox (see Chapter 97). Within several days, the vesicles become pustular, rupture, and encrust. Diagnosis is made clinically, or with viral culture, fluorescent antibody staining, or polymerase chain reaction. Scarring is uncommon, but there may be residual hyperpigmentation. After primary infection, the virus remains latent in nerve dorsal root ganglia. About 20% to 40% of adults experience recurrent oral episodes of HSV labialis throughout life. Recurrences occur in roughly the same location and may be preceded by prodromal symptoms of tingling or burning without fever or lymphadenopathy.

Viral paronychia (herpetic whitlow) is a painful, localized infection of a digit, usually of the distal pulp space, with erythematous and occasionally vesiculopustular eruption. It occurs in children who suck their thumbs, bite their nails, and those with herpetic gingivostomatitis. **Herpes gladiatorum** occurs in wrestlers and rugby players who acquire cutaneous herpes from close body contact with other players’ cutaneous infections. Cutaneous HSV infection in persons with an underlying skin disorder (e.g., atopic dermatitis) can result in eczema herpeticum (Kaposi varicelliform eruption), a
disseminated cutaneous infection. There may be hundreds of herpetic vesicles over the body, usually concentrated in the areas of skin affected by the underlying disorder.

Treatment with oral valacyclovir or famciclovir may shorten duration of disease for primary and recurrent infection. Prophylactic antiviral therapy may be warranted in those with frequent recurrences. Infants, persons with eczema, and persons with immunodeficiency are at increased risk for disseminated and severe HSV disease and should receive intravenous acyclovir therapy.

**Human Papillomaviruses (Warts)**

Warts are caused by the human papillomaviruses (HPVs), nonenveloped, double-stranded DNA viruses that infect skin and mucous membrane keratinocytes. More than 100 HPV serotypes have been identified, with different serotypes accounting for the variation in location and clinical presentations. There are 15 to 20 oncogenic (high-risk) types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, and 58. HPV types 16 and 18 are associated with 70% of cases of cervical cancer as well as vulvar and vaginal cancers. Common nononcogenic (low-risk) types include 1, 2, 3, 6, 10, 11, 40, 42, 43, 44, and 54. Regardless of the infecting serotype, all warts are associated with hyperplasia of the epidermal cells.

Warts occur at all ages. **Common warts** (verruca vulgaris), associated with HPV types 1 and 2, are the most common form (71%). They occur frequently in school-age children, with a prevalence of 4% to 20%. They are transmitted by direct contact or by fomites and have an incubation period of approximately 1 month before clinical presentation. The common wart is a painless, well-circumscribed, small (2- to 5-mm) papule with a papillated or verrucous surface typically distributed on the fingers, toes, elbows, and knees. They also may be found on the nose, ears, and lips. **Filiform warts** are verrucous, exophytic, 2-mm papules that have a narrow or pedunculated base. **Flat warts** (verruca plana) are associated with HPV types 3 and 10 and are multiple, flat-topped 2- to 4-mm papules clustered on the dorsal surface of the hands, on the soles of the feet (plantar warts), or on the face. Plantar warts may be painful because of the effect of pressure and friction on the lesions. **Genital warts** (condylomata acuminata) are associated with the HPV types 6 and 11 (90%). They are flesh-colored, hyperpigmented, or erythematous lesions that are filiform, fungating, or plaquelike in appearance and involve multiple sites on the vulva, vagina, penis, or perineum. Genital warts are the most common sexually transmitted infection, with 1 million new cases annually.

Warts typically are self-limited and resolve spontaneously over years without specific treatment. Treatment options are available for common and flat warts as well as condylomata acuminata. Topical preparations for common and flat warts disrupt infected epithelium (using salicylic acid, liquid nitrogen, or laser therapy) and result in the cure of approximately 75% of patients. Treatment of anogenital warts is complex, and specific treatments (www.cdc.gov/std/hpv/default.htm) may include topical podophyllotoxin or imiquimod. Additional treatment methods include laser ablation and immunotherapy with intralbiesional interferon; immunotherapy may result in significant toxicities.

The most serious consequence of HPV infection is cervical cancer (more than 12,000 new cases annually), vulvar, vaginal, penile, and anal cancers. A quadrivalent, recombinant HPV vaccine against serotypes 6, 11, 31, and 33 is recommended for all children at 11 to 12 years of age but may be given to children between 9 and 26 years of age. The three-dose regimen has 98% to 100% efficacy in preventing the precancerous dysplasia that precedes cervical cancer.

**Molluscum Contagiosum**

Molluscum contagiosum virus, a poxvirus that replicates in host epithelial cells, produces discrete, small (2 to 4 mm), pearly flesh-colored or pink, nontender, dome-shaped papules with central umbilication. Papules occur most commonly in intertriginous regions, such as the axillae, groin, and neck. They rarely occur on the face or in the periocular region. The infection typically affects toddlers and young children and is acquired through direct contact with infected individuals. Spread occurs by autoinoculation. Infection with molluscum contagiosum may be complicated by a surrounding dermatitis. Severely immunocompromised persons or persons with extensive atopic dermatitis often have widespread lesions.

Diagnosis is made clinically. Lesions are self-limited, resolving over months to years, and usually no specific treatment is recommended. Available treatment options are limited to destructive modalities, such as cryotherapy with topical liquid nitrogen, vesicant therapy with topical 0.9% cantharidin, or removal by curettage, and should be reserved for extensive disease.

**LYMPHADENOPATHY**

**ETIOLOGY**

Lymphoid tissue steadily enlarges until puberty and subsequently undergoes progressive atrophy. Lymph nodes are most prominent in children 4 to 8 years of age. Normal lymph node size is 10 mm in diameter, with the exceptions of 15 mm for inguinal nodes, 5 mm for epitrochlear nodes, and 2 mm for supraclavicular nodes, which are usually undetectable. **Lymphadenopathy** is enlargement of lymph nodes and occurs in response to a wide variety of infectious, inflammatory, and malignant processes. **Generalized lymphadenopathy** is enlargement of two or more noncontiguous lymph node groups, whereas **regional lymphadenopathy** involves one lymph node group only.
Lymphadenitis is acute or chronic inflammation of lymph nodes. Acute lymphadenitis usually results when bacteria and toxins from a site of acute inflammation are carried via lymph to regional nodes. Numerous infections cause lymphadenopathy and lymphadenitis (Tables 99-1 and 99-2). Causes of inguinal regional lymphadenopathy also include sexually transmitted infections (see Chapter 116). Regional lymphadenitis associated with a characteristic skin lesion at the site of inoculation defines various lymphocutaneous syndromes. Lymphangitis is an inflammation of subcutaneous lymphatic channels that presents as an acute bacterial infection, usually caused by *Staphylococcus aureus* and group A streptococci.

Cervical lymphadenitis is the most common regional lymphadenitis among children and is associated most commonly with pharyngitis caused by group A streptococcus (see Chapter 103), respiratory viruses, and Epstein-Barr virus (EBV). Other common infectious causes of cervical lymphadenitis include *Bartonella henselae* (cat-scratch disease) and nontuberculous mycobacteria.

EBV is the primary cause of infectious mononucleosis, a clinical syndrome characterized by fever, fatigue and malaise, cervical or generalized lymphadenopathy, tonsillitis, and pharyngitis. EBV, a member of the herpesvirus family, infects B lymphocytes and is spread by salivary secretions. After primary infection, EBV is maintained latently in multiple episodes in the cell nucleus of resting B lymphocytes and establishes lifelong infection that remains clinically inapparent. Most persons shed EBV intermittently, with approximately 20% of healthy individuals shedding EBV at any given time.

Cytomegalovirus (CMV), *Toxoplasma gondii*, adenoviruses, hepatitis B virus, hepatitis C virus, and initial human immunodeficiency virus (HIV) infection, known as acute retroviral syndrome, can cause an infectious mononucleosis-like syndrome with lymphadenopathy. The cause of cat-scratch disease is *B. henselae*, a small, pleomorphic, gram-negative bacillus that stains with Warthin-Starry silver stain. *B. henselae* causes apparently asymptomatic bacteremia in cats, and kittens under 1 year of age are more likely to harbor the organism. *B. henselae* is transmitted to humans by bites and scratches, which may be minor. *B. henselae* also causes bacillary angiomatosis and peliosis hepatitis in persons with HIV infection (see Chapter 125).

Nontuberculous mycobacteria are ubiquitous in soil, vegetation, dust, and water. *Mycobacterium* species commonly

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**Table 99-1** Infectious Causes of Generalized Lymphadenopathy

<table>
<thead>
<tr>
<th>VIRAL</th>
<th>NONVENEREAL ORIGIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus (infectious mononucleosis)</td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Cytomegalovirus (infectious mononucleosis-like syndrome)</td>
<td>Group A streptococcus</td>
</tr>
<tr>
<td>HIV (acute retroviral syndrome)</td>
<td>Group B streptococcus (in infants)</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Bartonella henselae (cat-scratch disease)</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>Yersinia pestis (plague)</td>
</tr>
<tr>
<td>Varicella</td>
<td>Francisella tularensis (glandular tularemia)</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>Rubeola (measles)</td>
<td>Nontuberculous mycobacteria</td>
</tr>
<tr>
<td>Rubella</td>
<td>Sporothrix schenckii (sporotrichosis)</td>
</tr>
</tbody>
</table>

**Table 99-2** Infectious Causes of Regional Lymphadenopathy

<table>
<thead>
<tr>
<th>BACTERIAL</th>
<th>SEXUALLY TRANSMITTED INFECTIONS (PRIMARILY INGUINAL LYMPHADENOPATHY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>Neisseria gonorrhoeae (gonorrhea)</td>
</tr>
<tr>
<td>Brucella (brucellosis)</td>
<td>Treponema pallidum (syphilis)</td>
</tr>
<tr>
<td>Leptospira interrogans (leptospirosis)</td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>Streptobacillus moniliformis (bacillary rat-bite fever)</td>
<td>Haemophilus ducreyi (chancroid)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis (tuberculosis)</td>
<td>Chlamydia trachomatis serovars L1–3 (lymphogranuloma venereum)</td>
</tr>
<tr>
<td>Treponema pallidum (secondary syphilis)</td>
<td><strong>LYMPHOCUTANEOUS SYNDROMES</strong></td>
</tr>
</tbody>
</table>

**Table 99-1** Infectious Causes of Generalized Lymphadenopathy

<table>
<thead>
<tr>
<th>FUNGAL</th>
<th>Bacillus anthracis (anthrax)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coccidioides immitis (coccidioidomycosis)</td>
<td><em>F. tularensis</em> (ulceroglandular tularemia)</td>
</tr>
<tr>
<td>Histoplasma capsulatum (histoplasmosis)</td>
<td>B. henselae (cat-scratch disease)</td>
</tr>
</tbody>
</table>

**Table 99-2** Infectious Causes of Regional Lymphadenopathy

<table>
<thead>
<tr>
<th>PROTOZOAL</th>
<th>Pasturella multocida (dog or cat bite)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxoplasma gondii (toxoplasmosis)</td>
<td>Rickettsialpox</td>
</tr>
<tr>
<td>Trypanosoma cruzi (Chagas disease)</td>
<td><em>S. schenckii</em> (sporotrichosis)</td>
</tr>
</tbody>
</table>

**Table 99-1** Infectious Causes of Generalized Lymphadenopathy

<table>
<thead>
<tr>
<th>Table 99-2</th>
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</tr>
</thead>
<tbody>
<tr>
<td>N. gonorrhoeae</td>
<td>Bacillus anthracis (anthrax)</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae (gonorrhea)</td>
<td>Pasturella multocida (dog or cat bite)</td>
</tr>
<tr>
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<td>Rickettsialpox</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td><em>S. schenckii</em> (sporotrichosis)</td>
</tr>
<tr>
<td>Haemophilus ducreyi (chancroid)</td>
<td><strong>LYMPHOCUTANEOUS SYNDROMES</strong></td>
</tr>
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<td>Chlamydia trachomatis serovars L1–3 (lymphogranuloma venereum)</td>
<td>Bacillus anthracis (anthrax)</td>
</tr>
<tr>
<td><strong>F. tularensis</strong> (ulceroglandular tularemia)</td>
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</tr>
<tr>
<td>B. henselae (cat-scratch disease)</td>
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</tr>
<tr>
<td>Nontuberculous mycobacteria</td>
<td>Pasturella multocida (dog or cat bite)</td>
</tr>
<tr>
<td>Sporothrix schenckii (sporotrichosis)</td>
<td>Rickettsialpox</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
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</tr>
<tr>
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<td>Bacillus anthracis (anthrax)</td>
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</table>
causing lymphadenitis in children includes \textit{M. avium} complex, \textit{M. scrofulaceum}, and \textit{M. kansasii}. \textit{M. tuberculosis} uncommonly causes cervical lymphadenitis.

**Epidemiology**

Acute cervical lymphadenitis as a complication of group A streptococcal infection parallels the incidence of streptococcal pharyngitis (see Chapter 103). Many cases are caused by \textit{S. aureus}. EBV and CMV are ubiquitous, with most infections occurring in young children, who may often be asymptomatic or only mildly symptomatic. Risk factors for other specific causes of lymphadenopathy may be indicated by past medical and surgical history; preceding trauma; exposure to animals; contact with persons infected with tuberculosis; sexual history; travel history; food and ingestion history, especially of undercooked meat or unpasteurized dairy products; and current medications.

**Clinical Manifestations**

The exact location and detailed measurement of the size, shape, characteristics, and number of involved nodes should be noted, including their consistency, mobility, tenderness, warmth, fluctuance, firmness, and adherence to adjacent tissues. Important findings include presence or absence of dental disease, oropharyngeal or skin lesions, ocular disease, other nodal enlargement, and any other signs of systemic illness, including hepatosplenomegaly and skin lesions.

Acute cervical lymphadenopathy associated with pharyngitis is characterized by small and rubbery lymph nodes in the anterior cervical chain with minimal to moderate tenderness. Suppurative cervical lymphadenitis, frequently caused by \textit{S. aureus} or group A streptococcus, shows erythema and warmth of the overlying skin with moderate to exquisite tenderness.

The characteristic triad of EBV infectious mononucleosis is fever, pharyngitis, and lymphadenopathy. The pharynx shows enlarged tonsils and exudate and, sometimes, an exanthem with pharyngeal petechiae. Lymphadenopathy is most prominent in the anterior and posterior cervical and submandibular lymph nodes and less commonly involves axillary and inguinal lymph nodes. Other findings include splenomegaly in 50% of cases, hepatomegaly in 10% to 20%, and maculopapular or urticarial rash in 5% to 15%. A diffuse, erythematous rash develops in approximately 80% of mononucleosis patients treated with amoxicillin. Compared with EBV infection, infectious mononucleosis-like illness caused by CMV has minimal pharyngitis and often more prominent splenomegaly; it often presents with fever only. The most common manifestation of toxoplasmosis is asymptomatic cervical lymphadenopathy, but approximately 10% of cases of acquired toxoplasmosis develop chronic posterior cervical lymphadenopathy and fatigue, usually without significant fever.

**Cat-scratch disease** typically presents with a cutaneous papule or conjunctival granuloma at the site of bacterial inoculation, followed by lymphadenopathy of the draining regional nodes. The nodes are tender, with suppuration in approximately 10% of cases. Lymphadenopathy may persist 1 to 4 months. Less common features of cat-scratch disease include erythema nodosum, osteolytic lesions, encephalitis, oculoglandular (Parinaud) syndrome, hepatic or splenic granulomas, endocarditis, polyneuritis, and transverse myelitis.

Lymphadenitis caused by \textit{nontuberculous mycobacteria} usually is unilateral in the cervical, submandibular, or preauricular nodes and is more common in toddlers. The nodes are relatively painless and firm initially, but gradually soften, rupture, and drain over time. The local reaction is circumscribed, and overlying skin may develop a violaceous discoloration without warmth. Fever and systemic symptoms are minimal or absent.

**Laboratory and Imaging Studies**

Initial laboratory tests of regional lymphadenopathy include a complete blood count and inflammatory markers. Infectious mononucleosis is characterized by lymphocytosis with atypical lymphocytes; thrombocytopenia and elevated hepatic enzymes are common.

Cultures of infected skin lesions and tonsillar exudates should be obtained. Isolation of group A streptococci from the oropharynx suggests, but does not confirm, streptococcal cervical lymphadenitis. A blood culture should be obtained from children with systemic signs and symptoms of bacteremia.

Serologic testing for EBV and for \textit{B. henselae} should be obtained if there are appropriate findings. The most reliable test for diagnosis of acute EBV infection is the IgM antiviral capsid antigen (Fig. 99-1). Heterophil antibody is also diagnostic but is not reliably positive in children younger than 4 years with infectious mononucleosis.

Extended diagnostic workup for lymphadenopathy is guided by the specific risk factors in the history and physical examination findings. Chest radiograph, throat culture, antistreptolysin O titer, and serologic tests for CMV, toxoplasmosis, syphilis, tularemia, \textit{Brucella}, histoplasmosis, and coccidioidomycosis may be indicated. Genital tract evaluation and specimens should be obtained with regional inguinal lymphadenopathy (see Chapter 116). Screening for tuberculosis can be performed using the standard tuberculin skin test or an interferon gamma release assay; both may be positive with atypical mycobacterial infection.

Aspiration is indicated for acutely inflamed, fluctuant cervical lymph nodes, especially those larger than 3 cm in diameter or not responding to antibiotic treatment. Ultrasound or computed tomography may help in establishing the extent of lymphadenopathy and defining whether the mass is solid, cystic, or suppurative with abscess formation. Pus from fluctuant lesions should be examined by Gram and acid-fast stains and cultured for aerobic and anaerobic bacteria and mycobacteria. Biopsy should be performed if lymphoma is suspected because of firm, matted, nontender nodes and other systemic findings.

If the diagnosis remains uncertain and lymphadenopathy persists despite empirical antibiotic therapy for presumed \textit{S. aureus} and group A streptococcus, excisional biopsy of the entire node should be performed, if possible. This is curative for nontuberculous mycobacterial lymphadenitis. Biopsy material should be submitted for histopathology as well as Gram, acid-fast, Giemsa, periodic acid-Schiff, Warthin-Starry silver (\textit{B. henselae}), and methenamine silver stains. Cultures for aerobic and anaerobic bacteria, mycobacteria, and fungi should be performed.
Figure 99-1 The development of antibodies to various Epstein-Barr virus antigens in patients with infectious mononucleosis. The titers are geometric mean values expressed as reciprocals of the serum dilution. The IgM response to viral capsid antigen (VCA) is divided because of the significant differences noted according to the age of the patient. (From Jenson HB, Ench Y: Epstein-Barr virus. In Rose NR, Hamilton RG, Detrick B: Manual of Clinical Laboratory Immunology, ed 7, Washington DC, 2006, American Society for Microbiology Press, p 640.)

DIFFERENTIAL DIAGNOSIS
Noninfectious causes of cervical swelling and/or lymphadenopathy include congenital and acquired cysts, Kawasaki disease, sarcoidosis, benign neoplasms, and malignancies. The differential diagnosis for generalized lymphadenopathy includes juvenile idiopathic arthritis; systemic lupus erythematosus; and serum sickness and other adverse drug reactions, especially with phenytoin and other antiepileptic medications, allopurinol, isoniazid, antithyroid medications, and pyrimethamine. Leukemia, lymphoma, and occasionally neuroblastoma may have lymph nodes that are usually painless, uninflamed, matted, and firm (see Chapters 155 and 156). A syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenitis is an occasional cause of recurrent fever and cervical lymphadenitis (see Chapter 103).

TREATMENT
Management of lymphadenopathy and lymphadenitis depends on patient age, associated findings, node size and location, and severity of the acute systemic symptoms. In children most cases of cervical lymphadenopathy, without other signs of acute inflammation, require no specific therapy and usually regress within 2 to 3 weeks. Progression to lymphadenitis or development of generalized lymphadenopathy requires further evaluation.

The specific treatment of cervical lymphadenitis depends on the underlying etiology. Empirical treatment targeting *S. aureus* and group A streptococcus includes a penicillinase-resistant penicillin (e.g., oxacillin) or first-generation cephalosporin (e.g., cefazolin). For patients with hypersensitivity to β-lactam antibiotics, or if community-acquired methicillin-resistant *S. aureus* is suspected, clindamycin is appropriate. Response to empirical antibiotic therapy for suppurative cervical lymphadenitis obviates the need for further evaluation. Absence of a clinical response within 48 to 72 hours is an indication for further laboratory evaluation and possible excisional biopsy and culture.

There is no specific treatment for infectious mononucleosis. Cat-scratch disease usually does not require treatment because the lymphadenopathy resolves in 2 to 4 months without sequelae. Azithromycin may hasten resolution and reduces node size at 30 days but no benefit is evident at 90 days. Aspiration is indicated for suppurative nodes. The recommended treatment of cervical lymphadenitis caused by nontuberculous mycobacteria is complete surgical excision. Antimycobacterial drugs are necessary only if there is recurrence or inability to excise infected nodes completely, or if *M. tuberculosis* is identified, which requires 6 months of antituberculous chemotherapy (see Chapter 124).

COMPLICATIONS AND PROGNOSIS
Most acute infections caused by *S. aureus* and group A streptococcus respond to treatment and have an excellent prognosis. Complications such as abscess formation, cellulitis, and bacteremia may occur. Abscess formation is treated with incision and drainage in conjunction with appropriate antibiotic therapy.

Infectious mononucleosis usually resolves in 2 to 4 weeks, but fatigue and malaise may wax and wane for several weeks to months. EBV also is associated with numerous complications during the acute illness. Neurologic complications include seizures, aseptic meningitis syndrome, Bell palsy, transverse myelitis, encephalitis, and Guillain-Barre syndrome. Hematologic complications include Coombs-positive hemolytic anemia, antibody-mediated thrombocytopenia, hemophagocytic syndrome, and, rarely, aplastic anemia. Corticosteroids have been used for respiratory compromise resulting from tonsillar hypertrophy, which responds rapidly, and for thrombocytopenia, hemolytic anemia, and neurologic complications. Splenic rupture is very rare. X-linked lymphoproliferative disease, which results from a mutation of the SH2D1A gene located in the Xq25 region, manifests as fulminant infectious mononucleosis with primary EBV infection and progresses to malignant lymphoproliferative disease or dysgammaglobulinemia.

EBV infection, as with other herpesviruses, persists for life, but no symptoms are attributed to intermittent reactivation in immunocompetent hosts. EBV is causally associated with nasopharyngeal carcinoma; Burkitt lymphoma; Hodgkin disease; leiomyosarcoma in immunocompromised persons; and EBV lymphoproliferative disease, especially in posttransplant patients and in those with acquired immunodeficiency syndrome (AIDS).
Lymphadenitis caused by nontuberculous mycobacteria has an excellent prognosis. Surgical excision of cervical lymphadenitis caused by nontuberculous mycobacteria is curative in >97% of cases.

**PREVENTION**
The incidence of suppurative regional lymphadenitis reflects the incidence of predisposing conditions, such as dental disease, streptococcal pharyngitis, otitis media, impetigo, and other infections involving the face and scalp. There are no guidelines to prevent lymphadenitis caused by nontuberculous mycobacteria.

### Chapter 100

**MENINGITIS**

**ETIOLOGY**

Meningitis, inflammation of the leptomeninges, can be caused by bacteria, viruses, or, rarely, fungi. The term aseptic meningitis refers principally to viral meningitis, but meningitis with negative cerebrospinal fluid (CSF) bacterial cultures may be seen with other infectious organisms (Lyme disease, syphilis, tuberculosis), parameningeal infections (brain abscess, epi-dural abscess, venous sinus empyema), chemical exposure (nonsteroidal anti-inflammatory drugs, intravenous immunoglobulin), autoimmune disorders, and other diseases.

The organisms commonly causing bacterial meningitis (Table 100-1) before the availability of current conjugate vaccines were *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. In the United States, the rates of *H. influenzae* type b and *S. pneumoniae* meningitis have declined substantially after the introduction of targeted vaccines. The bacteria causing neonatal meningitis are the same as those causing neonatal sepsis (see Chapter 65). Staphylococcal meningitis occurs primarily after neurosurgery or penetrating head trauma.

Partially treated meningitis refers to bacterial meningitis complicated by antibiotic treatment before the lumbar puncture, which may result in negative CSF cultures, although other CSF findings suggestive of bacterial infection persist. The etiology can sometimes be confirmed by polymerase chain reaction of the CSF.

Viral meningitis is caused principally by enteroviruses and parechoviruses. Fecal excretion and transmission are continuous and persist for several weeks. Enteroviruses, parechoviruses, and arboviruses (St. Louis, LaCrosse, West Nile, California encephalitis viruses) are the principal causes of meningoencephalitis (see Chapter 101). Other viruses that cause meningitis include herpes simplex virus, Epstein-Barr virus, cytomegalovirus, lymphocytic choriomeningitis virus, and human immunodeficiency virus (HIV). Mumps virus is a common cause of viral meningitis in unvaccinated children. Less frequent causes of meningitis include *Borrelia burgdorferi* (Lyme disease), *Bartonella henselae* (cat-scratch disease), *Mycobacterium tuberculosis*, *Toxoplasma*, fungi (*Cryptococcus*, *Histoplasma, Blastomyces*, and *Coccidiodes*), and parasites (*Angiostrongylus cantonensis*, *Naegleria fowleri*, and *Acanthamoeba*).

### Table 100-1

<table>
<thead>
<tr>
<th>AGE</th>
<th>MOST COMMON</th>
<th>LESS COMMON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td><em>Group B streptococcus</em></td>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
<td>Coagulase-negative staphylococci</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em></td>
<td><em>Enterococcus faecalis</em></td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter</em></td>
<td><em>Citrobacter diversus</em></td>
</tr>
<tr>
<td></td>
<td><em>Salmonella</em></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae</em> types a, b, c, d, e, f, and nontypable*</td>
<td></td>
</tr>
<tr>
<td>&gt;1 mo</td>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>H. influenzae</em> type b</td>
</tr>
<tr>
<td></td>
<td><em>Neisseria meningitidis</em></td>
<td><em>Group A streptococcus</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Gram-negative bacilli</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>L. monocytogenes</em></td>
</tr>
</tbody>
</table>

**CLINICAL MANIFESTATIONS**

Decision-Making Algorithms

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- Apnea
- Stiff or Painful Neck
- Headaches
- Hearing Loss
- Fever without a Source
- Irritable Infant

Preceding upper respiratory tract symptoms are common. Rapid onset is typical of *S. pneumoniae* and *N. meningitidis*. Indications of meningeal inflammation include headache, irritability, nausea, nuchal rigidity, lethargy, photophobia, and vomiting. Fever usually is present. Kernig and Brudzinski

### EPIDEMIOLOGY

The incidence of bacterial meningitis is highest among children under 1 year of age. Extremely high rates are found in Native Americans, Alaskan Natives, and Australian aboriginals, suggesting that genetic factors play a role in susceptibility. Other risk factors include acquired or congenital immunodeficiencies, hemoglobinopathies such as sickle cell disease, functional or anatomic asplenia, and crowding as occurs in some households, day care centers, or college and military dormitories. A CSF leak (fistula), resulting from congenital anomaly or following a basilar skull fracture, increases the risk of meningitis, especially that caused by *S. pneumoniae*.

Enteroviruses and parechoviruses cause meningitis with peaks during summer and fall in temperate climates. These infections are more prevalent among low socioeconomic groups, young children, and immunocompromised persons. The prevalence of arboviral meningitis is determined by geographic distribution and seasonal activity of the arthropod (mosquito) vectors. In the United States, most arboviral infections occur during the summer and fall.
signs of meningeal irritation are often positive in children older than 12 months. In young infants, signs of meningeal inflammation may be minimal with only irritability, restlessness, depressed mental status, and poor feeding present. Focal neurologic signs, seizures, arthralgia, myalgia, petechial or purpuric lesions, sepsis, shock, and coma may occur. Symptoms of increased intracranial pressure include headache, diplopia, and vomiting; a bulging fontanelle may be present in infants. Ptosis, sixth nerve palsy, anisocoria, bradycardia with hypertension, and apnea are signs of increased intracranial pressure with brain herniation. Papilledema is uncommon, unless there is occlusion of the venous sinuses, subdural empyema, or brain abscess.

LABORATORY AND IMAGING STUDIES
If bacterial meningitis is suspected, a lumbar puncture should be performed unless there is evidence of cardiovascular instability or of increased intracranial pressure (because of the risk of herniation), other than a bulging fontanelle. Routine CSF examination includes a white blood cell count, differential, protein and glucose levels, and Gram stain (Table 100-2). CSF should be cultured for bacteria and, when appropriate, fungi, viruses, and mycobacteria. The polymerase chain reaction is used to diagnose enteroviruses, parechoviruses, and herpes simplex virus; it is more sensitive and rapid than viral culture. Peripheral leukocytosis is common, and blood cultures are positive in 90% of cases of bacterial meningitis. An electroencephalogram may confirm an encephalitis component (see Chapter 101).

DIFFERENTIAL DIAGNOSIS
Many disorders may show signs of meningeal irritation and increased intracranial pressure, including the infectious causes of meningitis or encephalitis, hemorrhage, rheumatic diseases, and malignancies. Seizures are associated with meningitis, encephalitis, and intracranial abscess or can be the sequelae of brain edema, cerebral infarction or hemorrhage, or vasculitis.

TREATMENT
Treatment of bacterial meningitis focuses on sterilization of the CSF by antibiotics (Table 100–3) and maintenance of
has not improved or has worsened and for those who received adjunct steroids, which can interfere with the ability to monitor clinical response.

Even with appropriate antibiotic therapy, the mortality rate for bacterial meningitis in children is significant: 25% for S. pneumoniae, 15% for N. meningitidis, and 8% for H. influenzae. Of survivors, 35% have sequelae, particularly after pneumococcal infection, including deafness, seizures, learning disabilities, blindness, paraplegia, ataxia, or hydrocephalus. All patients with meningitis should have a hearing evaluation before discharge and at follow-up. Poor prognosis is associated with young age, long duration of illness before effective antibiotic therapy, seizures, coma at presentation, shock, low or absent CSF white blood cell count in the presence of visible bacteria on CSF Gram stain, and immunocompromised status.

Rarely relapse may occur 3 to 14 days after treatment, possibly from parameningeal foci or resistant organisms. Recurrence may indicate an underlying immunologic or anatomic defect that predisposes the patient to meningitis.

### Prevention
Routine immunizations against H. influenzae and S. pneumoniae are recommended for children beginning at 2 months of age. Quadrivalent vaccines against N. meningitidis (serotypes A, C, Y, and W-135) are recommended for adolescents, college freshmen, military personnel, and travelers to highly endemic areas (see Chapter 94), and are licensed down to 2 years of age. Chemoprophylaxis with rifampin, ciprofloxacin, or ceftriaxone to eradicate the carrier state and decrease transmission is recommended both for index cases with N. meningitidis or H. influenzae and for their close contacts.

## Encephalitis
### Etiology
Encephalitis is an inflammatory process of the brain parenchyma leading to cerebral dysfunction. It is usually an acute process but may be a postinfectious encephalomyelitis, a chronic degenerative disease, or a slow viral infection. Encephalitis may be diffuse or localized. Organisms cause encephalitis by one of two mechanisms: (1) direct infection of the brain parenchyma or (2) an apparent immune-mediated response in the central nervous system that usually begins several days after the appearance of extraneural manifestations of the infection.

Viruses are the principal causes of acute infectious encephalitis (Table 101-1). The most common viral causes of encephalitis in the United States are the enteroviruses, arboviruses, and herpesviruses. Human immunodeficiency virus (HIV) is an important cause of subacute encephalitis in children and adolescents and may present as an acute febrile illness but, more commonly, is insidious in onset (see Chapter 125).

### COMPLICATIONS AND PROGNOSIS
SIADH may complicate meningitis and necessitates monitoring of urine output and fluid administration. Computed tomography or magnetic resonance imaging commonly detects subdural effusions with S. pneumoniae and H. influenzae meningitis. Most effusions are sterile and asymptomatic and do not necessitate drainage unless associated with increased intracranial pressure or focal neurologic signs. Persistent fever is common during treatment but also may be related to infective treatment or immune complex-mediated pericardial or joint effusions, thrombophlebitis, drug fever, or nosocomial infection. A repeat lumbar puncture after 48 hours of therapy should be considered for those whose condition

### Table 100-3
<table>
<thead>
<tr>
<th>AGE</th>
<th>RECOMMENDED TREATMENT</th>
<th>ALTERNATIVE TREATMENTS</th>
</tr>
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<tbody>
<tr>
<td>Newborns (0–28 days)</td>
<td>Cefotaxime or ceftriaxone plus ampicillin with or without gentamicin</td>
<td>Ampicillin plus gentamicin or cefazidime plus ampicillin</td>
</tr>
<tr>
<td>Infants and toddlers (1 mo–4 yr)</td>
<td>Ceftriaxone or cefotaxime plus vancomycin</td>
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**Decision-Making Algorithm**

**Chapter 101**

**Encephalitis**

**COMPLICATIONS AND PROGNOSIS**

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**Chapter 101**

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**Chapter 101**

**Encephalitis**

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**Chapter 101**

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Other causes of subacute encephalitis include measles, slow viruses (e.g., JC virus), and prion-associated diseases (e.g., Creutzfeldt-Jakob disease). Encephalitis also may result from metabolic, toxic, and neoplastic disorders.

**Acute disseminated encephalomyelitis (ADEM)** is the abrupt development of multiple neurologic signs related to an inflammatory, demyelinating disorder of the brain and spinal cord. ADEM follows childhood viral infections (such as measles and chickenpox) or vaccinations and resembles multiple sclerosis clinically.

**EPIDEMIOLOGY**

Arboviral and enteroviral encephalitides characteristically appear in clusters or epidemics that occur from midsummer to early fall, although sporadic cases of enteroviral encephalitis occur throughout the year. Herpesviruses and other infectious agents account for additional sporadic cases throughout the year.

Arboviruses tend to be limited to certain geographic areas, reflecting the reservoir and mosquito vector. St. Louis encephalitis virus is present throughout the United States in birds. California encephalitis virus, common in the Midwest, is carried by rodents and spread by mosquitoes. Eastern equine encephalitis virus is limited to the East Coast in birds. Western equine encephalitis virus is present throughout the Midwest and West in birds. West Nile virus infection occurs worldwide and causes outbreaks of summer encephalitis in North America. The principal vector for West Nile virus is the *Culex pipiens* mosquito, but the organism can be isolated in nature from a wide variety of *Culex* and *Aedes* species. A broad range of birds serves as the major reservoir for West Nile virus.

**CLINICAL MANIFESTATIONS**

Acute infectious encephalitis usually is preceded by a prodrome of several days of nonspecific symptoms such as sore throat, fever, headache, and abdominal complaints followed by the characteristic symptoms of progressive lethargy, behavioral changes, and neurologic deficits. Seizures are common at presentation. Children with encephalitis also may have a maculopapular rash and severe complications such as fulminating coma, transverse myelitis, anterior horn cell disease, or peripheral neuropathy.

West Nile encephalitis produces a broad spectrum of illness from asymptomatic infection to death. Severity of disease increases with advancing age. Most children are asymptomatic. Typical symptoms include mild, nonspecific extraneurologic illness characterized by fever, rash, arthralgias, lymphadenopathy, gastrointestinal complaints, and conjunctivitis.

**DIFFERENTIAL DIAGNOSIS**

The diagnosis is established presumptively by the presence of characteristic neurologic signs, typical epidemiologic findings, and evidence of infection by cerebrospinal fluid (CSF) analysis, electroencephalogram (EEG), and brain imaging techniques. Encephalitis may result from infections with bacteria, *Mycoplasma, Rickettsia*, fungi, and parasites and from many noninfectious diseases, including metabolic diseases (encephalopathy), such as Reye syndrome, hypoglycemia, collagen vascular disorders, drugs, hypertension, and malignancies.

**LABORATORY AND IMAGING STUDIES**

The diagnosis of viral encephalitis is supported by examination of the CSF, which typically shows a lymphocytic pleocytosis, slight elevation in protein content, and normal glucose level. The CSF occasionally may be normal. Extreme elevations of protein and reductions of glucose suggest tuberculous, cryptococcal infection, or meningal carcinomatosis. The EEG is the definitive test and shows diffuse, slow wave activity, although focal changes may be present. Neuroimaging studies may be normal or may show diffuse cerebral swelling of the parenchyma or focal abnormalities. A temporal lobe focus on EEG or brain imaging is the characteristic feature of herpes simplex virus (HSV) infection.

Serologic studies should be obtained for arboviruses (including West Nile virus, if indicated by the patient risk factors), Epstein-Barr virus, *Mycoplasma pneumoniae*, cat-scratch disease, and Lyme disease. Additional serologic testing for less common pathogens should be performed as indicated by the travel, social, or medical history. In most cases of viral encephalitis, the virus is difficult to isolate from the CSF. Polymerase chain reaction tests for HSV, enteroviruses, West Nile virus, and other viruses are available and should be sent. Viral cultures of stool and a nasopharyngeal swab may also be obtained. Even with extensive testing and the use of

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**Table 101-1**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterovirus and parechovirus</td>
<td>+++</td>
</tr>
<tr>
<td>Herpes simplex viruses (HSV 1, 6, 7)</td>
<td>++</td>
</tr>
<tr>
<td>Arthropod-borne viruses (especially West Nile virus, St. Louis, California, LaCrosse, and equine encephalitis viruses)</td>
<td>++</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>+</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>+</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>+</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em> (Lyme disease)</td>
<td>+</td>
</tr>
<tr>
<td><em>Bartonella henselae</em> (cat-scratch disease)</td>
<td>+</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>+</td>
</tr>
<tr>
<td><em>Rickettsia rickettsii</em></td>
<td>+</td>
</tr>
</tbody>
</table>

polymerase chain reaction assays, the cause of encephalitis remains undetermined in one third of cases.

Brain biopsy is seldom performed but may be useful in patients with focal neurologic findings. It may be appropriate for patients with severe encephalopathy who show no clinical improvement if the diagnosis remains obscure. Rabies encephalitis and prion-related diseases (Creutzfeldt-Jakob disease and kuru) may be routinely diagnosed by culture or pathologic examination of brain biopsy tissue. Brain biopsy may be helpful to identify arbovirus and enterovirus infections, tuberculosis, fungal infections, and noninfectious illnesses, particularly primary central nervous system vasculopathies and malignancies.

**TREATMENT**

With the exception of HSV, varicella-zoster virus, cytomegalovirus, and HIV, there is no specific therapy for viral encephalitis. Management is supportive and frequently requires intensive care unit admission to facilitate aggressive therapy for seizures, timely detection of electrolyte abnormalities, and, when necessary, airway monitoring and protection or reduction of increased intracranial pressure and maintenance of adequate cerebral perfusion pressure.

Intravenous acyclovir is the treatment of choice for HSV and varicella-zoster virus infections. Cytomegalovirus infection is treated with ganciclovir. HIV infections may be treated with a combination of antiretroviral agents. \( M. \) pneumoniae infections may be treated with doxycycline, erythromycin, azithromycin, or clarithromycin, although the clinical value of treating encephalitis associated with mycoplasmal disease is uncertain.

ADEM has been treated with high-dose intravenous corticosteroids, but it is unclear whether the improved outcome with corticosteroids reflects milder cases recognized by magnetic resonance imaging, fewer cases of ADEM caused by measles (which causes severe ADEM), or improved supportive care.

**COMPLICATIONS AND PROGNOSIS**

Among survivors, symptoms usually resolve over several days to 2 to 3 weeks. Although most patients with epidemic forms of infectious encephalitis (St. Louis, California, West Nile, and enterovirus infections) in the United States recover without sequelae, severe cases leading to death or substantial neurologic sequelae can occur with virtually any of these neurotropic viruses. About two thirds of patients with neurologic sequelae recover some or all of their function. The overall mortality for infectious encephalitis is approximately 5%.

Disease caused by HSV, Eastern equine encephalitis, or \( M. \) pneumoniae is associated with a worse prognosis. The prognosis may be worse for encephalitis in children younger than 1 year of age or with coma. Rabies, with very rare exceptions, is fatal.

Relapses of ADEM occur in 14%, usually within 1 year with the same or new clinical signs. Recurrences of ADEM may represent onset of multiple sclerosis in childhood.

**PREVENTION**

The best prevention for arboviral encephalitis is to avoid mosquito-borne or tick-borne exposures and to remove ticks carefully (see Chapter 122). There are no vaccines in use in the United States for the prevention of arboviral infection or for enteroviruses except for poliomyelitis. There are no specific preventive measures for HSV encephalitis except for cesarean section for mothers with active genital lesions (see Chapter 65). Rabies can be prevented by preexposure or postexposure vaccination. Influenza encephalitis can be prevented by use of influenza vaccination. Reye syndrome can be prevented by avoiding use of aspirin or aspirin-containing compounds for children with fever as well as use of varicella and influenza vaccines.

**THE COMMON COLD**

**ETIOLOGY**

The common cold is a viral infection with prominent symptoms of rhinorrhea and nasal obstruction, absent or mild fever, and no systemic manifestations. It is often referred to as rhinitis but usually involves the sinus mucosa and is more correctly termed rhinosinusitis.

The viruses primarily associated with colds are rhinoviruses and, less commonly, coronaviruses. Other viruses that cause common cold symptoms include respiratory syncytial virus and, less commonly, influenza, parainfluenza, and adenoviruses. Viral infection of nasal epithelium causes an acute inflammatory response with mucosal infiltration by inflammatory cells and release of cytokines. The inflammatory response is partly responsible for many of the symptoms.

**EPIDEMIOLOGY**

Colds occur throughout the year with peak incidence from early fall through late spring, reflecting the seasonal prevalence of viral pathogens and confined habitation during colder months. Young children have an average of 6 to 7 colds each year, and 10% to 15% of children have at least 12 colds each year. The annual number of colds decreases with age, to two to three colds each year by adulthood. Children in out-of-home day care during the first year of life have 50% more colds than children cared for at home only. This difference diminishes during subsequent years in day care.

**CLINICAL MANIFESTATIONS**

Decision-Making Algorithms
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Common cold symptoms typically develop 1 to 3 days after viral infection and include nasal obstruction, rhinorrhea, sore or scratchy throat, and occasional nonproductive cough. Colds usually persist about 1 week, although 10% last 2 weeks. There is often a change in the color or consistency of nasal secretions, which is not indicative of sinusitis or bacterial superinfection. Examination of the nasal mucosa may reveal swollen, erythematous nasal turbinates.

**LABORATORY AND IMAGING STUDIES**
Laboratory studies often are not helpful. A nasal smear for eosinophils may be useful in the evaluation for allergic rhinitis (see Chapter 79).

**DIFFERENTIAL DIAGNOSIS**
The differential diagnosis of the common cold includes allergic rhinitis, foreign body (especially with unilateral nasal discharge), sinusitis, pertussis, and streptococcal nasopharyngitis. Allergic rhinitis is characterized by absence of fever, eosinophils in the nasal discharge, and other manifestations, such as allergic shiners, nasal polyps, a transverse crease on the nasal bridge, and pale, edematous, nasal turbinate mucosa. Rare causes of rhinorrhea are choanal atresia or stenosis, cerebrospinal fluid fistula, diphtheria, tumor, congenital syphilis (with snuffles), nasopharyngeal malignancy, and Wegener granulomatosis.

**TREATMENT**
There is no specific therapy for the common cold. Antibacterial therapy is not beneficial. Management consists of symptomatic therapies. Antihistamines, decongestants, and combination antihistamine-decongestants are not recommended for children younger than 6 years of age because of adverse effects and lack of benefits. Low-grade fever is seen with colds, particularly in the first few days of illness and can be treated with antipyretic medications. Cough suppressants and expectorants have not been shown to be beneficial. Vitamin C and inhalation of warm, humidified air are no more effective than placebo. The benefit of zinc lozenges or sprays has been inconsistent.

**COMPLICATIONS AND PROGNOSIS**
Otitis media is the most common complication and occurs in 5% to 20% of children with a cold (see Chapter 105). Other complications include bacterial sinusitis, which should be considered if rhinorrhea or daytime cough persists without improvement for at least 10 to 14 days or if severe signs of sinus involvement develop, such as fever, facial pain, or facial swelling (see Chapter 104). Colds may lead to exacerbation of asthma and may result in inappropriate antibiotic treatment.

**PREVENTION**
There are no proven methods for prevention of colds other than good hand washing and avoiding contact with infected persons. No significant effect of vitamin C or Echinacea for prevention of the common cold has been confirmed.

**PHARYNGITIS**
Many infectious agents can cause pharyngitis (Table 103-1). **Group A streptococci** (*Streptococcus pyogenes*) are gram-positive, nonmotile cocci that are facultative anaerobes. On sheep blood agar, the colonies are small (1 to 2 mm in diameter) and have a surrounding zone of β (clear) hemolysis. Other bacterial organisms less often associated with pharyngitis include group C streptococcus (also β-hemolytic), *Arcanobacterium haemolyticum* (β-hemolytic, gram-positive rod), and *Francisella tularensis* (gram-negative coccobacillus and cause of tularemia). *Chlamydia pneumoniae*, strain TWAR, is associated with lower respiratory disease but also causes sore throat. *Mycoplasma pneumoniae* is associated with atypical pneumonia and may cause mild pharyngitis without distinguishing clinical manifestations. Other bacteria, including *Staphylococcus aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, are cultured frequently from the throats of children with pharyngitis, but their role in causing pharyngitis is unclear. Many viruses cause acute pharyngitis. Some viruses, such as adenoviruses, are more likely than others to cause pharyngitis as a prominent symptom, whereas other viruses, such as rhinoviruses, are more likely to cause pharyngitis as a minor part of an illness that primarily features other symptoms, such as rhinorrhea or cough. Epstein-Barr virus, enteroviruses (herpangina), herpes simplex virus, and primary human immunodeficiency virus (HIV) infection also produce pharyngitis.

**EPIDEMIOLOGY**
Sore throat is the primary symptom in approximately one third of upper respiratory tract illnesses. Streptococcal pharyngitis is relatively uncommon before 2 to 3 years of age, but the incidence increases in young school-age children and then declines in late adolescence and adulthood. *Streptococcus pneumoniae* pharyngitis occurs throughout the year in temperate climates, with a peak during the winter and early spring. The illness often spreads to siblings and classmates. Viral infections generally spread via close contact with an infected person and peak during winter and spring.

**CLINICAL MANIFESTATIONS**
Pharyngeal inflammation causes cough, sore throat, dysphagia, and fever. If involvement of the tonsils is prominent, the term *tonsillitis* or *tonsillopharyngitis* is often used.
The onset of streptococcal pharyngitis is often rapid and associated with prominent sore throat and moderate to high fever. Headache, nausea, vomiting, and abdominal pain are frequent. In a typical, florid case, the pharynx is distinctly red. The tonsils are enlarged and covered with a yellow, blood-tined exudate. There may be petechiae or doughnut-shaped lesions on the soft palate and posterior pharynx. The uvula may be red, stippled, and swollen. Anterior cervical lymph nodes are enlarged and tender to touch. Many children, however, present with only mild pharyngeal erythema without tonsillar exudate or cervical lymphadenitis. Conjunctivitis, cough, coryza, hoarseness, or ulcerations suggest a viral etiology. The diagnosis of streptococcal pharyngitis cannot be made on clinical features alone.

In addition to sore throat and fever, some patients exhibit the stigmata of scarlet fever: circumsoral pallor, strawberry tongue, and a fine diffuse erythematous macular-papular rash that has the feeling of goose flesh. The tongue initially has a white coating, but red and edematous lingual papillae later project through this coating, producing a white strawberry tongue. When the white coating peels off, the resulting red strawberry tongue is beefy red with prominent papillae. Patients infected with \( A. \) haemolyticum may present with similar findings.

Compared with classic streptococcal pharyngitis, the onset of viral pharyngitis is typically more gradual, and symptoms more often include rhinorrhea, cough, and diarrhea. Many upper respiratory tract infections present with symptoms of rhinorrhea and nasal obstruction, whereas systemic symptoms and signs, such as myalgia and fever, are absent or mild.

Gingivostomatitis is characteristic of herpes simplex virus-1 (see Chapter 65). Herpangina is an entero viral infection with sudden onset of high fever, vomiting, headache, malaise, myalgia, backache, conjunctivitis, poor intake, drooling, sore throat, and dysphagia. The oral lesions of herpangina may be nonspecific, but classically there are one or more small, tender, papular, or pinpoint vesicular lesions on an erythematous base scattered over the soft palate, uvula, and tongue. These vesicles enlarge from 1 to 2 mm to 3 to 4 mm over 3 to 4 days, rupture, and produce small, punched-out ulcers that persist for several days.

### Mononucleosis

SEE CHAPTER 99

### LABORATORY EVALUATION

The principal challenge is to distinguish pharyngitis caused by group A streptococcus from pharyngitis caused by nonstreptococcal (usually viral) organisms. A rapid streptococcal antigen test, a throat culture, or both are often performed to improve diagnostic precision and to identify children most likely to benefit from antibiotic therapy of streptococcal disease.

Many rapid diagnostic techniques for streptococcal pharyngitis are available with excellent specificity of 95% to 99%. The sensitivity of these rapid tests varies, however, and negative rapid tests should be confirmed by a throat culture.

Throat culture is the diagnostic gold standard for establishing the presence of streptococcal pharyngitis. False-positive cultures can occur if other organisms are incorrectly identified as group A streptococcus. As many as 20% of positive cultures in children during winter months reflect streptococcal carriers and not acute pharyngitis.

The predictive values of white blood cell count and differential, erythrocyte sedimentation rate, and C-reactive protein are not sufficient to distinguish streptococcal from nonstreptococcal pharyngitis, and these tests are not routinely recommended. The white blood cell count in patients with infectious mononucleosis usually shows a predominance of atypical lymphocytes.

### DIFFERENTIAL DIAGNOSIS

#### Decision-Making Algorithm

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Lymphadenopathy

The differential diagnosis of infectious pharyngitis includes other local infections of the oral cavity, retropharyngeal abscesses (\( S. \) aureus, streptococci, anaerobes), diphtheria...
(if unimmunized), peritonsillar abscesses (with quinsy sore throat or unilateral tonsil swelling caused by streptococci, anaerobes, or, rarely, *S. aureus*), and epiglottitis. In addition neutropenic mucositis (leukemia, aplastic anemia), thrush (candidiasis secondary to T-cell immune deficiency), autoimmune ulceration (systemic lupus erythematosus, Behçet disease), and Kawasaki disease may cause pharyngitis. Pharyngitis is often a prominent feature of Epstein-Barr virus-associated mononucleosis (see Chapter 99).

**Vincent infection** or **trench mouth** is a fulminant form of **acute necrotizing ulcerative gingivitis** with synergistic infection with certain spirochetal organisms, notably *Treponema vincentii*, with anaerobic *Selenomonas* and *Fusobacterium*. **Vincent angina** refers to a virulent form of anaerobic pharyngitis; gray pseudomembranes are found on the tonsils. **Lemierre syndrome** is acute pharyngitis complicated by thrombosis of the internal jugular vein and septic emboli (most often to the lungs). It occurs primarily in adolescents and is caused by *Fusobacterium necrophorum*.

**Ludwig angina** is a mixed anaerobic bacterial cellulitis of the submandibular and sublingual regions. Although often applied to any infection of the sublingual or submandibular region, the term originally was reserved for a rapidly spreading bilateral cellulitis of the sublingual and submandibular spaces. It typically is due to spreading from a periapical abscess of the second or third mandibular molar. It also has been associated with tongue piercing. A propensity for rapid spread, glottic and lingual swelling, and consequent airway obstruction makes prompt intervention imperative.

A syndrome of **periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis** is a rare cause of recurrent fever in children. Recurring nonspecific pharyngitis is accompanied by fever and painful solitary vesicular lesions in the mouth. The fevers begin at a young age (usually <5 years). Episodes last approximately 5 days, with a mean of 28 days between episodes. Episodes are shorter with oral prednisone and unresponsive to nonsteroidal anti-inflammatory drugs or antibiotics. The syndrome resolves in some but persists in other children. Long-term sequelae do not develop.

### TREATMENT

Even if untreated, most episodes of streptococcal pharyngitis resolve uneventfully over a few days. Early antimicrobial therapy accelerates clinical recovery by 12 to 24 hours. The major benefit of antimicrobial therapy is prevention of acute rheumatic fever (see Chapter 146). Because the latent (incubation) period of acute rheumatic fever is relatively long (1 to 3 weeks), treatment instituted within 9 days of illness is virtually 100% successful in preventing rheumatic fever. Treatment begun more than 9 days after the onset of illness, although less than 100% successful, has some preventive value. Antibiotic therapy should be started promptly in children with a positive rapid test for group A streptococcus, scarlet fever, symptomatic pharyngitis whose sibling has documented streptococcal pharyngitis, a past history of rheumatic fever or a recent family history of rheumatic fever, or symptomatic pharyngitis and living in an area experiencing an epidemic of acute rheumatic fever or poststreptococcal glomerulonephritis.

A variety of antimicrobial agents can be used to treat streptococcal pharyngitis (Table 103-2). Cephalosporins have superior pharyngeal bacterial eradication rates compared to penicillin. One proposed explanation is that staphylococci or anaerobes in the pharynx produce β-lactamase, which inactivates penicillin and reduces its efficacy. Another possible explanation is that cephalosporins are more effective in eradicating streptococcal carriage.

Children with recurrent throat culture episodes of group A streptococcal pharyngitis pose a particular problem. An alternative antibiotic may be chosen to treat β-lactamase producing flora, which may be responsible for the recurrences. Either amoxicillin-clavulanate or clindamycin is an effective regimen for eliminating streptococcal carriage.

Specific antiviral therapy is unavailable for most cases of viral pharyngitis. Patients with primary herpetic gingivostomatitis benefit from early treatment with oral acyclovir.

### COMPLICATIONS AND PROGNOSIS

Pharyngitis caused by streptococci or respiratory viruses usually resolves completely. The complications of group A streptococcal pharyngitis include local supplicative complications, such as parapharyngeal abscess and other infections of the deep fascial spaces of the neck, and nonsuppurative complications, such as acute rheumatic fever and acute postinfectious glomerulonephritis. Viral respiratory tract infections, including infections caused by influenza A, adenoviruses, parainfluenza type 3, and rhinoviruses, may predispose to bacterial middle ear infections.

### PREVENTION

Antimicrobial prophylaxis with daily oral penicillin V prevents recurrent streptococcal infections and is recommended only to prevent recurrences of rheumatic fever.
SINUSITIS

ETIOLOGY
Sinusitis is a suppurative infection of the paranasal sinuses and often complicates the common cold and allergic rhinitis. The maxillary and ethmoid sinuses are present at birth, but only the ethmoidal sinuses are pneumatized. The maxillary sinuses become pneumatized at 4 years of age. Frontal sinuses begin to develop at 7 years of age and are not completely developed until adolescence. The sphenoid sinuses are present by 5 years of age. The ostia draining the sinuses are narrow (1 to 3 mm) and drain into the middle meatus in the ostiomeatal complex. The mucociliary system maintains the sinuses as normally sterile.

Obstruction to mucociliary flow, such as mucosal edema resulting from the common cold, impedes sinus drainage and predisposes to bacterial proliferation. In 90% of children with acute sinusitis, the bacterial causes are *Streptococcus pneumoniae*, non-typable *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and group A streptococcus. Anaerobes emerge as important pathogens in subacute and chronic sinusitis. Indwelling nasogastric and nasotracheal tubes predispose to nosocomial sinusitis, which may be caused by gram-negative bacteria (*Klebsiella* or *Pseudomonas*). Antibiotic therapy predisposes to infection with antibiotic-resistant organisms. Sinusitis in neutropenic and immunocompromised persons may be caused by *Aspergillus* or the Zygomycetes (e.g., *Mucor, Rhizopus*).

EPIDEMIOLOGY
The true incidence of sinusitis is unknown. The common cold is the major predisposing factor for developing sinusitis at all ages. Other risk factors include allergy, cystic fibrosis, immunodeficiency, human immunodeficiency virus (HIV) infection, nasogastric or nasotracheal intubation, immotile cilia syndrome, nasal polyps, and nasal foreign body. Sinusitis also is a frequent problem in immunocompromised children after organ transplantation.

CLINICAL MANIFESTATIONS

Clinical manifestations most commonly include persistent, mucopurulent, unilateral or bilateral rhinorrhea, nasal stuffiness, and cough, especially at night. Less common symptoms include a nasal quality to the voice, halitosis, facial swelling, facial tenderness and pain, and headache. Sinusitis may exacerbate asthma.

LABORATORY AND IMAGING STUDIES
Culture of the nasal mucosa is not useful. Sinus aspirate culture is the most accurate diagnostic method but is not practical or necessary in immunocompetent patients.

Plain x-ray and computed tomography may reveal sinus clouding, mucosal thickening, or an air-fluid level. Abnormal radiographic findings do not differentiate infection from allergic disease; computed tomography and magnetic resonance imaging often show abnormalities, including air-fluid levels, in the sinuses of asymptomatic persons. Conversely normal radiographs have high negative predictive value for bacterial sinusitis.

DIFFERENTIAL DIAGNOSIS
The diagnosis usually is based on history and physical findings for longer than 10 to 14 days without improvement or increased severity of symptoms compared to the common cold.

TREATMENT
Amoxicillin-clavulanate for 10 to 14 days is recommended as first-line therapy of sinusitis in children. High-dose therapy is recommended for children at increased risk for resistant bacteria (antibiotic treatment in the preceding 1 to 3 months, day care attendance, age <2 years, high rates of antimicrobial resistance locally). Levofloxacin is recommended for children with type I hypersensitivity to penicillins. Clindamycin plus a third generation cephalosporin (cefoxime, cefpodoxime) is recommended for children with non-type I hypersensitivity.

COMPLICATIONS AND PROGNOSIS
Complications include orbital cellulitis, epidural or subdural empyema, brain abscess, dural sinus thrombosis, osteomyelitis of the outer or inner table of the frontal sinus (Pott puffy tumor), and meningitis. These all should be managed with sinus drainage and broad-spectrum parenteral antibiotics. Sinusitis also may exacerbate bronchoconstriction in asthmatic patients.

Orbital cellulitis is a serious complication of sinusitis that follows bacterial spread into the orbit through the wall of the infected sinus. It typically begins as ethmoid sinusitis and spreads through the lamina papyracea, a thin, bony plate that separates the medial orbit and the ethmoid sinus. Orbital involvement can lead to subperiosteal abscess, opthalmo-plegia, cavernous sinus thrombosis, and vision loss. Manifestations of orbital cellulitis include orbital pain, proptosis, chemosis, opthalmoplegia and limited extraocular muscle motion, diplopia, and reduced visual acuity. Infection of the orbit must be differentiated from that of the preseptal (anterior to the palpebral fascia) or periorbital space. Preseptal (peri orbital) cellulitis usually occurs in children younger than 3 years of age; these children do not have proptosis or ophthalmoplegia. Periorbital cellulitis may be associated with a skin lesion or trauma and usually is caused by *S. aureus* or group A streptococcus.

The diagnosis of orbital cellulitis is confirmed by a computed tomography scan of the orbit, which determines the extent of orbital infection and the need for surgical drainage. Disorders to be considered in the differential diagnosis are zygomycosis...
(mucormycosis), aspergillosis, rhabdomyosarcoma, neuroblastoma, Wegener granulomatosis, inflammatory pseudotumor of the orbit, and trichinosis. Therapy for orbital cellulitis involves broad-spectrum parenteral antibiotics, such as vancomycin and ceftriaxone.

More than half of children with acute bacterial sinusitis recover without any antimicrobial therapy. Fever and nasal discharge should improve dramatically within 48 hours of initiating treatment. Persistent symptoms suggest another etiology.

**PREVENTION**

The best means of prevention are good hand washing to minimize acquisition of colds and management of allergic rhinitis.

**OTITIS MEDIA**

**ETIOLOGY**

**Otitis media (OM)** is a suppurative infection of the middle ear cavity. Bacteria gain access to the middle ear when the normal patency of the eustachian tube is blocked by upper airway infection or hypertrophied adenoids. Air trapped in the middle ear is resorbed, creating negative pressure in this cavity and facilitating reflux of nasopharyngeal bacteria. Obstructed flow of secretions from the middle ear to the pharynx combined with bacterial reflux leads to infected middle ear effusion.

Both bacteria and viruses can cause OM. The common bacterial pathogens are *Streptococcus pneumoniae*, non-typable *Haemophilus influenzae*, Moraxella catarrhalis, and, less frequently, group A streptococcus. *S. pneumoniae* that is relatively resistant to penicillin (minimal inhibitory concentration 0.1 to 1 μg/mL) or highly resistant to penicillin (minimal inhibitory concentration ≥2 μg/mL) is isolated with increasing frequency from young children, particularly those who attend day care or have received antibiotics recently. Viruses, including rhinoviruses, influenza, and respiratory syncytial virus, are recovered alone or as co-pathogens in 20% to 25% of patients.

**EPIDEMIOLOGY**

Diseases of the middle ear account for approximately one third of office visits to pediatricians. The peak incidence of acute OM is between 6 and 15 months of life. By the first birthday, 62% of children experience at least one episode. Few first episodes occur after 18 months of age. OM is more common in boys and in patients of lower socioeconomic status. There is increased incidence of OM in Native Americans and Alaskan Natives and in certain high-risk populations, such as children with human immunodeficiency virus (HIV), cleft palate, and trisomy 21. In most of the United States, OM is a seasonal disease with a distinct peak in January and February, which corresponds to the rhinovirus, respiratory syncytial virus, and influenza seasons. The major risk factors for acute OM are young age, lack of breastfeeding, passive exposure to tobacco smoke, and increased exposure to infectious agents (day care).

As defined by the presence of six or more acute OM episodes in the first 6 years of life, at least 12% of children in the general population have recurrent OM and would be considered *otitis-prone*. Craniofacial anomalies and immunodeficiencies often are associated with recurrent OM; most children with recurrent acute OM are otherwise healthy.

**CLINICAL MANIFESTATIONS**

In infants, the most frequent symptoms of acute OM are non-specific and include fever, irritability, and poor feeding. In older children and adolescents, acute OM usually is associated with fever and *otalgia* (acute ear pain). Acute OM also may present with *otorrhea* (ear drainage) after spontaneous rupture of the tympanic membrane. Signs of a common cold, which predisposes to acute OM, are often present (see Chapter 102). A bulging tympanic membrane, air fluid level, or visualization of purulent material by otoscopy are reliable signs of infection (Table 105-1).

Examination of the ears is essential for diagnosis and should be part of the physical examination of any child with fever. The hallmark of OM is the presence of effusion in the middle ear cavity (see Table 105-1). The presence of an effusion does not define its nature or potentially infectious etiology, but it does define the need for appropriate diagnosis and therapy.

**Pneumatic otoscopy**, using an attachment to a hermetically sealed otoscope, allows evaluation of ventilation of the middle ear and is a standard for clinical diagnosis. The tympanic membrane of the normal, air-filled middle ear has much greater compliance than if the middle ear is fluid-filled. With acute OM, the tympanic membrane is characterized by *hyperemia*, or red color rather than the normal pearly gray color, but it can be pink, white, or yellow with a full to bulging position and with poor or absent mobility to negative and positive pressure. The light reflex is lost, and the middle ear structures are obscured and difficult to distinguish. A hole in the tympanic membrane or purulent drainage confirms perforation. Occasionally bullae are present on the lateral aspect of the tympanic membrane, which characteristically are associated with severe ear pain.

**LABORATORY AND IMAGING STUDIES**

Routine laboratory studies, including complete blood count and erythrocyte sedimentation rate, are not useful in the evaluation of OM. **Tympanometry** provides objective acoustic measurements of the tympanic membrane-middle ear system by reflection or absorption of sound energy from the external
ear duct as pressure in the duct is varied. Measurements of the resulting tympanogram correlate well with the presence or absence of middle ear effusion.

Instruments using acoustic reflectometry are available for office and home use. Use of reflectometry as a screening test for acute OM should be followed by examination with pneumatic otoscopy when abnormal reflectometry is identified.

Bacteria recovered from the nasopharynx do not correlate with bacteria isolated by tympanocentesis. Tympanocentesis and middle ear exudate culture are not always necessary, but they are required for accurate identification of bacterial pathogens and may be useful in neonates, immunocompromised patients, and patients not responding to therapy.

DIFFERENTIAL DIAGNOSIS

The major difficulty is differentiation of acute OM from OM with effusion, which also is referred to as chronic OM. Acute OM is accompanied by signs of acute illness, such as fever, pain, and upper respiratory tract inflammation. OM with effusion is the presence of effusion without any of the other signs and symptoms.

TREATMENT

Recommendations for treatment are based on certainty of diagnosis and severity of illness. A certain diagnosis can be made if there is rapid onset, signs of middle ear effusion, and signs and symptoms of middle ear inflammation. The recommended first-line therapy for most children with a certain diagnosis of acute OM or those with an uncertain diagnosis but who are younger than 2 years of age or have fever greater than 39°C or otalgia is amoxicillin (80 to 90 mg/kg/day in two divided doses). Children with an uncertain diagnosis who are older than 2 years of age may be observed if appropriate follow-up can be arranged. Failure of initial therapy with amoxicillin at 3 days suggests infection with β-lactamase-producing H. influenza, M. catarrhalis or resistant S. pneumoniae. Recommended next-step treatments include high-dose amoxicillin-clavulanate (amoxicillin 80 to 90 mg/kg/day), cefuroxime axetil, cefdinir, or ceftriaxone (50 mg/kg intramuscularly in daily doses for 1 to 3 days). Intramuscular ceftriaxone is especially appropriate for children younger than 3 years of age with vomiting that precludes oral treatment. Tympanocentesis may be required for patients who are difficult to treat or who do not respond to therapy. Acetaminophen and ibuprofen are recommended for fever. Decongestants or antihistamines are not effective.

COMPLICATIONS AND PROGNOSIS

The complications of OM are chronic effusion, hearing loss, cholesteatoma (mass-like keratinized epithelial growth), petrositis, intracranial extension (brain abscess, subdural empyema, or venous thrombosis), and mastoiditis. Acute mastoiditis is a suppurative complication of OM with inflammation and potential destruction of the mastoid air spaces. The disease progresses from a periostitis to an osteitis with mastoid abscess formation. Posterior auricular tenderness, swelling, and erythema, in addition to the signs of OM, are present. The pinna is displaced downward and outward. Radiographs or computed tomography scan of the mastoid reveals clouding of the air cells, demineralization, or bone destruction. Treatment includes systemic antibiotics and drainage if the disease has progressed to abscess formation.

OM with effusion is the most frequent sequela of acute OM and occurs most frequently in the first 2 years of life. Persistent middle ear effusion may last for many weeks or months in some children but usually resolves by 3 months following infection. Evaluating young children for this condition is part of all well-child examinations.

Conductive hearing loss should be assumed to be present with persistent middle ear effusion; the loss is mild to moderate and often is transient or fluctuating. Normal tympanograms after 1 month of treatment obviate the need for further follow-up. In children at developmental risk or with frequent episodes of recurrent acute OM, 3 months of persistent effusion with significant bilateral hearing loss is a reasonable indicator of need for intervention with insertion of pressure equalization tubes.

PREVENTION

Parents should be encouraged to continue exclusive breastfeeding as long as possible and should be cautioned about the risks of bottle-propping and of children taking a bottle to bed. The home should be a smoke-free environment.

Children identified at high-risk for recurrent acute OM are candidates for prolonged courses of antimicrobial prophylaxis, which can reduce recurrences significantly. Amoxicillin (20 to 30 mg/kg/day) or sulfisoxazole (50 mg/kg/day) given...
once daily at bedtime for 3 to 6 months or longer is used for prophylaxis.

The conjugate *S. pneumoniae* vaccine reduces pneumococcal OM caused by vaccine serotypes by 50%, all pneumococcal OM by 33%, and all OM by 6%. Annual immunization against influenza virus may be helpful in high-risk children.

**LABORATORY AND IMAGING STUDIES**

The diagnosis of uncomplicated otitis externa usually is established solely on the basis of the clinical symptoms and physical examination findings without the need for additional laboratory or microbiologic evaluation. In malignant otitis externa, an elevated erythrocyte sedimentation rate is a constant finding. Cultures are required to identify the etiologic agent, which is usually *P. aeruginosa*, and the antimicrobial susceptibility.

**DIFFERENTIAL DIAGNOSIS**

Otitis media with tympanic perforation and discharge into the auditory canal may be confused with otitis externa. Pain on movement of the pinnae or tragus, typical of otitis externa, is not present. Local and systemic signs of mastoiditis indicate a process more extensive than otitis externa. Malignancies or cholesteatoma presenting in the auditory canal are rare in children but may present with discharge, unusual pain, or hearing loss.

**TREATMENT**

Topical antimicrobial/corticosteroid otic preparations (such as oxolacox, ciprofloxacin with hydrocortisone or dexamethasone, and polymyxin B-neosporin-hydrocortisone) are sufficient in most cases of otitis externa. These preparations are equally effective and are active against *S. aureus* and most gram-negative bacteria, including *P. aeruginosa*. None of these antibiotics has any antifungal activity. Use of aminoglycosides such as neomycin should be avoided in cases of tympanic membrane rupture due to their ototoxicity. *Tympanostomy tube otorrhea* is best treated with quinolone otic drugs, which is considered less likely to be ototoxic.

Treatment with topical otic analgesics and cerumenolytics is usually unnecessary. It is important with any topical therapy to remove purulent discharge from the external auditory canal with a swab or with suction to permit instillation of the solution. Excess water should be removed after bathing and the ear canal dried using a hairdryer. The predisposing activity, such as swimming or diving, should be avoided until the inflammation has resolved.

Fungi such as *Aspergillus*, *Candida*, and dermatophytes occasionally are isolated from the external ear. It may be difficult to determine whether they represent normal flora or are the cause of inflammation. In most cases, local therapy and restoration of normal pH as recommended for bacterial otitis externa are sufficient.

**Malignant otitis externa** is treated by parenteral antimicrobials with activity against *P. aeruginosa*, such as an expanded-spectrum penicillin (mezlocillin, piperacillin-tazobactam) or a cephalosporin with activity against *P. aeruginosa* (ceftazidime, cefepime) plus an aminoglycoside.

**COMPLICATIONS AND PROGNOSIS**

Acute otitis externa usually resolves promptly without complications within 1 to 2 days of initiating treatment. Persistent pain, especially if severe or if accompanied by other symptoms such as fever, should prompt re-evaluation for other conditions.

Complications of malignant otitis externa include invasion of the bones of the base of the skull, which may cause cranial
nerve palsy. A mortality of 15% to 20% occurs in adults with malignant otitis media. Relapses within the first year after treatment are common.

PREVENTION
Overvigorous cleaning of an asymptomatic auditory canal should be avoided. Drying the auditory canals with acetic acid (2%), Burrow solution, or diluted isopropyl alcohol (rubbing alcohol) after swimming may be used prophylactically to help prevent the maceration that facilitates bacterial invasion. Often underwater gear, such as earplugs or diving equipment, must be avoided to prevent recurrent disease. There is no role for prophylactic otic antibiotics.

Chapter 107

CROUP (LARYNGOTRACHEOBRONCHITIS)

ETIOLOGY AND EPIDEMIOLOGY
Croup, or laryngotracheobronchitis, is the most common infection of the middle respiratory tract (Table 107-1). The most common causes of croup are parainfluenza viruses (types 1, 2, 3, and 4) and respiratory syncytial virus. Laryngotracheal airway inflammation disproportionately affects children because a small decrease in diameter secondary to mucosal edema and inflammation exponentially increases airway resistance and the work of breathing. During inspiration, the walls of the subglottic space are drawn together, aggravating the obstruction and producing the stridor characteristic of croup. Croup is most common in children 6 months to 3 years of age, with a peak in fall and early winter. It typically follows a common cold. Symptomatic reinfection is common, yet reinfections are usually mild. In adolescents, it manifests as laryngitis.

CLINICAL MANIFESTATIONS

The manifestations of croup are a harsh cough described as barking or brassy, hoarseness, inspiratory stridor, low-grade fever, and respiratory distress that may develop slowly or quickly. Stridor is a harsh, high-pitched respiratory sound produced by turbulent airflow. It is usually inspiratory, but it may be biphasic and is a sign of upper airway obstruction. Signs of upper airway obstruction, such as labored breathing and marked suprasternal, intercostal, and subcostal retractions, may be evident on examination (see Chapter 135). Wheezing may be present if there is associated lower airway involvement.

LABORATORY AND IMAGING STUDIES
Anteroposterior radiographs of the neck often show the diagnostic subglottic narrowing of croup known as the steeple sign (Fig. 107-1). Routine laboratory studies are not useful in establishing the diagnosis. Leukocytosis is uncommon and suggests epiglottitis or bacterial tracheitis. Many rapid tests (using polymerase chain reaction or fluorescent antibodies) are available for parainfluenza viruses, respiratory syncytial virus, and other less common viral causes of croup, such as influenza and adenoviruses.

DIFFERENTIAL DIAGNOSIS
The diagnosis of croup usually is established by clinical manifestations. The infectious differential diagnosis includes epiglottitis, bacterial tracheitis, and parapharyngeal abscess. Noninfectious causes of stridor include mechanical and anatomic causes (foreign body aspiration, laryngomalacia, subglottic stenosis, hemangioma, vascular ring, vocal cord paralysis). Stridor in infants younger than 4 months of age or persistence of symptoms for longer than 1 week indicates an increased probability of another lesion and the need for imaging and direct laryngoscopy (see Chapter 135). Epiglottitis is a medical emergency because of the risk of sudden airway obstruction. This illness is now rare and usually caused by group A streptococcus or Staphylococcus aureus or Haemophilus influenza type b in unimmunized patients. Patients typically prefer sitting, often with the head held forward, the mouth open, and the jaw thrust forward (sniffing position). Lateral radiograph reveals thickened and bulging epiglottis (thumb sign) and swelling of the aryepiglottic folds. The diagnosis is confirmed by direct observation of the inflamed and swollen supraglottic structures and swollen, cherry-red epiglottitis, which should be performed only in the operating room with an anesthesiologist and a competent surgeon prepared to place an endotracheal tube or perform a tracheostomy if needed. Epiglottitis requires antibiotic therapy and endotracheal intubation to maintain the airway. Clinical recovery is rapid, and most children can be extubated safely within 48 to 72 hours.

Bacterial tracheitis is a rare but serious superinfection of the trachea that may follow viral croup and is most commonly caused by S. aureus. Spasmodic croup describes sudden onset of croup symptoms, usually at night, but without a significant upper respiratory tract prodrome. These episodes may be recurrent and severe but usually are of short duration. Spasmodic croup has a milder course than viral croup and responds to relatively simple therapies, such as exposure to cool or humidified air. The etiology is not well understood and may be allergic.

TREATMENT
Oral or intramuscular dexamethasone for children with mild, moderate, or severe croup reduces symptoms, the need for hospitalization, and shortens hospital stays. Dexamethasone
Table 107-1  Clinical Features of Laryngotracheal Respiratory Tract Infections

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>VIRAL LARYNGOTRA-</th>
<th>EPIGLOTTITIS</th>
<th>BACTERIAL TRACHEITIS</th>
<th>SPASMODIC CROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral prodromal illness</td>
<td>++</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mean age</td>
<td>6–36 mo (60% &lt;24 mo)</td>
<td>3–4 yr (25% &lt;2 yr)</td>
<td>4–5 yr</td>
<td>6–36 mo (60% &lt;24 mo)</td>
</tr>
<tr>
<td>Onset of illness</td>
<td>Gradual</td>
<td>Acute</td>
<td>Acute</td>
<td>Sudden (at night)</td>
</tr>
<tr>
<td>(2–3 days)</td>
<td>(6–24 hr)</td>
<td>(1–2 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Toxicity</td>
<td>–</td>
<td>++</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Quality of stridor</td>
<td>Harsh</td>
<td>Mild</td>
<td>Harsh</td>
<td>Harsh</td>
</tr>
<tr>
<td>Drooling, neck hyperextension</td>
<td>–</td>
<td>++</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Cough</td>
<td>++</td>
<td>–</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Sore throat</td>
<td>±</td>
<td>++</td>
<td>±</td>
<td>–</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>–</td>
<td>+</td>
<td>±</td>
<td>–</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Recurrence</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Hospitalization and endotracheal intubation</td>
<td>Rare</td>
<td>Frequent</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
</tbody>
</table>


+, frequently present; –, absent; ±, may or may not be present; ++, present and usually pronounced.

Figure 107-1  Croup (laryngotracheobronchitis). A, Posteroanterior view of the upper airway shows the so-called steeple sign, the tapered narrowing of the immediate subglottic airway (arrows). B, Lateral view of the upper airway shows good delineation of the supraglottic anatomy. The subglottic trachea is hazy and poorly defined (arrow) because of the inflammatory edema that has obliterated the sharp undersurface of the vocal cords and extends down the trachea in a diminishing manner. (From Bell LM: Middle respiratory tract infections. In Jenson HB, Baltimore RS: Pediatric Infectious Diseases: Principles and Practice, ed 2, Philadelphia, 2002, Saunders, p 774.)

phosphate (0.6 to 1 mg/kg) may be given once intramuscularly or dexamethasone (0.6 to 1 mg/kg) once orally. Alternatively prednisolone (2 mg/kg per day) may be given orally in two to three divided doses. For significant airway compromise, administration of aerosolized racemic (D- and L-) epi-nephrine reduces subglottic edema by adrenergic vasoconstriction, temporarily producing marked clinical improvement. The peak effect is within 10 to 30 minutes and fades within 60 to 90 minutes. A rebound effect may occur, with worsening of symptoms as the effect of the drug dissipates. Aerosol treatment may need to be repeated every 20 minutes (for no more than 1 to 2 hours) in severe cases.

Children should be kept as calm as possible to minimize forceful inspiration. One useful calming method is for a child with croup to sit on the parent’s lap. Sedatives should be used cautiously and in the intensive care unit only. Cool mist administered by face mask may help prevent drying of the secretions around the larynx.
Hospitalization is often required for children with stridor at rest. Children receiving aerosol treatment should be hospitalized or observed for at least 2 to 3 hours because of the risk of rebound airway obstruction. Decreased symptoms may indicate improvement or fatigue and impending respiratory failure.

**COMPLICATIONS AND PROGNOSIS**

The most common complication of croup is viral pneumonia, which occurs in 1% to 2% of children. Parainfluenza virus pneumonia and secondary bacterial pneumonia are more common in immunocompromised persons. Bacterial tracheitis may also be a complication of croup.

The prognosis for croup is excellent. Illness usually lasts approximately 5 days. As children grow, they become less susceptible to the airway effects of viral infections of the middle respiratory tract.

**PREVENTION**

There is no vaccine for parainfluenza.

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**PERTUSSIS**

**ETIOLOGY**

Classic pertussis (whooping cough) is caused by *B. pertussis*, a gram-negative pleomorphic bacillus with fastidious growth requirements. *B. pertussis* infects only humans and is transmitted person to person by coughing.

**EPIDEMIOLOGY**

The incubation period is 7 to 10 days. Patients are most contagious during the first 2 weeks of cough. The peak incidence of pertussis in the United States is among those less than 4 months of age—infants too young to be completely immunized and most likely to have severe complications. The annual rate of pertussis was approximately 100 to 200 cases per 100,000 population in the prevaccination era; worldwide there are an estimated 30 to 50 million cases of pertussis and 300,000 deaths annually. In the United States, the incidence of pertussis decreased after the introduction of vaccine but has increased steadily since the 1980s with more than 27,000 cases reported in 2010. Infections in adolescents have also been rising, likely due to waning immunity from previous vaccines. Likewise when vaccination rates are low, pertussis rates increase: there was a steady decline in the incidence of pertussis until the late 1970s in the United Kingdom, when the incidence increased dramatically as the vaccination rate declined. Epidemics also occur in fully immunized patients, as vaccine-induced immunity wanes.

**CLINICAL MANIFESTATIONS**

Classic pertussis is seen in children between 1 and 10 years old. The progression of the disease is divided into catarrhal, paroxysmal, and convalescent stages. The **catarrhal stage** is marked by nonspecific signs (increased nasal secretions and low-grade fever) lasting 1 to 2 weeks. The **paroxysmal stage** is the most distinctive stage of pertussis and lasts 2 to 4 weeks. Coughing occurs in **paroxysms** during expiration, causing young children to lose their breath. This pattern of coughing is needed to dislodge plugs of necrotic bronchial epithelial tissues and thick mucus. The forceful inhalation against a narrowed glottis that follows this paroxysm of cough produces the characteristic **whoop**. Posttussive emesis is common. The **convalescent stage** is marked by gradual resolution of symptoms over 1 to 2 weeks. Coughing becomes less severe, and the paroxysms and whoops slowly disappear. Although the disease typically lasts 6 to 8 weeks, residual cough may persist for months, especially with physical stress or respiratory irritants.

Infants may not display the classic findings, and the first sign in the neonate may be apnea. Young infants are unlikely to have the classic whoop, more likely to have central nervous system damage as a result of hypoxia, and more likely to have secondary bacterial pneumonia. Adolescents and adults with pertussis usually present with a prolonged bronchitic illness with persistent, nonproductive cough that often begins as a nonspecific upper respiratory tract infection. Generally adolescents and adults do not have a whoop with the cough, although they may have severe paroxysms. The cough may persist many weeks to months.

**LABORATORY AND IMAGING STUDIES**

The diagnosis depends on isolation of *B. pertussis* or detection of its nucleic acids. Culture on specialized media is usually accomplished during the early phases of illness on specimens from nasopharyngeal swabs or aspirates but can be difficult to accomplish given the organism’s fastidious nature. Polymerase chain reaction, although potentially lacking sensitivity in previously immunized individuals, is likely as sensitive as culture and is available in many clinical laboratories. False positive results can occur. Direct fluorescent antibody staining is not recommended. Serologic tests are not useful for diagnosing acute infection but can be confirmatory in the convalescent phase of illness, though there are no commercial kits approved by the U.S. Food and Drug Administration.

**Lymphocytosis** is present in 75% to 85% of infants and young children but is not diagnostic. The white blood cell count may increase from 20,000 cells/mm$^3$ to more than 50,000 cells/mm$^3$, consisting primarily of mature lymphocytes. Physical examination and radiographic signs of segmental lung atelectasis may develop during pertussis, especially during the paroxysmal stage. Perihilar infiltrates are common and are similar to those seen in viral pneumonia.
DIFFERENTIAL DIAGNOSIS
For a young child with classic pertussis, the diagnosis based on the pattern of illness is quite accurate. The paroxysmal stage is the most distinctive part of the syndrome. Other causes of pertussis-like prolonged cough illnesses include Bordetella parapertussis, which causes a similar but milder illness and is not prevented by B. pertussis vaccination, Mycoplasma pneumoniae, Chlamydia pneumoniae and Chlamydophila pneumoniae, adenoviruses, and respiratory syncytial virus.

TREATMENT
Azithromycin, clarithromycin, or erythromycin are recommended for children under 1 month of age. Azithromycin should be used in neonates due to the association between erythromycin treatment and the development of pyloric stenosis. Treatment during the catarrhal phase eradicates nasopharyngeal carriage of organisms within 3 to 4 days and may lessen symptom severity. Treatment in the paroxysmal stage does not alter the course of illness but decreases the potential for spread to others. Trimethoprim-sulfamethoxazole is an alternative therapy among children older than 2 months, though studies of its use for this indication are limited.

COMPLICATIONS AND PROGNOSIS
Major complications are most common among infants and young children and include hypoxia, apnea, pneumonia, seizures, encephalopathy, malnutrition, and death. The most frequent complication is pneumonia caused by B. pertussis itself or resulting from secondary bacterial infection with Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus. Atelectasis may develop secondary to mucous plugs. The force of the paroxysm may produce pneumomediastinum, pneumothorax, or interstitial or subcutaneous emphysema; epistaxis; hernias; and retinal and subconjunctival hemorrhages. Otitis media and sinusitis may occur.

Most children recover normal pulmonary function with complete healing of the respiratory epithelium. Most permanent disability is a result of encephalopathy.

PREVENTION
Active immunity is induced with acellular pertussis components given as a vaccine in combination with the tetanus and diphtheria toxoids (DTaP). The acellular pertussis vaccines contain two to five antigens of B. pertussis, including pertussis toxin, pertactin, filamentous hemagglutinin, and fimbrial agglutinogens, FIM-2 and FIM-3. DTaP vaccine is recommended at 2, 4, 6, and 15 to 18 months, with a booster at 4 to 6 years, and has an efficacy of 70% to 90%. A single booster dose of Tdap vaccine is recommended at 11 to 12 years or once for all adults.

Macrolides are effective in preventing secondary cases in contacts exposed to pertussis. Underimmunized close contacts under 7 years of age should receive a booster dose of DTaP (unless a booster dose has been given within the preceding 3 years), whereas those 7 to 10 years of age should receive Tdap. All close contacts should receive prophylactic antibiotics for 5 days (azithromycin) or 7 to 14 days (clarithromycin or erythromycin, duration based on age).

BRONCHIOLITIS

ETIOLOGY
Bronchiolitis is a disease of small bronchioles with increased mucus production and occasional bronchospasm, sometimes leading to airway obstruction. It is most commonly caused by a viral lower respiratory tract infection. Bronchiolitis is most commonly seen in infants and young children, with most severe cases occurring among infants. Bronchiolitis is potentially life-threatening.

Respiratory syncytial virus (RSV) is a primary cause of bronchiolitis, followed in frequency by human metapneumovirus, parainfluenza viruses, influenza viruses, adenoviruses, rhinoviruses, coronaviruses, and, infrequently, Mycoplasma pneumoniae. Viral bronchiolitis is extremely contagious and is spread by contact with infected respiratory secretions. Although coughing produces aerosols, hand carriage of contaminated secretions is the most frequent mode of transmission.

EPIDEMIOLOGY
Bronchiolitis is a leading cause of hospitalization of infants. Bronchiolitis occurs almost exclusively during the first 2 years of life, with a peak age at 2 to 6 months. Many healthy children with bronchiolitis can be managed as outpatients; however, premature infants and children with chronic lung disease of prematurity, hemodynamically significant congenital heart disease, neuromuscular weakness, or immunodeficiency are at increased risk of severe, potentially fatal disease. Children acquire infection after exposure to infected family members, who typically have symptoms of an upper respiratory tract infection, or from infected children in day care. In the United States, annual peaks are usually in the late winter months from December through March.

CLINICAL MANIFESTATIONS

Bronchiolitis caused by RSV has an incubation period of 4 to 6 days. Bronchiolitis classically presents as a progressive respiratory illness similar to the common cold in its early phase with cough and rhinorrhea. It progresses over 3 to 7 days to noisy, raspy breathing and audible wheezing. There is usually a low-grade fever accompanied by irritability, which may reflect the increased work of breathing. In contrast to the classic progression of disease, young infants infected with RSV may not have a prodrome and may have apnea as the first sign of infection.
Physical signs of bronchiolar obstruction include prolongation of the expiratory phase of breathing, nasal flaring, intercostal retractions, suprasternal retractions, and air trapping with hyperexpansion of the lungs. During the wheezing phase, percussion of the chest usually reveals only hyperresonance, but auscultation usually reveals diffuse wheezes and crackles throughout the breathing cycle. With more severe disease, grunting and cyanosis may be present.

LABORATORY AND IMAGING STUDIES
Routine laboratory tests are not required to confirm the diagnosis. It is important to assess oxygenation in severe cases of bronchiolitis. Pulse oximetry is adequate for monitoring oxygen saturation. Frequent, regular assessments and cardiorespiratory monitoring of infants are necessary because respiratory failure may develop precipitously in very tired infants even though blood gas values taken before rapid decompensation are reassuring.

Antigen tests (usually by immunofluorescence or enzyme-linked immunosorbent assay [also referred to as ELISA]) of nasopharyngeal secretions for RSV, parainfluenza viruses, influenza viruses, and adenoviruses are sensitive tests to confirm the infection. Rapid viral diagnosis also is performed by polymerase chain reaction. Identifying the viral agent is helpful for cohorting children with the same infection but is not necessary to make the diagnosis of bronchiolitis.

Chest radiographs frequently show signs of lung hyperinflation, including increased lung lucency and flattened or depressed diaphragms. Areas of increased density may represent either viral pneumonia or localized atelectasis.

DIFFERENTIAL DIAGNOSIS
The major difficulty in the diagnosis of bronchiolitis is to differentiate other diseases associated with wheezing. It may be difficult to differentiate asthma from bronchiolitis by physical examination, but age of presentation, presence of fever, and absence of personal or family history of asthma are the major differential factors. Bronchiolitis occurs primarily in the first year of life and is accompanied by fever, whereas asthma usually presents in older children with previous wheezing episodes typically unaccompanied by fever unless a respiratory tract infection is the trigger for the asthma exacerbation.

Wheezing also may be due to an airway foreign body, congenital airway obstructive lesion, cystic fibrosis, exacerbation of chronic lung disease, viral or bacterial pneumonia, and other lower respiratory tract diseases (see Chapter 78). Cardiogenic asthma, which can be confused with bronchiolitis in infants, is wheezing associated with pulmonary congestion secondary to left-sided heart failure.

Wheezing associated with gastroesophageal reflux is likely to be chronic or recurrent, and the patient may have a history of frequent emesis. Cystic fibrosis is associated with poor growth, chronic diarrhea, and a positive family history. A focal area on radiography that does not inflate or deflate suggests foreign body aspiration.

TREATMENT
Bronchiolitis treatment consists of supportive therapy, including respiratory monitoring, control of fever, hydration, upper airway suctioning, and, if needed, oxygen administration. Indications for hospitalization include moderate to marked respiratory distress, hypoxemia, apnea, inability to tolerate oral feeding, and lack of appropriate care available at home. Hospitalization of high-risk children with bronchiolitis should be considered. Among hospitalized infants, supplemental oxygen by nasal cannula is often necessary, but intubation and ventilatory assistance for respiratory failure or apnea are required in fewer than 10% of these infants. Bronchodilators and corticosteroids are seldom effective and are not generally recommended.

COMPLICATIONS AND PROGNOSIS
Most hospitalized children show marked improvement in 2 to 5 days with supportive treatment alone. The course of the wheezing phase varies, however. Tachypnea and hypoxia may progress to respiratory failure requiring assisted ventilation. Apnea is a major concern for very young infants with bronchiolitis.

Most cases of bronchiolitis resolve completely, although minor abnormalities of pulmonary function and bronchial hyperreactivity may persist for several years. Recurrence is common but tends to be mild and should be assessed and treated similarly to the first episode. The incidence of asthma seems to be higher for children hospitalized for bronchiolitis as infants, but it is unclear whether this is causal or whether children prone to asthma are more likely to be hospitalized with bronchiolitis. There is a 1% to 2% mortality rate, highest among infants with preexisting cardiopulmonary or immunologic impairment.

PREVENTION
Monthly injections of palivizumab, an RSV-specific monoclonal antibody, initiated just before the onset of the RSV season confers some protection from severe RSV disease. Palivizumab is indicated for some infants under 2 years old with chronic lung disease, very low birth weight, and those with hemodynamically significant cyanotic and acyanotic congenital heart disease. Immunization with influenza vaccine is recommended for all children older than 6 months and may prevent influenza-associated disease.

PNEUMONIA

ETIOLOGY
Pneumonia is an infection of the lower respiratory tract that involves the airways and parenchyma with consolidation of the alveolar spaces. The term lower respiratory tract infection is often used to encompass bronchitis, bronchiolitis (see Chapter 109), pneumonia, or any combination of the three. Pneumonitis is a general term for lung inflammation that may or may not be associated with consolidation. Lobar pneumonia describes pneumonia localized to one or more lobes of the
lungs. **Atypical pneumonia** describes patterns typically more diffuse or interstitial than lobar pneumonia. **Bronchopneumonia** refers to inflammation of the lung that is centered in the bronchioles and leads to the production of a mucopurulent exudate that obstructs some of these small airways and causes patchy consolidation of the adjacent lobules. **Interstitial pneumonia** refers to inflammation of the interstitium, which is composed of the walls of the alveoli, the alveolar sacs and ducts, and the bronchioles. Interstitial pneumonia is characteristic of acute viral infections but also may be a chronic inflammatory or fibrosing process.

Defects in host defenses increase the risk of pneumonia. Lower airways and secretions are sterile as a result of a multifactorial system. Airway contaminants are caught in the mucous secreted by the goblet cells. Cilia on epithelial surfaces, composing the ciliary elevator system, beat synchronously to move particles upward toward central airways and into the throat, where they are swallowed or expectorated. Polymorphonuclear neutrophils from the blood and tissue macrophages ingest and kill microorganisms. IgA secreted into the upper airway fluid protects against invasive infections and facilitates viral neutralization.

Infectious agents that commonly cause community-acquired pneumonia vary by age (Table 110-1). Most common causes are respiratory syncytial virus (RSV) in infants (see Chapter 109), other respiratory viruses (parainfluenza viruses, influenza viruses, human metapneumovirus, adenoviruses) in children younger than 5 years old, and *Mycoplasma pneumoniae* in children older than age 5 years. *Streptococcus pneumoniae* is the most common bacterial cause of lobar pneumonia, and occurs in children of any age outside the neonatal period. *M. pneumoniae* and *Chlamydia pneumoniae* are principal causes of atypical pneumonia.

*Chlamydia trachomatis* and less commonly *Mycoplasma hominis*, *Ureaplasma urealyticum*, and cytomegalovirus (CMV) cause a similar respiratory syndrome in infants 1 to 3 months of age with subacute onset of an afibrile pneumonia; cough and hyperinflation are the predominant signs. These infections are difficult to diagnose and to distinguish from each other. In adults these organisms are carried primarily as part of the genital mucosal flora. Women who harbor these agents may transmit them perinatally to newborns.

Additional agents occasionally cause pneumonia. **Severe acute respiratory syndrome** (SARS) is due to SARS-associated coronavirus (SARS-CoV). **Avian influenza (bird flu)** is a highly contagious viral disease of poultry and other birds caused by influenza A (H5N1). There were outbreaks among humans in South East Asia in 1997 and 2003 to 2004 with high mortality rates. A novel influenza A (H1N1) of swine origin began circulating in 2009. Other etiologic agents to consider, based on specific exposure history, include *Mycobacterium tuberculosis*, *Francisella tularensis*, *Brucella* spp., *Coxiella burnetii*, *Chlamydia psittaci*, *Legionella pneumophila*, hantavirus, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*.

Causes of pneumonia in immunocompromised persons include gram-negative enteric bacteria, mycobacteria (*M. avium complex*), fungi (aspergillosis), viruses (CMV), and *Pneumocystis jiroveci* (carinii). Pneumonia in patients with cystic fibrosis usually is caused by *Staphylococcus aureus* in infancy and *Pseudomonas aeruginosa* or *Burkholderia cepacia* in older patients.

**EPIDEMIOLOGY**

Immunizations have had a great impact on the incidence of pneumonia caused by pertussis, diphtheria, measles, *Haemophilus influenza* type b, and *S. pneumoniae*. Where used, bacille Calmette-Guerin (BCG) for tuberculosis also has had an impact. An estimated 2 million deaths in developing countries are due to acute respiratory tract infections annually. Risk factors for lower respiratory tract infections include gastroesophageal reflux, neurologic impairment (aspiration), immunocompromised states, anatomic abnormalities of the respiratory tract, residence in residential care facilities, and hospitalization, especially in an intensive care unit.

**CLINICAL MANIFESTATIONS**

Age is a determinant in the clinical manifestations of pneumonia. Neonates may have fever or hypoxia only, with subtle or absent physical examination findings (see Chapter 65). With a young infant, apnea may be the first sign of pneumonia. Fever, chills, tachypnea, cough, malaise, pleuritic chest pain, retractions, and apprehension, because of difficulty breathing or shortness of breath, are common in older infants and children. Physical examination findings cannot reliably distinguish viral and bacterial pneumonias, but complete physical examination may help identify other foci of disease or associated findings to suggest an etiology.

In general viral pneumonias are associated more often with cough, wheezing, or stridor; fever is less prominent than with bacterial pneumonia. Mucosal congestion and upper airway inflammation suggest a viral infection. Bacterial pneumonias typically are associated with higher fever, chills, cough, dyspnea, and auscultatory findings of lung consolidation. Atypical pneumonia in young infants is characterized by tachypnea, cough, crackles on auscultation, and concomitant (chlamydial) conjunctivitis (infants) may be present. Other signs of respiratory distress include nasal flaring, intercostal and subcostal retractions, and grunting.

Asymmetry or shallow breathing may be due to splinting from pain. Hyperexpansion, common in asthma but also frequently accompanying viral lower respiratory infections, may cause a low diaphragm or liver. Poor diaphragmatic excursion may indicate hyperexpanded lungs or an inability for expansion due to a large consolidation or effusion. Dullness to percussion may be due to lobar or segmental infiltrates or pleural fluid. Auscultation may be normal in early or very focal pneumonia, but the presence of localized crackles, rhonchi, and wheezes may help one detect and locate pneumonia. Distant breath sounds may indicate a large, poorly ventilated area of consolidation or pleural fluid.
### Table 110-1

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>COMMON PATHOGENS* (IN APPROXIMATE ORDER OF FREQUENCY)</th>
<th>LESS COMMON PATHOGENS</th>
<th>OUTPATIENTS† (7–10 DAYS TOTAL DURATION OF TREATMENT)</th>
<th>PATIENTS REQUIRING HOSPITALIZATION‡ (10–14 DAYS TOTAL DURATION OF TREATMENT)</th>
<th>PATIENTS REQUIRING INTENSIVE CARE*ǂ (10–14 DAYS TOTAL DURATION OF TREATMENT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates (up to 1 month of age)</td>
<td>Group B streptococcus, Escherichia coli, other gram-negative bacilli, Streptococcus pneumoniae</td>
<td>Cytomegalovirus, Herpes simplex virus, Listeria monocytogenes, Treponema pallidum, Haemophilus influenzae (type b,† nontypable)</td>
<td>Outpatient management not recommended</td>
<td>Ampicillin plus cefotaxime or an aminoglycoside plus an antistaphylococcal agent if Staphylococcus aureus is suspected</td>
<td>Ampicillin plus cefotaxime or an aminoglycoside plus an antistaphylococcal agent if S. aureus is suspected</td>
</tr>
<tr>
<td>1 to 3 months</td>
<td>Febrile pneumonia</td>
<td>Respiratory syncytial virus, other respiratory viruses (parainfluenza viruses, influenza viruses, adenoviruses), S. pneumoniae, H. influenzae (type b,† nontypable)</td>
<td>Initial outpatient management not recommended</td>
<td>Cefotaxime or ceftriaxone plus nafcillin, oxacillin, clindamycin, or vancomycin</td>
<td>Cefotaxime or ceftriaxone plus nafcillin, oxacillin, clindamycin, or vancomycin</td>
</tr>
<tr>
<td>Afebrile pneumonia</td>
<td>Chlamydia trachomatis, Mycoplasma hominis, Ureaplasma urealyticum, cytomegalovirus Bordetella pertussis</td>
<td>Amoxicillin or amoxicillin plus clarithromycin or clarithromycin with close follow-up</td>
<td>Amoxicillin or amoxicillin plus clarithromycin or clarithromycin</td>
<td>Erythromycin, azithromycin, or clarithromycin if atypical pneumonia suspected.</td>
<td>Erythromycin, azithromycin, or clarithromycin plus cefotaxime or ceftriaxone plus nafcillin, oxacillin, clindamycin, or vancomycin</td>
</tr>
<tr>
<td>3 months to 5 years</td>
<td>Respiratory syncytial virus, other respiratory viruses (parainfluenza viruses, influenza viruses, human metapneumovirus adenoviruses), S. pneumoniae, H. influenzae (type b,† nontypable)</td>
<td>C. trachomatis, Mycoplasma pneumoniae, Chlamyphila pneumoniae, group A streptococci, Staphylococcus aureus, Mycobacterium tuberculosis</td>
<td>Amoxicillin plus erythromycin, azithromycin, or clarithromycin if atypical pneumonia suspected</td>
<td>Ampicillin Alternatives: cefotaxime or ceftriaxone if not fully immunized or local S. pneumoniae penicillin resistance is significant, with clindamycin if MRSA suspected</td>
<td>Cefuroxime or ceftriaxone plus azithromycin, erythromycin or clarithromycin if atypical pneumonia suspected</td>
</tr>
<tr>
<td>5 to 18 years</td>
<td>M. pneumoniae, S. pneumoniae, C. pneumoniae, H. influenzae (type b,† nontypable), influenza viruses, adenoviruses, other respiratory viruses</td>
<td>Legionella pneumophila, M. tuberculosis</td>
<td>Amoxicillin or erythromycin, azithromycin, or clarithromycin if atypical pneumonia suspected</td>
<td>Ampicillin plus erythromycin, azithromycin, or clarithromycin if atypical pneumonia suspected</td>
<td>Cefuroxime or ceftriaxone plus azithromycin, erythromycin or clarithromycin if atypical pneumonia or clarithromycin if without clindamycin or vancomycin</td>
</tr>
<tr>
<td>≥18 years‡</td>
<td>M. pneumoniae, S. pneumoniae, C. pneumoniae, H. influenzae (type b,† nontypable), influenza viruses, adenoviruses, other respiratory viruses</td>
<td></td>
<td>Amoxicillin or erythromycin, azithromycin, clarithromycin, doxycycline, moxifloxacin, gatifloxacin, levofloxacin, or gemifloxacin if atypical pneumonia suspected</td>
<td></td>
<td></td>
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</tbody>
</table>
LABORATORY AND IMAGING STUDIES

Bacterial flora of the upper respiratory tract do not accurately reflect flora present in lower respiratory tract infections, and high-quality sputum is rarely obtainable from children. In otherwise healthy children without life-threatening disease, invasive procedures to obtain lower respiratory tissue or secretions usually are not indicated. Serologic tests are not useful for the most common causes of bacterial pneumonia.

The white blood cell (WBC) count with viral pneumonias is often normal or mildly elevated, with a predominance of lymphocytes, whereas with bacterial pneumonias the WBC count is elevated (>20,000/mm³) with a predominance of neutrophils. Mild eosinophilia is characteristic of infant C. trachomatis pneumonia. Blood cultures should be performed on hospitalized children to attempt to diagnose a bacterial cause of pneumonia. Blood cultures are positive in 10% to 20% of bacterial pneumonia and are considered to be confirmatory of the cause of pneumonia if positive for a recognized respiratory pathogen. Urinary antigen tests are especially useful for L. pneumophila (legionnaires’ disease). Viral respiratory pathogens can be diagnosed using polymerase chain reaction (PCR) or rapid viral antigen detection, but neither rules out concomitant bacterial pneumonia. M. pneumoniae should be suspected if cold agglutinins are present in peripheral blood samples and can be confirmed by Mycoplasma PCR. CMV and enterovirus can be cultured from the nasopharynx, urine, or bronchoalveolar lavage fluid. The diagnosis of M. tuberculosis is established by tuberculin skin test, serum interferon-gamma release assay, or analysis of sputum or gastric aspirates by culture, antigen detection, or PCR.

The need to establish an etiologic diagnosis of pneumonia is greater for patients who are ill enough to require hospitalization, immunocompromised patients, patients with recurrent pneumonia, or patients with pneumonia unresponsive to empirical therapy. For these patients, bronchoscopy with bronchoalveolar lavage and brush mucosal biopsy, needle aspiration of the lung, and open lung biopsy are methods of obtaining material for microbiologic diagnosis.

When there is a pleural effusion or empyema, a thoracentesis to obtain pleural fluid can be diagnostic and therapeutic. Evaluation differentiates between empyema and a sterile parapneumonic effusion caused by irritation of the pleura contiguous with the pneumonia. Gram stain, culture, or broad-range bacterial PCR may lead to microbiologic diagnosis. The pleural fluid should be cultured for bacteria, mycobacteria, fungi, and viruses. If the fluid is grossly purulent, removal reduces the patient’s toxicity and associated discomfort and may facilitate more rapid recovery. If the accumulation is large and impairs the ability of the lung to expand, removal of the fluid improves pulmonary mechanics and gas exchange.

Frontal and lateral radiographs are required to localize disease and adequately visualize retrocardiac infiltrates and are recommended for diagnosis among hospitalized children, but they are not necessary to confirm the diagnosis in well-appearing outpatients. Although there are characteristic radiographic findings of pneumonia, radiography alone cannot provide a definitive microbiologic diagnosis. Bacterial pneumonia characteristically shows lobar consolidation, or a round pneumonia, with pleural effusion in 10% to 30% of cases (Fig. 110-1). Viral pneumonia characteristically shows diffuse, streaky infiltrates of bronchopneumonia (Fig. 110-2) and hyperinflation. Atypical pneumonia, such as with M. pneumoniae and C. pneumoniae, shows increased interstitial markings or bronchopneumonia (Fig. 110-3). Chest radiographs may be normal in early pneumonia, with infiltrates appearing during treatment as hydration is restored. Hilar lymphadenopathy is uncommon with bacterial pneumonia but may be a sign of tuberculosis, histoplasmosis, or an underlying malignant neoplasm. Decubitus views or ultrasound should be used to assess size of pleural effusions and whether they are freely mobile.
Computed tomography (CT) is used to evaluate serious disease, pleural abscesses, bronchiectasis, and effusion characteristics. Unusual etiologies or recurrent pneumonias require special considerations (Table 110-2). Lung abscesses, pneumatoceles, and empyema all require special management.

**DIFFERENTIAL DIAGNOSIS**

Pneumonia must be differentiated from other acute pulmonary diseases, including allergic pneumonitis, asthma, and cystic fibrosis; cardiac diseases, such as pulmonary edema caused by heart failure; and autoimmune diseases, such as certain vasculitides and systemic lupus erythematosus. Radiographically pneumonia must be differentiated from lung trauma and concussion, hemorrhage, foreign body aspiration, and sympathetic effusion due to subdiaphragmatic inflammation.

**TREATMENT**

Therapy for pneumonia includes supportive and specific treatment and depends on the degree of illness, complications, and knowledge of the infectious agent likely causing the pneumonia. Most cases of pneumonia in healthy children can be managed on an outpatient basis. However children with hypoxemia, inability to maintain adequate hydration, or moderate to severe respiratory distress should be hospitalized. Hospitalization should be considered in infants under 6 months with suspected bacterial pneumonia, those in whom there is a concern for a pathogen with increased virulence (e.g., methicillin-resistant *Staphylococcus aureus*), or when concern exists about a family’s ability to care for the child and to assess symptom progression.

Because viruses cause most community-acquired pneumonias in young children, not all children require empirical antibiotic treatment for pneumonia. Recommended therapies in those without recent antibiotic exposure are listed in Table 110-1. Exceptional situations include lack of response to empirical therapy, unusually severe presentations, nosocomial pneumonia, and immunocompromised children susceptible to infections with opportunistic pathogens (Table 110-3). In contrast to pneumococcal meningitis, presumed pneumococcal pneumonia can be treated with high-dose cephalosporin therapy even with high-level penicillin resistance. Vancomycin can be used if the isolate shows high-level resistance and the patient is severely ill. For infants 4 to 18 weeks old with afebrile pneumonia most likely caused by *C. trachomatis*, a macrolide is the recommended treatment. Oseltamivir or zanamivir should be used if influenza is identified or suspected, ideally within 48 hours of symptom onset.

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**Table 110-2** Differential Diagnosis of Recurrent Pneumonia

<table>
<thead>
<tr>
<th>HEREDITARY DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Sickle cell disease</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>DISORDERS OF IMMUNITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
</tr>
<tr>
<td>Bruton agammaglobulinemia</td>
</tr>
<tr>
<td>Selective IgG subclass deficiencies</td>
</tr>
<tr>
<td>Common variable immunodeficiency syndrome</td>
</tr>
<tr>
<td>Severe combined immunodeficiency syndrome</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>DISORDERS OF LEUKOCYTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic granulomatous disease</td>
</tr>
<tr>
<td>Hyperimmunoglobulin E syndrome (Job syndrome)</td>
</tr>
<tr>
<td>Leukocyte adhesion defect</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DISORDERS OF CILIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immotile cilia syndrome</td>
</tr>
<tr>
<td>Kartagener syndrome</td>
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</table>

<table>
<thead>
<tr>
<th>ANATOMIC DISORDERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequestration</td>
</tr>
<tr>
<td>Lobar emphysema</td>
</tr>
<tr>
<td>Esophageal reflux</td>
</tr>
<tr>
<td>Foreign body</td>
</tr>
<tr>
<td>Tracheoesophageal fistula (H type)</td>
</tr>
<tr>
<td>Cystic adenomatoid malformation</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Bronchiectasis</td>
</tr>
<tr>
<td>Aspiration (oropharyngeal incoordination)</td>
</tr>
</tbody>
</table>

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**Figure 110-3** *Mycoplasma pneumoniae* infection (atypical pneumonia) in a 14-year-old boy with malaise, dry cough, and mild shortness of breath for 1 week. Frontal chest radiograph shows a diffuse pattern of increased interstitial markings, including Kerley lines. The heart is normal, and there are no focal infiltrates. Cold agglutinins were markedly elevated, and the patient responded to erythromycin. This radiographic pattern of reticulonodular interstitial disease is observed in 25% to 30% of patients with pneumonia caused by *Mycoplasma pneumoniae*. (From Baltimore RS: Pneumonia. In Jenson HB, Baltimore RS, editors: Pediatric Infectious Diseases: Principles and Practice, ed 2, Philadelphia, Saunders, 2002, p 808.)
**COMPLICATIONS AND PROGNOSIS**

Bacterial pneumonias frequently cause inflammatory fluid to collect in the adjacent pleural space, causing a *parapneumonic effusion* or, if grossly purulent, an *empyema*. Small effusions may not require any special therapy. Large effusions may restrict breathing and require drainage. Air dissection within lung tissue results in a *pneumatocele*. Scarring of the lung tissue results in a *pneumatocele*. Scarring of the lung tissue results in a *cavitary lesion*, often with an air-fluid level.

*Pneumonia that causes necrosis of lung tissue may evolve into a *lung abscess*. Lung abscess is an uncommon problem in children and usually is caused by aspiration, infection behind an obstructed bronchus, or certain virulent organisms. Anaerobic bacteria usually predominate, along with various streptococci, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Chest radiograph or CT scan reveals a cavitory lesion, often with an air-fluid level, surrounded by parenchymal inflammation. If the cavity communicates with the bronchi, organisms may be isolated from sputum. Diagnostic bronchoscopy may be indicated to exclude a foreign body and obtain microbiologic specimens. Lung abscesses usually respond to appropriate antimicrobial therapy with clindamycin, penicillin G, or ampicillin-sulbactam.

Most children recover from pneumonia rapidly and completely, although radiographic abnormalities may take 6 to 8 weeks to return to normal. In a few children, pneumonia may persist longer than 1 month or may be recurrent. In such cases, the possibility of underlying disease must be investigated further, such as with tuberculosis skin test, sweat chloride determination for cystic fibrosis, serum immunoglobulin and IgG subclass determinations, bronchoscopy to identify anatomic abnormalities or foreign body, and barium swallow for gastroesophageal reflux.

Severe adenovirus pneumonia may result in *bronchiolitis obliterans*, a subacute inflammatory process in which the small airways are replaced by scar tissue, resulting in a reduction in lung volume and lung compliance. *Unilateral hyperlucent lung*, or *Swyer-James syndrome*, is a focal sequela of severe necrotizing pneumonia in which all or part of a lung has increased translucency radiographically; it has been linked to adenovirus type 21.

**PREVENTION**

Annual influenza vaccine is recommended for all children over 6 months of age (see Chapter 94). Trivalent, inactivated influenza vaccine is licensed for use beginning at 6 months of age; live, attenuated vaccine can be used for persons 2 to 49 years of age. Universal childhood vaccination with conjugate vaccines for *H. influenzae* type b and *S. pneumoniae* has greatly

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**Table 110-3 Antimicrobial Therapy for Pneumonia Caused by Specific Pathogens**

<table>
<thead>
<tr>
<th>PATHOGEN</th>
<th>RECOMMENDED TREATMENT</th>
<th>ALTERNATIVE TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em> with MIC for penicillin ≤ 2.0 μg/mL</td>
<td>Ampicillin or penicillin IV; amoxicillin PO</td>
<td>Ceftriaxone, cefotaxime, clindamycin or vancomycin IV; Cefuroxime, cefpodoxime, levofloxacin†, or linezolid PO</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> with MIC for penicillin &gt; 2.0 μg/mL</td>
<td>Ceftriaxone IV; levofloxacin† or linezolid PO</td>
<td>Ampicillin, levofloxacin†, clindamycin or vancomycin IV; clindamycin PO</td>
</tr>
<tr>
<td>Group A streptococcus</td>
<td>Penicillin or ampicillin IV; amoxicillin or penicillin PO</td>
<td>Ceftriaxone, cefotaxime, clindamycin or vancomycin IV; clindamycin PO</td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>Penicillin or ampicillin IV; amoxicillin or penicillin PO</td>
<td>Ceftriaxone, cefotaxime, clindamycin or vancomycin IV; clindamycin PO</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Ampicillin IV or amoxicillin PO if β-lactamase negative; ceftriaxone or cefotaxime IV or amoxicillin-clavulanate PO if β-lactamase positive</td>
<td>Ciprofloxacin† or levofloxacin† IV; cefdinir, cefixime, or cefpodoxime PO</td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em>, <em>Chlamydia pneumoniae</em>, or <em>Chlamydia trachomatis</em></td>
<td>Azithromycin IV or PO</td>
<td>Erythromycin or levofloxacin IV; clarithromycin, erythromycin, doxycycline†, or a fluoroquinolone† PO</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>, methicillin susceptible (MSSA)</td>
<td>Cefazolin, oxacillin, or nafcillin IV; cephalexin PO</td>
<td>Clindamycin or vancomycin IV; clindamycin PO</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em>, methicillin resistant (MRSA)</td>
<td>Clindamycin or vancomycin IV; clindamycin PO</td>
<td>Linezolid IV or PO</td>
</tr>
<tr>
<td>Gram-negative aerobic bacilli (except <em>P. aeruginosa</em>)</td>
<td>Cefotaxime or ceftriaxone with or without an aminoglycoside IV; amoxicillin-clavulanate, cefdinir, or cefixime PO</td>
<td>Piperacillin-tazobactam plus an aminoglycoside†; fluoroquinolone† PO</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Cefazidime IV with or without an aminoglycoside†; ciprofloxacin† if susceptible PO</td>
<td>Piperacillin-tazobactam IV plus an aminoglycoside†</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Acyclovir IV</td>
<td></td>
</tr>
</tbody>
</table>

†IV Intravenous, MIC minimum inhibitory concentration, PO, per os (orally); TMP-SMX trimethoprim-sulfamethoxazole.

*Oral outpatient therapy may be used for mild illness. Intravenous inpatient therapy should be used for moderate to severe illness.

1Appropriate fluoroquinolones include moxifloxacin, gatifloxacin, levofloxacin, and gemifloxacin. Fluoroquinolones are contraindicated for children younger than 18 years of age and pregnant or lactating women. Tetracyclines are not recommended for children younger than 9 years.

1Aminoglycoside dosing should be guided by serum antibiotic concentrations after a steady state has been reached.
diminished the incidence of these pneumonias. The severity of RSV infections can be reduced by use of palivizumab in high-risk patients (see Chapter 109).

Reducing the duration of mechanical ventilation and administering antibiotics judiciously reduces the incidence of ventilator-associated pneumonias. The head of the bed should be raised to 30 to 45 degrees for intubated patients to minimize risk of aspiration, and all suctioning equipment and saline should be sterile. Hand washing before and after every patient contact and use of gloves for invasive procedures are important measures to prevent nosocomial transmission of infections. Hospital staff with respiratory illnesses or who are carriers of certain organisms, such as methicillin-resistant S. aureus, should comply with infection control policies to prevent transfer of organisms to patients. Treating sources of aerosols, such as air coolers, can prevent Legionella pneumonia.

**INFECTIVE ENDOCARDITIS**

**ETIOLOGY**

Infective endocarditis is an infection on the endothelial surface of the heart, including the heart valves. The management of infections on the endothelial surfaces of blood vessels is very similar. Infectious endothelial lesions, called vegetations, usually occur on the valve leaflets and are composed of microorganisms trapped in a fibrin mesh that extends into the bloodstream.

Many microorganisms have been reported to cause endocarditis, although there are only a few principal causes in children (Table 111-1). Viridans streptococci are the principal causes in children with congenital heart diseases without previous surgery. *Staphylococcus aureus* and coagulase-negative staphylococci are important causes of endocarditis, especially following cardiac surgery and in the presence of prosthetic cardiac and endovascular materials.

**Epidemiology**

Infective endocarditis among children is primarily a complication of congenital heart disease and cardiac surgery, although it can occur in a previously normal native valve. Patients at high risk for infective endocarditis include those with prosthetic cardiac valves or prior infective endocarditis; children who have unrepaired cyanotic congenital heart disease, are within 6 months of repair using prosthetic material, or have residual defects at or near a site of prosthetic material; or transplant patients who develop valvular lesions. The risk is increased after dental and oral procedures or instrumentation or surgical procedures of the respiratory tract, genitourinary tract, or gastrointestinal tract. Rheumatic heart disease is a risk factor but is uncommon. Neonatal endocarditis is associated with the use of central vascular catheters and surgery in neonates. Endocarditis is a sporadic disease with no geographic predisposition and little gender or socioeconomic predisposition in children.

**Clinical Manifestations**

The most common early symptoms of infective endocarditis are nonspecific and include fever, malaise, and weight loss. Tachycardia and a new or changed heart murmur are common findings. The subtle and nonspecific findings underscore the need to obtain blood cultures if endocarditis is suspected, especially for children with congenital heart disease and for unexplained illness after dental or surgical procedures. Endocarditis is usually a subacute, slowly progressive process, but acute endocarditis is often due to *S. aureus* and may resemble sepsis. Heart failure, splenomegaly, petechiae, and embolic phenomena (Osler nodes, Roth spots, Janeway lesions, and splinter hemorrhages) may be present.

**Laboratory Studies and Imaging**

The key to diagnosis is confirming continuous bacteremia or fungemia by culturing the blood. Multiple blood cultures are

| Table 111-1: Pathogens Causing Infective Endocarditis in Children |
|-------------------|-------------------|
| **Bacteria**      |                   |
| Viridans streptococci (the most common causative organism at all ages) |
| *Staphylococcus aureus* |
| Enterococcus |
| Coagulase-negative staphylococci |
| Hemolytic streptococci: groups A, B (in neonates and elderly), C, G, D |
| *Streptococcus pneumoniae* |
| Gram-negative enteric bacilli |
| HACEK organisms (i.e., *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*) |
| **Fungi**         |                   |
| Candida albicans |
| Non-albicans Candida |
| Aspergillus |
| *Cryptococcus neoformans* |
| **Others**        |                   |
| *Coxiella burnetii* (Q fever) |
| Chlamydia |
| Agents of culture-negative endocarditis |

*Most common causes of infective endocarditis in children.
performed before initiating antibiotic therapy. Three separate
venipunctures for blood culture achieve near-maximal sensi-
tivity (about 95%) among patients who have not been treated
recently with antibiotics. Patients who have been treated with
antibiotics recently or who are currently receiving antibiotics
should have additional serial cultures performed. Despite ade-
quate blood culture techniques, the microbiologic diagnosis
is not confirmed in 10% to 15% of cases, known as culture-
negative endocarditis.

Erythrocyte sedimentation rate and C-reactive protein are
often elevated. Leukocytosis, anemia, and hematuria are com-
mon laboratory findings. A positive rheumatoid factor or anti-
nuclear antibody may also be seen.

Echocardiography visualizes endocardial and valvular
vegetations measuring 2 mm or greater. Transeosophageal
echocardiography is more sensitive than transthoracic echo-
cardiography for adolescents and adults and for patients
with prosthetic valves but is often unnecessary in children.

DIFFERENTIAL DIAGNOSIS
Infective endocarditis must be differentiated from other
causes of bacteremia or other cardiac conditions using the
Modified Duke Criteria for categorizing the strength of the
endocarditis diagnosis (Table 111-2). Noninfectious causes of
endocardial vegetations must be excluded, such as sterile clots
and vegetations associated with rheumatoid disease and lupus
erythematosus. Prolonged bacteremia can be caused by infec-
tious endothelial foci outside of the heart, often associated
with congenital malformations, vascular trauma, an infected
venous thrombosis, and previous vascular surgery.

TREATMENT
Severely ill patients must be stabilized with supportive ther-
apies for cardiac failure, pulmonary edema, and low cardiac
output (see Chapter 145). Empirical antibiotic therapy may be
started for acutely ill persons after blood cultures are obtained.
With subacute disease, awaiting results of blood cultures to con-
firm the diagnosis is recommended to direct therapy ac-
cording to the susceptibility of the isolate. Because antibiot-
ics must reach the organisms by passive diffusion through the
fibrin mesh, high doses of bactericidal antibiotics are required
for an extended period of treatment (4 to 8 weeks). Infective
endocarditis from susceptible viridans streptococci can be treated
with monotherapy penicillin G for 4 weeks. A 2-week regimen
of penicillin G plus an aminoglycoside is effective in adults.
Surgery is indicated if medical treatment is unsuccessful, with
persistent bacteremia, an unusual or difficult to treat pathogen
(fungal endocarditis), valve anulus or myocardial abscess, rup-
ture of a valve leaflet, valvular insufficiency with acute or
refractory heart failure, recurrent serious embolic complica-
tions, or refractory prosthetic valve disease.

COMPLICATIONS AND PROGNOSIS
The major complications of infective endocarditis are direct
damage to the heart and heart valves and distant complica-
tions secondary to sterile and septic emboli from vegetations.
Damage to the heart and heart valves may include regurgita-
tion with vegetations or actual defects in the leaflets resulting
from embolization of the leaflet tissue, abscess of the valve
ring, or myocardial abscess. These complications should be
monitored by physical examination and echocardiography.
Cerebral abscesses or aneurysms can cause a stroke-like pic-
ture. Splenic abscesses can cause fatal bleeding.

The outcome of infective endocarditis caused by the most
common organisms is often good. The cure rate is greater than
90% in uncomplicated endocarditis caused by viridans strep-
tococci on a natural valve, 75% to 90% for Enterococcus endo-
carditis treated by a synergistic combination of antibiotics,
and 60% to 75% for S. aureus endocarditis with an acute, severe presentation. The prognosis for endocarditis caused by gram-negative bacilli and rarer organisms is poor. Fungal endocarditis has the poorest prognosis, with a cure rate of about 50% even with valve replacement.

PREVENTION
In high-risk patients, prophylactic antibiotics are required before and during all dental procedures that involve manipulation of gingival tissue or the periapical region as well as invasive procedures of the respiratory tract, infected skin, or muscle. In most cases, oral amoxicillin 50 mg/kg (maximum dose, 2 g) taken 30 to 60 minutes before the procedure is the recommended regimen. Clindamycin or azithromycin are alternative regimens indicated for most patients allergic to β-lactams. Prolonged or continuous antibiotic prophylaxis is not recommended.

ACUTE GASTROENTERITIS

ETIOLOGY AND EPIDEMIOLOGY
Acute enteritis or acute gastroenteritis refers to diarrhea, which is abnormally frequent, and liquidity of fecal discharges. Diarrhea is caused by different infectious or inflammatory processes in the intestine that directly affect enterocyte secretory and absorptive functions. Enteritis has many viral, bacterial, and parasitic causes (Table 112-1). Some of these processes act by increasing cyclic adenosine monophosphate levels (Vibrio cholerae, Escherichia coli heat-labile toxin). Other processes (Shigella toxin) cause secretory diarrhea by affecting ion channels or by unknown mechanisms (Table 112-2).

Diarrhea is a leading cause of morbidity and a common disease in children in the United States. In the developing world, it is a major cause of childhood mortality. The epidemiology of gastroenteritis depends on the specific organisms. Some organisms are spread person to person, others are spread via contaminated food or water, and some are spread from animal to human. Many organisms spread by multiple routes. The ability of an organism to infect relates to the mode of spread, ability to colonize the gastrointestinal tract, and minimum number of organisms required to cause disease.

Viral causes of gastroenteritis in children include rotaviruses, caliciviruses (including the noroviruses), astroviruses, and enteric adenoviruses (serotypes 40 and 41). Rotavirus is the most frequent cause of diarrhea during the winter months. Vomiting may last 3 to 4 days, and diarrhea may last 7 to 10 days. Dehydration is common in younger children. Primary infection with rotavirus may cause moderate to severe disease in infancy but is less severe later in life. This illness is much less common in areas where infants receive the rotavirus vaccine.

Typhoid fever is caused by Salmonella typhi and, occasionally, Salmonella paratyphi. Worldwide, there are an estimated 16 million cases of typhoid fever annually, resulting in 600,000 deaths. The typhoid bacillus infects humans only. These infections are distinguished by prolonged fever and extraintestinal manifestations, despite inconsistent presence of diarrhea. In the United States, approximately 400 cases of typhoid fever occur each year. Most occur in travelers returning from other countries. The incubation period of typhoid fever is usually 7 to 14 days (range 3 to 60 days). Infected persons without symptoms, or chronic carriers, serve as reservoirs and sources of continuous spread. Carriers often have cholelithiasis.

Nontyphoidal Salmonella produces diarrhea by invading the intestinal mucosa. The organisms are transmitted through
contact with infected animals (chickens, pet iguanas, other reptiles, turtles) or from contaminated food products, such as dairy products, eggs, and poultry. A large inoculum of 1000 to 10 billion organisms, is required because Salmonella is killed by gastric acidity. The incubation period for gastroenteritis ranges from 6 to 72 hours but usually is less than 24 hours.

Shigella dysenteriae may cause disease by producing Shiga toxin, either alone or combined with tissue invasion. The incubation period is 1 to 7 days. Infected adults may shed organisms for 1 month. Infection is spread by person-to-person contact or by the ingestion of contaminated food with 10 to 100 organisms. The colon is selectively affected. High fever and febrile seizures may occur in addition to diarrhea.

Only certain strains of E. coli produce diarrhea. E. coli strains associated with enteritis are classified by the mechanism of diarrhea: enterotoxigenic (ETEC), enterohemorrhagic (EHEC), enteroinvasive (EIEC), enteropathogenic (EPEC), or enteroaggregative (EAEC). ETEC strains produce heat-labile (cholera-like) enterotoxin, heat-stable enterotoxin, or both. ETEC causes 40% to 60% of cases of traveler’s diarrhea. ETEC adhere to the epithelial cells in the upper small intestine and produce disease by liberating toxins that induce intestinal secretion and limit absorption. EHEC, especially the E. coli O157:H7 strain, produce a Shiga-like toxin that is responsible for a hemorrhagic colitis and most cases of diarrhea associated with hemolytic uremic syndrome (HUS), which is a syndrome of microangiopathic hemolytic anemia, thrombocytopenia, and renal failure (see Chapter 164). EHEC is associated with contaminated food, including unpasteurized fruit juices and, especially, undercooked beef. EHEC is associated with a self-limited form of gastroenteritis, usually with bloody diarrhea, but production of this toxin blocks host cell protein synthesis and affects vascular endothelial cells and glomeruli, resulting in the clinical manifestations of HUS. EIEC invades the colonic mucosa, producing widespread mucosal damage with acute inflammation, similar to Shigella. EPEC is responsible for many of the epidemics of diarrhea in newborn nurseries and in day care centers.

Campylobacter jejuni is spread by person-to-person contact and by contaminated water and food, especially poultry, raw milk, and cheese. The organism invades the mucosa of the jejunum, ileum, and colon. Yersinia enterocolitica is transmitted by pets and contaminated food, especially chitterlings. Infants and young children characteristically have a diarreal disease, whereas older children usually have acute lesions of the terminal ileum or acute mesenteric lymphadenitis mimicking appendicitis or Crohn’s disease. Postinfectious arthritis, rash, and spondylarthropathy may develop.

Clostridium difficile causes C. difficile-associated diarrhea or antibiotic-associated diarrhea, secondary to its toxin. The organism produces spores that spread from person to person. C. difficile-associated diarrhea may follow exposure to any antibiotic.

Important enteric parasites found in North America include Entamoeba histolytica (amebiasis), Giardia lamblia, and Cryptosporidium parvum. Amebiasis occurs in warmer climates, whereas giardiasis is endemic throughout the United States and is common among infants in day care centers. E. histolytica infects the colon; amebae may pass through the bowel wall and invade the liver, lung, and brain. Diarrhea is of acute onset, is bloody, and contains leukocytes. G. lamblia is transmitted through ingestion of cysts, either from contact with an infected individual or from food or freshwater or well water contaminated with infected feces. The organism adheres to the microvilli of the duodenal and jejunal epithelium. Insidious onset of progressive anorexia, nausea, gaseousness, abdominal distension, watery diarrhea, secondary lactose intolerance, and weight loss is characteristic of giardiasis. Cryptosporidium causes mild, watery diarrhea in immunocompetent persons that resolves without treatment. It produces severe, prolonged diarrhea in persons with acquired immunodeficiency syndrome (AIDS) (see Chapter 125).
Typhoid fever is characterized by bacteremia and fever that usually precede the final enteric phase. Fever, headache, and abdominal pain worsen over 48 to 72 hours with nausea, decreased appetite, and constipation over the first week. If untreated, the disease persists for 2 to 3 weeks marked by significant weight loss and, occasionally, hematochezia or melena. Bowel perforation is a common complication in adults but is rare in children. Infected persons without symptoms, or chronic carriers, serve as reservoirs and sources of continuous spread.

Dysentery is enteritis involving the colon and rectum, with blood and mucus, possibly foul smelling stools, and fever. Shigella is the prototype cause of dysentery, which must be differentiated from infection with EIEC, EHEC, E. histolytica (amebic dysentery), C. jejuni, Y. enterocolitica, and nontyphoidal Salmonella. Gastrointestinal bleeding and blood loss may be significant.

Enterotoxigenic disease is caused by agents that produce enterotoxins, such as V. cholerae and ETEC. Fever is absent or low grade. Diarrhea usually involves the ileum with watery stools without blood or mucus and usually lasts 3 to 4 days with four to five loose stools per day.

A chief consideration in management of a child with diarrhea is to assess the degree of dehydration as evident from clinical signs and symptoms, ongoing losses, and daily requirements (see Chapter 33). The degree of dehydration dictates the urgency of the situation and the volume of fluid needed for rehydration. Mild to moderate dehydration usually can be treated with oral rehydration; severe dehydration usually requires intravenous (IV) rehydration and may require ICU admission.

**LABORATORY AND IMAGING STUDIES**

Initial laboratory evaluation of moderate to severe diarrhea includes electrolytes, blood urea nitrogen, creatinine, and urinalysis for specific gravity as an indicator of hydration. Stool specimens should be examined for mucus, blood, and leukocytes, which indicate colitis in response to bacteria that diffusely invade the colonic mucosa, such as Shigella, Salmonella, C. jejuni, and invasive E. coli. Patients infected with Shiga toxin-producing E. coli and E. histolytica generally have minimal fecal leukocytes.

A rapid diagnostic test for rotavirus in stool should be performed, especially during the winter. Bacterial stool cultures are recommended for patients with fever, profuse diarrhea, and dehydration or if HUS or pseudomembranous colitis is suspected. If the stool test result is negative for blood and leukocytes, and there is no history to suggest contaminated food ingestion, a viral etiology is most likely. Stool evaluation for parasitic agents should be considered for acute dysenteric illness, especially in returning travelers, and in protracted cases of diarrhea in which there is no history to suggest contaminated food ingestion, and stool cultures become positive only after the secondary bacteremia.

**DIFFERENTIAL DIAGNOSIS**

Diarrhea can be caused by infection, toxins, gastrointestinal allergy (including allergy to milk or soy proteins), malabsorption defects, inflammatory bowel disease, celiac disease, or any injury to enterocytes. Specific infections are differentiated from each other by the use of stool cultures and enzyme-linked immunosorbent assay or polymerase chain reaction tests, when necessary. Acute enteritis may mimic other acute diseases, such as intussusception and acute appendicitis, which are best identified by diagnostic imaging. Many noninfectious causes of diarrhea produce chronic diarrhea, with persistence for more than 14 days. Persistent or chronic diarrhea may require tests for malabsorption or invasive studies, including endoscopy and small bowel biopsy (see Chapter 129).

**Common-source diarrhea** usually is associated with ingestion of contaminated food. In the United States, the most common bacterial food-borne causes (in order of frequency) are nontyphoidal Salmonella, Campylobacter, Shigella, E. coli O157:H7, Yersinia, Listeria monocytogenes, and V. cholerae. The most common parasitic food-borne causes are Cryptosporidium parvum and Cyclospora cayetanensis.

Common-source diarrhea also includes ingestion of preformed enterotoxins produced by bacteria, such as S. aureus and Bacillus cereus, which multiply in contaminated foods, and nonbacterial toxins such as from fish, shellfish, and mushrooms. After a short incubation period, vomiting and cramps are prominent symptoms, and diarrhea may or may not be present. Heavy metals that leach into canned food or drinks causing gastric irritation and emetic syndromes may mimic symptoms of acute infectious enteritis.

**TREATMENT**

Most infectious causes of diarrhea in children are self-limited. Management of viral and most bacterial causes of diarrhea is primarily supportive and consists of correcting dehydration and ongoing fluid and electrolyte deficits and managing secondary complications resulting from mucosal injury.

Hyponatremia is common; hypernatremia is less common. Metabolic acidosis results from losses of bicarbonate in stool, lactic acidosis results from shock, and phosphate retention results from transient prerenal-renal insufficiency. Traditionally therapy for 24 hours with oral rehydration solutions alone is effective for viral diarrhea. Therapy for severe fluid and electrolyte losses involves IV hydration. Less severe degrees of dehydration (<10%) in the absence of excessive vomiting or shock may be managed with oral rehydration solutions containing glucose and electrolytes. Ondansetron may be administered to reduce emesis when persistent.
Antibiotic therapy is necessary only for patients with *S. typhi* (typhoid fever) and sepsis or bacteremia with signs of systemic toxicity, those with metastatic foci, or infants younger than 3 months with nontyphoidal salmonella. Antibiotic treatment of *Shigella* produces a bacteriologic cure in 80% of patients after 48 hours, reducing the spread of the disease. Many *Shigella sonnei* isolates, the predominant strain affecting children, are resistant to amoxicillin and trimethoprim–sulfamethoxazole. Recommended treatment for children is an oral third-generation cephalosporin or a fluoroquinolone for patients 18 years and older.

Treatment of *C. difficile* (pseudomembranous colitis) includes discontinuation of the antibiotic and, if diarrhea is severe, oral metronidazole or vancomycin. *E. histolytica* dysentery is treated with metronidazole followed by a luminal agent, such as iodoquinol. The treatment of *G. lamblia* is with albendazole, metronidazole, furazolidone, or quinacrine. Nitazoxanide can be used in children younger than 12 months of age for the treatment of *Cryptosporidium*.

**COMPLICATIONS AND PROGNOSIS**

The major complication of gastroenteritis is dehydration and hypovolemic shock. Seizures may occur with high fever, especially with *Shigella*. Intestinal abscesses can form with *Shigella* and *Salmonella* infections, especially typhoid fever, leading to intestinal perforation, a life-threatening complication. Severe vomiting associated with gastroenteritis can cause esophageal tears or aspiration pneumonia.

Deaths resulting from diarrhea reflect the principal problem of disruption of fluid and electrolyte homeostasis, which leads to dehydration, electrolyte imbalance, vascular instability, and shock. In the United States, approximately 75 to 150 deaths occur annually from diarrheal disease, primarily in children under 1 year of age. These deaths occur in a seasonal pattern between October and February, concurrent with the rotavirus season.

At least 10% of patients who have typhoid fever shed *S. typhi* for about 3 months, and 4% become chronic carriers. The risk of becoming a chronic carrier is low in children. Ciprofloxacin is recommended for adult carriers with persistent *Salmonella* excretion.

**PREVENTION**

The most important means of preventing childhood diarrhea is the provision of clean, uncontaminated water and proper hygiene in growing, collecting, and preparing foods. Good hygienic measures, especially good hand washing with soap and water, are the best means of controlling person-to-person spread of most organisms causing gastroenteritis. Similarly, poultry products should be considered potentially contaminated with *Salmonella* and should be handled and cooked appropriately.

Immunization against rotavirus infection is recommended for all children beginning at 6 weeks of age, with the first dose by 14 weeks 6 days and the last dose by 8 months (see Chapter 94). Two typhoid vaccines are licensed in the United States: an oral live attenuated vaccine (Ty21a) for children 6 years and older, and a capsular polysaccharide vaccine (ViCPS) for intramuscular administration for persons 2 years and older. These are recommended for travelers to endemic areas of developing countries or for household contacts of *S. typhi* chronic carriers.

Families should be aware of the risk of acquiring salmonellosis from household reptile pets. Transmission of *Salmonella* from reptiles can be prevented by thorough hand washing with soap and water after handling reptiles or reptile cages. Children under 5 years of age and immunocompromised persons should avoid contact with reptiles.

The risk for traveler’s diarrhea, caused primarily by *ETEC*, may be minimized by avoiding uncooked food and untreated drinking water. Prophylaxis with bismuth subsalicylate (Pepto-Bismol) for adults (2 oz or two tablets orally four times a day) may be effective for prevention but is not recommended for children. Symptomatic self-treatment for mild diarrhea with loperamide (Imodium) and WHO oral rehydration solution is recommended for children for at least 6 years of age and adults. Self-treatment of moderate diarrhea and fever with a fluoroquinolone is recommended in adults of at least 18 years old. Prompt medical evaluation is indicated for disease persisting more than 3 days, bloody stools, fever above 102°F (38.9°C) or chills, persistent vomiting, or moderate to severe dehydration, especially in children.

*Lactobacillus acidophilus* is a probiotic and reduces the incidence of community-acquired and antibiotic-associated diarrhea in children treated with oral antibiotics for other infectious diseases.

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*Lactobacillus acidophilus* is a probiotic and reduces the incidence of community-acquired and antibiotic-associated diarrhea in children treated with oral antibiotics for other infectious diseases.

**VIRAL HEPATITIS**

**ETIOLOGY**

There are six primary hepatotropic viruses:

- Hepatitis A virus (HAV)
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- Hepatitis D virus (HDV)
- Hepatitis E virus (HEV)
- Hepatitis G virus (HGV)

They differ in their virologic characteristics, transmission, severity, likelihood of persistence, and subsequent risk of hepatocellular carcinoma (Table 113-1). HDV, also known as the delta agent, is a defective virus that requires HBV for spread and causes either coinfection with HBV or superinfection in chronic HBsAg (hepatitis B surface antigen) carriers. HBV, HCV, and HDV infections can result in chronic hepatitis, or a chronic carrier state, which facilitates spread. The cause of 10% to 15% of cases of acute hepatitis is unknown.

**EPIDEMIOLOGY**

HAV causes approximately half of all cases of viral hepatitis in the United States. Among U.S. children, approximately 70% to 80% of all new cases of viral hepatitis are caused by HAV, 5% to 30% by HBV, and 5% to 15% by HCV. The major risk factors for HBV and HCV are injectable drug use, frequent exposure
Infectious Diseases

to blood products, and prenatal transmission from maternal infection. HEV occurs following travel to endemic areas outside of the United States. HGV is prevalent in HIV-infected persons. HBV and HCV cause chronic infection, which may lead to cirrhosis and is a significant risk factor for hepatocellular carcinoma and represents a persistent risk of transmission.

**Table 113-1** Characteristics of Agents Causing Acute Viral Hepatitis

<table>
<thead>
<tr>
<th>HEPATITIS VIRUSES</th>
<th>FEATURE</th>
<th>HAV*</th>
<th>HBV</th>
<th>HCV†</th>
<th>HDV</th>
<th>HEV‡</th>
<th>HGV</th>
<th>TTV, SEN-V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral structure</td>
<td>27-nm ssRNA virus</td>
<td>42-nm dsDNA virus</td>
<td>30- to 60-nm ssRNA virus</td>
<td>36-nm circular ssRNA virus hybrid particle with HBsAg coat</td>
<td>27–34 nm ssRNA virus</td>
<td>50- to 100-nm ssRNA virus</td>
<td>30- to 50-nm ssDNA virus</td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td>Picornavirus</td>
<td>Hepadnavirus</td>
<td>Flavivirus</td>
<td>Satellite</td>
<td>Flavivirus</td>
<td>Flavivirus</td>
<td>Circovirus</td>
<td></td>
</tr>
<tr>
<td>Transmission</td>
<td>Fecal-oral, rarely parenteral</td>
<td>Transfusion, sexual, inoculation, perinatal</td>
<td>Parenteral, transfusion, perinatal</td>
<td>Similar to HBV</td>
<td>Fecal-oral (endemic and epidemic)</td>
<td>Parenteral, transfusion</td>
<td>Parenteral, perinatal</td>
<td></td>
</tr>
<tr>
<td>Incubation period</td>
<td>15–30 days</td>
<td>60–180 days</td>
<td>30–60 days</td>
<td>Coinfection with HBV</td>
<td>35–60 days</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Serum markers</td>
<td>Anti-HAV</td>
<td>HBsAg, HBeAg, anti-HBc, anti-Hbc</td>
<td>Anti-HCV (IgG, IgM), RIBA, PCR assay for HCV RNA</td>
<td>Anti-HDV, RNA</td>
<td>Anti-HEV</td>
<td>RNA by RT-PCR assay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulminant liver failure</td>
<td>Rare</td>
<td>&lt;1% unless coinfection with HDV</td>
<td>Uncommon</td>
<td>2%–20%</td>
<td>20%</td>
<td>Probably no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent infection</td>
<td>No</td>
<td>5%–10% (90% with perinatal infection)</td>
<td>85%</td>
<td>2%–70%</td>
<td>No</td>
<td>Persistent infection common; chronic disease rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased risk of hepatocellular carcinoma</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Vaccine: immune serum globulin</td>
<td>Vaccine: hepatitis B immunoglobulin (HBIG)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

dsDNA, Double-stranded DNA; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HGV, hepatitis G virus; PCR, polymerase chain reaction; RIBA, recombinant immunoblot assay; RT-PCR, reverse transcriptase-polymerase chain reaction; ssDNA/ssRNA, single-stranded DNA/RNA; TTV, transfusion-transmitted virus.

*Formerly posttransfusion non-A, non-B virus.
†Formerly enteral non-A, non-B virus.
‡Formerly enteral non-A, non-B virus.

**CLINICAL MANIFESTATIONS**

- Jaundice
- Hepatomegaly
- Fever without a Source

There is considerable overlap in the characteristic clinical courses of HAV, HBV, and HCV (Fig. 113-1). The *preicteric phase*, which lasts approximately 1 week, is characterized by headache, anorexia, malaise, abdominal discomfort, nausea, and vomiting and usually precedes the onset of clinically detectable disease. Infants with perinatal acquired HBV may have immune complexes accompanied by urticaria and arthritis before the onset of icterus. Jaundice and tender hepatomegaly are the most common physical findings and are characteristic of the *icteric phase*. Prodromal symptoms, particularly in children, may abate during the icteric phase. Asymptomatic or mild, nonspecific illness without icterus is common with HAV, HBV, and HCV, especially in young children. Hepatic enzymes may increase 15- to 20-fold. Resolution of the hyperbilirubinemia and normalization of the transaminases may take 6 to 8 weeks.

**LABORATORY AND IMAGING STUDIES**

Alanine aminotransferase and aspartate aminotransferase levels are elevated and generally reflect the degree of parenchymal inflammation. Alkaline phosphatase, 5α-nucleotidase, and total and direct (conjugated) bilirubin levels indicate the degree of cholestasis, which results from hepatocellular and bile duct damage. The *prothrombin time* is a good predictor...
of severe hepatocellular injury and progression to fulminant hepatic failure (see Chapter 130).

The diagnosis of viral hepatitis is confirmed by serologic testing (see Table 113-1 and Fig. 113-1). The presence of IgM-specific antibody to HAV with low or absent IgG antibody to HAV is presumptive evidence of HAV. There is no chronic carrier state of HAV. The presence of HBsAg signifies acute or chronic infection with HBV. Antigenemia appears early in the illness and is usually transient but is characteristic of chronic infection. Maternal HBsAg status should always be determined when HBV infection is diagnosed in children younger than 1 year of age because of the likelihood of vertical transmission. Hepatitis B early antigen (HBeAg) appears in the serum with acute HBV. The continued presence of HBsAg and HBeAg in the absence of antibody to e antigen (anti-HBe) indicates high risk of transmissibility that is associated with ongoing viral replication. Clearance of HBsAg from the serum precedes a variable window period followed by the emergence of the antibody to surface antigen (anti-HBs), which indicates development of lifelong immunity and is also a marker of immunization. Antibody to core antigen (anti-HBc) is a useful marker for recognizing HBV infection during the window phase (when HBsAg has disappeared but before the appearance of anti-HBs). Anti-HBe is useful in predicting a low degree of infectivity during the carrier state. Seroconversion after HCV infection may occur 6 months after infection. A positive result of HCV enzyme-linked immunosorbent assay should be confirmed with the more specific recombinant immunoblot assay, which detects antibodies to multiple HCV antigens. Detection of HCV RNA by polymerase chain reaction (PCR) is a sensitive marker for active infection, and results of this test may be positive 3 days after inoculation.

DIFFERENTIAL DIAGNOSIS

Many other viruses may cause hepatitis as part of systemic infection, including Epstein-Barr virus, cytomegalovirus, varicella zoster virus (chickenpox), herpes simplex virus, and adenoviruses. Bacterial infections that may cause hepatitis include Escherichia coli sepsis and leptospirosis. Patients with cholecystitis, cholangitis, and choledocholithiasis may present with acute symptoms and jaundice. Other causes of acute liver disease in childhood include drugs (isoniazid, phenytoin, valproic acid, carbamazepine, oral contraceptives, acetaminophen), toxins (ethanol, poisonous mushroom), Wilson disease, metabolic disease (galactosemia, tyrosinemia), α1-antitrypsin deficiency, tumor, shock, anoxia, and graft-versus-host disease (see Chapter 130).

TREATMENT

The treatment of acute hepatitis is largely supportive and involves rest, hydration, and adequate nutrition. Hospitalization is indicated for persons with severe vomiting and dehydration, a prolonged prothrombin time, or signs of hepatic encephalopathy. When the diagnosis of viral hepatitis is established, attention should be directed toward preventing its spread to close contacts. For HAV, hygienic measures include hand washing and careful disposal of excreta, contaminated diapers or clothing, needles, and other blood-contaminated items.

Chronic HBV infection may be treated with interferon alfa-2b or lamivudine, and HCV may be treated with
interferon alfa alone or usually in combination with ribavirin. Mostly adults experience these treatment regimens. The decision to treat is based on the patient’s current age, age at HBV acquisition, development of viral mutations during therapy, and stage of viral infection. Transmission of HBV by vertical transmission or infection early in life often results in chronic HBV infection in an immune tolerant phase, in which interferon usually is not effective.

**COMPLICATIONS AND PROGNOSIS**

A protracted or relapsing course may develop in 10% to 15% of cases of HAV in adults, lasting up to 6 months with an undulating course before eventual clinical resolution. Fulminant hepatitis with encephalopathy, gastrointestinal bleeding from esophageal varices or coagulopathy, and profound jaundice is uncommon but is associated with a high mortality rate.

Most cases of acute viral hepatitis resolve without specific therapy, with less than 0.1% of cases progressing to fulminant hepatic necrosis. HAV and HEV cause acute infection only. HBV, HCV, and HDV may persist as chronic infection with chronic inflammation, fibrosis, and cirrhosis and the associated risk of hepatocellular carcinoma.

From 5% to 10% of adults with HBV develop persistent infection, defined by persistence of HBsAg in the blood for more than 6 months, compared with 90% of children who acquire HBV by perinatal transmission. Chronic HBsAg carriers are usually HBeAg-negative and have no clinical, biochemical, or serologic evidence of active hepatitis, unless there is superinfection with HDV. Approximately 10% to 15% of HBsAg carriers eventually clear HBsAg.

Approximately 85% of persons infected with HCV remain chronically infected, which is characterized by fluctuating transaminase levels (see Fig. 113-1). There is poor correlation of symptoms with ongoing liver damage. Approximately 20% of persons with chronic infection develop cirrhosis, and approximately 25% of those develop hepatocellular carcinoma. HIV infection and ethanol use increase the risk of HCV progression.

**PREVENTION**

Good hygienic practices significantly reduce the risk of fecal-oral transmission of HAV. Screening blood donors for evidence of hepatitis significantly reduces the risk of blood-borne transmission. Specific postexposure measures are recommended to prevent secondary cases in susceptible persons.

HAV vaccine is recommended for routine immunization of all children beginning at 12 months and for unvaccinated older children in areas with targeted vaccination programs. Unvaccinated household and sexual contacts of persons with HAV should receive postexposure prophylaxis as soon as possible and within 2 weeks of the last exposure. A single dose of HAV vaccine at the age-appropriate dose is preferred for persons 12 months to 40 years of age. Immunoglobulin (0.02 mL/kg) given intramuscularly is preferred for children under 12 months of age, persons over 40 years of age, and immunocompromised persons. Unvaccinated travelers to endemic regions should receive a single dose of HAV vaccine administered at any time before departure.

HBV vaccine is recommended for routine immunization of all infants beginning at birth and for all children and adolescents through 18 years of age who have not been immunized previously (see Fig. 94-1). It also is recommended as a preexposure vaccination for older children and adults at increased risk of exposure to HBV, including persons undergoing hemodialysis, recipients of clotting factor concentrates, residents and staff of institutions for developmentally disabled persons, men who have sex with men, injectable drug users, inmates of juvenile detention and other correctional facilities, and health care workers. HBV vaccine already has shown effectiveness in reducing the incidence of hepatocellular carcinoma in high-risk populations. Routine prenatal screening for HBsAg is recommended for all pregnant women in the United States. Infants born to HBsAg-positive mothers should receive HBV vaccine and hepatitis B immunoglobulin (HBIG) (0.5 mL) within 12 hours of birth, with subsequent vaccine doses at 1 month and 6 months of age followed by testing for HBsAg and anti-HBs at 9 to 15 months of age. Infants born to mothers whose HBsAg status is unknown should receive vaccine within 12 hours of birth. If maternal testing is positive for HBsAg, the infant should receive HBIG as soon as possible (no later than 1 week of age). The combination of HBIG and vaccination is 99% effective in preventing vertical transmission of HBV. Vaccination alone without HBIG may prevent 75% of cases of perinatal HBV transmission and approximately 95% of cases of asymptomatic childhood HBV infection.

Postexposure prophylaxis of unvaccinated persons using HBIG and vaccine is recommended following needle stick injuries with blood from an HBsAg-positive patient and for household members with intimate contact, including sex partners.

**ETIOLOGY**

Urinary tract infections (UTIs) include cystitis (infection localized to the bladder), pyelonephritis (infection of the renal parenchyma, calyces, and renal pelvis), and renal abscess, which may be intrarenal or perinephric. The urinary tract and urine are normally sterile. *Escherichia coli*, ascending from bowel flora, accounts for 90% of first infections and 75% of recurrent infections. Over 90% of nephritogenic *E. coli* possess P fimbriae that binds to uroepithelial cells and P blood group antigens. Individuals with high-level expression of P1 blood group antigen are predisposed to pyelonephritis and bacteremia, as well as recurrent UTIs. Other bacteria commonly causing infection include *Klebsiella*, *Proteus*, *Enterococcus*, and *Pseudomonas*. *Staphylococcus saprophyticus* is associated with UTI in some children and in sexually active adolescent girls. *S. saprophyticus*, *Chlamydia trachomatis*, and *E. coli* are the chief causes of the acute urethral syndrome, or postcoital urethritis, which typically occur 12 to 72 hours after sexual intercourse.
EPIDEMIOLOGY

Approximately 8% of girls and 2% of boys have a UTI by 11 years of age. The lifetime incidence of UTI in females is about 30% compared to only 1% in males. Approximately 75% of infants younger than 3 months of age with bacteriuria are male compared with only 10% between 3 and 8 months of age. After 12 months of age, UTI in healthy children usually is seen in girls.

A short urethra predisposes girls to UTI. Uncircumcised male infants are at 5- to 12-fold increased risk for UTI compared with circumcised male infants. Obstruction to urine flow and urethral stasis is the major risk factor and may result from anatomic abnormalities, nephrolithiasis, renal tumor, indwelling urinary catheter, ureteropelvic junction obstruction, megaureter, extrinsic compression, and pregnancy. Vesicoureteral reflux, whether primary (70% of cases) or secondary to urinary tract obstruction, predisposes to chronic infection and renal scarring. Scarring also may develop in the absence of reflux.

CLINICAL MANIFESTATIONS

The symptoms and signs of UTI vary markedly with age. Few have high positive predictive values in neonates, with failure to thrive, feeding problems, and fever as the most consistent symptoms. Direct hyperbilirubinemia may develop secondary to gram-negative endotoxin. Infants 1 month to 2 years old may present with feeding problems, failure to thrive, diarrhea, vomiting, or unexplained fever. The symptoms may masquerade as gastrointestinal illness with colic, irritability, and screaming periods. At 2 years of age, children begin to show the classic signs of UTI such as urgency, dysuria, frequency, and abdominal or back pain. The presence of UTI should be suspected in all infants and young children with unexplained fever and in patients of all ages with fever and congenital anomalies of the urinary tract.

LABORATORY AND IMAGING STUDIES

The diagnosis of UTI in infants and young children requires the presence of both pyuria and at least 50,000 CFU/mL of a single pathogenic organism. For older children and adolescents, >100,000 CFU/mL indicates infection. Urine samples for urinalysis should be examined promptly (within 20 minutes) or refrigerated until cultured. Urine obtained by midstream, clean-catch technique for older children and adolescents is an appropriate collection method, whereas transurethral catheterization is the appropriate method for younger children and infants in which antibiotics are being started. Perineal bags for urine collection are prone to contamination and are not recommended for urine collection for culture. If there is uncertainty about diagnosis of UTI in a younger child or infant, urine can be collected by the most convenient method for urinalysis and if suggestive of infection, collect urine by catheterization prior to starting antibiotics.

Empirical therapy should be initiated for symptomatic children and for all children with a urine culture confirming UTI. For an older child who does not appear ill but has a positive urine culture, oral antibiotic therapy should be initiated. For an older child who does not appear ill but has a positive urine culture, oral antibiotic therapy should be initiated. For a child with suspected UTI who appears toxic, appears dehydrated, or is unable to retain oral fluids, initial antibiotic therapy should be administered parenterally, and hospitalization should be considered.

Neonates with UTI are treated for 10 to 14 days with parenteral antibiotics because of the higher rate of bacteremia. Older children with UTI are treated for 7 to 14 days. Initial treatment with parenteral antibiotics is determined by clinical
invasion. At puberty estrogen increases, and the pH of the atrophic vaginal epithelium that is susceptible to bacterial infections, although the effect is small. The impact of secondary prophylaxis may prevent more severe symptomatic recurrent infections such as chronic constipation, encopresis, and daytime and nighttime urinary incontinence. There is evidence that antibiotic prophylaxis may prevent more severe symptomatic recurrent infections, although the effect is small. The impact of secondary prophylaxis to prevent renal scarring is unknown. 

The relapse rate of UTI is approximately 25% to 40%. Most relapses occur within 2 to 3 weeks of treatment. Parents should be counseled to follow up for evaluation for subsequent fevers to evaluate for the possibility of a recurrence of UTI. If a recurrent UTI is diagnosed, further imaging studies (VCUG) are indicated to evaluate the possibility of vesicoureteral reflux (see Chapter 167).

COMPLICATIONS AND PROGNOSIS
Bacteremia occurs in 2% to 5% of episodes of pyelonephritis and is more likely in infants than in older children. Focal renal abscesses are an uncommon complication. The degree of toxicity, dehydration, and ability to retain oral intake of fluids should be assessed carefully. Restoring or maintaining adequate hydration, including correction of electrolyte abnormalities that are often associated with vomiting or poor oral intake, is important.

The primary symptoms of vulvovaginitis are vaginal discharge, erythema, and pruritus. Characteristics of specific etiologies are outlined in Table 115-1.

LABORATORY AND IMAGING STUDIES
Wet mount microscopic examination, prepared by mixing vaginal secretions with normal saline solution, and culture may be used to confirm a specific diagnosis (see Table 115-1). Clue cells are vaginal epithelial cells that are covered with G. vaginalis and have a granular appearance. Vagal cultures for G. vaginalis are not useful. Candida may be identified by saline wet mount or by culture.

DIFFERENTIAL DIAGNOSIS
Noninfectious causes of vulvovaginitis include physical agents (foreign body, sand), chemical agents (bubble bath, soap, detergent), and vulvar skin disease (atopic dermatitis, seborrhea, psoriasis). Physiologic vaginal discharge or physiologic leukorrhea of desquamated vaginal cells and mucus occurs normally in girls soon after birth, with discharge lasting for about 1 week, and appears again at 6 to 12 months before menarche. The discharge is minimal, clear, and thin without pruritus or inflammation. No treatment is necessary.

TREATMENT
The treatment of vulvovaginitis depends on the etiology (see Table 115-1). Treatment of nonspecific vaginitis focuses on improving perineal hygiene. The recommended treatment for bacterial vaginosis is oral metronidazole or clindamycin. Imidazole creams and vaginal tablets and suppositories all are effective for the treatment of acute vaginosis.
vulvovaginal candidiasis. Douching or vaginal irrigation is not beneficial and is not recommended.

**COMPLICATIONS AND PROGNOSIS**
Complications are rare. The prognosis is excellent.

**PREVENTION**
There are no recognized prophylactic measures for bacterial vaginosis or nonspecific vaginitis. Douching is not protective and reduces normal vaginal flora, which are protective against pathogenic organisms.
Adolescents have the highest rates of sexually transmitted infections (STIs). Compared with adults, sexually active adolescents are more likely to believe they will not contract an STI, more likely to come into contact with an infected sexual partner, less likely to receive health care when an STI develops, and less likely to be compliant with treatment for an STI.

Although numerous organisms cause STIs, the diseases can be grouped by the characteristic clinical presentation. **Urethritis** and **endocervicitis** (Table 116-1) are characteristic of *Neisseria gonorrhoeae* and *C. trachomatis* and are the most common STIs. Note that more than 70% of genital chlamydial infections in women are asymptomatic. **Genital ulcers** (Table 116-2) are characteristic of syphilis (*Treponema pallidum*), genital herpes simplex virus (HSV) infections, chancreoid (*Haemophilus ducreyi*), and granuloma inguinale, also known as donovanosis (*Klebsiella granulomatis*). **Vaginal discharge** (Table 116-3) is a symptom of trichomoniasis (*Trichomonas vaginalis*) and is part of the spectrum of vulvovaginitis (see Chapter 115), which is not always associated with sexual activity. Human papillomavirus (HPV) causes **condylomata acuminata**, or genital warts (Table 116-4), and is the major risk factor for cervical, vulvar, and vaginal cancers.

STIs are associated with significant physiologic and psychological morbidity. Early diagnosis and treatment are important.

### Table 116-1 Features of Sexually Transmitted Infections Caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae* *

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>C. TRACHOMATIS</th>
<th>N. GONORRHOEAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>5–12 days</td>
<td>3–14 days</td>
</tr>
<tr>
<td>Possible presentations</td>
<td>Pharyngitis, conjunctivitis (including neonatal conjunctivitis), disseminated disease (arthritis, dermatitis, endocarditis, meningitis)</td>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
<td>Asymptomatic</td>
<td>Urethritis</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Urethritis</td>
<td>Epididymo-orchitis</td>
</tr>
<tr>
<td>Urethritis</td>
<td>Cervical erythema, friability, with thick creamy discharge</td>
<td>Proctitis</td>
</tr>
<tr>
<td>Skeneitis/bartholinitis</td>
<td>Gram-negative intracellular diplococci</td>
<td></td>
</tr>
<tr>
<td>PID</td>
<td>Mucopurulent cervicitis</td>
<td></td>
</tr>
<tr>
<td>Signs/symptoms of common syndromes</td>
<td>Cervical erythema, friability, with thick creamy discharge</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Mucopurulent cervical discharge (variable)</td>
<td></td>
</tr>
<tr>
<td>Penile discharge</td>
<td>Menstrual irregularities (variable)</td>
<td></td>
</tr>
<tr>
<td>&gt;10 PMNs/hpf</td>
<td>Nausea, vomiting (variable)</td>
<td></td>
</tr>
<tr>
<td>Mucopurulent cervical discharge (variable)</td>
<td>Weakness, syncope, dizziness (variable)</td>
<td></td>
</tr>
<tr>
<td>Mild cervical tenderness</td>
<td>Perihepatitis (5%)</td>
<td></td>
</tr>
<tr>
<td>Gram-negative intracellular diplococci</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>Onset of symptoms day 3–10 of menstrual cycle</td>
<td></td>
</tr>
<tr>
<td>Lower abdominal pain (95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adnexal tenderness, mass (95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain on cervical motion (95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucopurulent cervical discharge (variable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual irregularities (variable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting (variable)</td>
<td>airy, chronic, indistinguishable from the symptoms of gonorrhea</td>
<td></td>
</tr>
<tr>
<td>Weakness, syncope, dizziness (variable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perihepatitis (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>NAAT, culture (using Thayer-Martin selective media)</td>
<td>NAAT</td>
</tr>
<tr>
<td>Treatment</td>
<td>Ceftriaxone plus doxycycline or azithromycin</td>
<td></td>
</tr>
</tbody>
</table>

*Coinfection is common, and clinical presentations have significant overlap.

hpf, High-powered field; NAAT, nucleic acid amplification test; PID, pelvic inflammatory disease; PMN, polymorphonuclear cells.
### Table 116-2  Features of Sexually Transmitted Infections Characterized by Genital Ulcers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Agent</th>
<th>Granuloma Inguinale (Donovanosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Agent</td>
<td>Agent</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>HSV-1, HSV-2</td>
<td>Haemophilus ducreyi</td>
</tr>
<tr>
<td>HSV-1, HSV-2</td>
<td>Haemophilus ducreyi</td>
<td>Klebsiella granulomatis</td>
</tr>
<tr>
<td>Incubation: 10–90 days</td>
<td>Incubation: 4–14 days</td>
<td>Incubation: 3–10 days</td>
</tr>
<tr>
<td>Systemic findings: Fever, rash, malaise, anorexia, arthralgia, lymphadenopathy</td>
<td>Systemic findings: Headache, fever, malaise, myalgia in one third of cases</td>
<td>Systemic findings: None</td>
</tr>
<tr>
<td>Inguinal lymphadenopathy: Late, bilateral, nontender, no suppuration</td>
<td>Inguinal lymphadenopathy: Early, bilateral, tender, no suppuration</td>
<td>Inguinal lymphadenopathy: Early, rapid, tender, and unilateral; suppuration likely</td>
</tr>
<tr>
<td>Primary lesion: Papule</td>
<td>Primary lesion: Vesicle</td>
<td>Primary lesion: Papule to pustule</td>
</tr>
</tbody>
</table>

#### Ulcer characteristics

<table>
<thead>
<tr>
<th>Number</th>
<th>Edges</th>
<th>Depth</th>
<th>Base</th>
<th>Secretion</th>
<th>Induration</th>
<th>Pain</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1</td>
<td>Distinct</td>
<td>Shallow</td>
<td>Red, smooth</td>
<td>Serous</td>
<td>Firm</td>
<td>None</td>
<td>Serology: VDRL or RPR</td>
</tr>
<tr>
<td>Multiple</td>
<td>Reddened, ragged</td>
<td>Shallow</td>
<td>Red, smooth</td>
<td>Serous</td>
<td>None</td>
<td>Usual</td>
<td>MHA-TP or FTA-ABS</td>
</tr>
<tr>
<td>&lt;3</td>
<td>Ragged, undermined</td>
<td>Deep</td>
<td>Necrotic</td>
<td>Pus, blood</td>
<td>None to mild</td>
<td>Often</td>
<td>None</td>
</tr>
<tr>
<td>&gt;1, may coalesce</td>
<td>Rolled, distinct</td>
<td>Raised</td>
<td>Beefy red, clean</td>
<td>None</td>
<td>Firm</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

#### Treatment

- Early: Benzathine penicillin G (2.4 million U IM) once
- Acyclovir or famciclovir or valacyclovir
- Aspirate fluctuant nodes
- Incision and drainage of buboes >5 cm
- Azithromycin or ceftriaxone or ciprofloxacin or erythromycin

**FTA-ABS, Fluorescent treponemal antibody-absorption; HSV, herpes simplex virus; MHA-TP, microhemagglutination assay-Treponema pallidum; PCR, polymerase chain reaction; RPR, rapid plasma reagin; TMP-SMX, trimethoprim-sulfamethoxazole; VDRL, Venereal Disease Research Laboratory.**

### Table 116-3  Features of Sexually Transmitted Infections Characterized by Vaginal Discharge

<table>
<thead>
<tr>
<th>Feature</th>
<th>Physiologic Leukorrhea (Normal)</th>
<th>Trichomoniasis</th>
<th>Bacterial Vaginosis (Gardnerella vaginalis-Associated Vaginitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Normal flora</td>
<td>Trichomonas vaginalis</td>
<td>G. vaginalis and anaerobes</td>
</tr>
<tr>
<td>Incubation</td>
<td>---</td>
<td>5–28 days</td>
<td>Not necessarily sexually transmitted</td>
</tr>
<tr>
<td>Predominant symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>None</td>
<td>Mild to moderate</td>
<td>None to mild</td>
</tr>
<tr>
<td>Discharge</td>
<td>Minimal</td>
<td>Moderate to severe</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Pain</td>
<td>None</td>
<td>Mild</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
### Table 116-3 | Features of Sexually Transmitted Infections Characterized by Vaginal Discharge—cont’d

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>PHYSIOLOGIC LEUKORRHEA (NORMAL)</th>
<th>TRICHOMEONIASIS</th>
<th>BACTERIAL VAGINOSIS (GARDNERELLA VAGINALIS-ASSOCIATED VAGINITIS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvar inflammation</td>
<td>None</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Characteristics of discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount</td>
<td>Small</td>
<td>Profuse</td>
<td>Moderate</td>
</tr>
<tr>
<td>Color</td>
<td>Clear, milky</td>
<td>Yellow-green or grey</td>
<td>Grey</td>
</tr>
<tr>
<td>Consistency</td>
<td>Flocculent</td>
<td>Frothy</td>
<td>Homogeneous</td>
</tr>
<tr>
<td>Viscosity</td>
<td>Thin</td>
<td>Thin</td>
<td>Thin</td>
</tr>
<tr>
<td>Foul odor</td>
<td>None</td>
<td>Possible</td>
<td>Yes</td>
</tr>
<tr>
<td>Odor with</td>
<td>None</td>
<td>Possible</td>
<td>Characteristic fishy odor</td>
</tr>
<tr>
<td>KOH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>$&lt;4.5$</td>
<td>$&gt;5.0$</td>
<td>$&gt;4.5$</td>
</tr>
</tbody>
</table>

#### Diagnosis

**Saline drop**
- Squamous and few WBCs
- WBC; Motile flagellates, slightly larger than WBCs
- Squamous cells studded with bacteria (“clue cells”) and WBCs

**Gram stain**
- Gram-positive and gram-negative rods and cocci
- Trichomonas
- Predominance of gram-negative rods and cocci with paucity of gram-positive rods

**Culture**
- Mixed flora with Lactobacillus predominant
- Culture generally not indicated; antibody and nucleic acid tests available
- Culture not useful

**Treatment**
- Reassurance
- Metronidazole or tinidazole
- Metronidazole, tinidazole, or clindamycin

**KOH**, Potassium hydroxide; **WBCs**, white blood cells.

### Table 116-4 | Features of Sexually Transmitted Infections Characterized by Nonulcerative External Genital Symptoms

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>GENITAL WARTS</th>
<th>VULVOVAGINAL CANDIDIASIS</th>
<th>PEDICULOSIS PUBIS (CRABS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Human papillomavirus</td>
<td>Candida albicans</td>
<td>Phthirus pubis</td>
</tr>
<tr>
<td>Incubation/transmission</td>
<td>30–90 days</td>
<td>Uncommon sexual transmission</td>
<td>5–10 days</td>
</tr>
<tr>
<td>Presenting complaints</td>
<td>Genital warts are seen or felt</td>
<td>Vulvar itching or discharge</td>
<td>Pubic itching; live organisms may be seen; sexual partner has “crabs”</td>
</tr>
<tr>
<td>Signs</td>
<td>Firm, gray-to-pink, single or multiple, fimbriated, painless excrescences on vulva, introitus, vagina cervix, penis, perineum, anus</td>
<td>Inflammation of vulva, with thick, white, “cottage cheese” discharge, pH $&lt;5$; friable mucosa that easily bleeds</td>
<td>Eggs (nits) at base of pubic hairs, lice may be visible; excoriated, red skin secondary to infestation</td>
</tr>
<tr>
<td>Clinical associations</td>
<td>Cervical neoplasia, dysplasia</td>
<td>Oral contraceptives, diabetes, antibiotics</td>
<td>—</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Clinical appearance; most infections asymptomatic; acetowhite changes on colposcopy; enlarged cells with perinuclear halo and hyperchromatic nuclei</td>
<td>KOH (10%): pseudohyphae; Gram stain: gram-positive pseudohyphae; Nickerson or Sabouraud medium for culture</td>
<td>History and clinical appearance</td>
</tr>
<tr>
<td>Treatment</td>
<td>Patient-applied therapies: Podofilox solution or gel or Imiquimod cream</td>
<td>Intravaginal agents: butoconazole or clotrimazole or miconazole</td>
<td>Permethrin 1% cream</td>
</tr>
<tr>
<td></td>
<td>Provider-applied therapies: cryotherapy with liquid nitrogen or cryoprobe or topical podophyllin resin or trichloroacetic acid or dichloroacetic acid or surgical removal</td>
<td>or nystatin or toconazole or terconazole Oral agent: fluconazole</td>
<td>or pyrethrin with piperonyl butoxide</td>
</tr>
</tbody>
</table>

**KOH**, Potassium hydroxide.
PELVIC INFLAMMATORY DISEASE

Direct extension of *N. gonorrhoeae*, often in combination with *C. trachomatis*, to the endometrium, fallopian tubes, and peritoneum causes pelvic inflammatory disease (PID). PID complications include tubo-ovarian abscess, perihepatitis (*Fitz-Hugh-Curtis syndrome*), an inflammation of the liver capsule), and infertility. The differential diagnosis of PID includes ectopic pregnancy, septic abortion, ovarian cyst torsion or rupture, urinary tract infection, appendicitis, mesenteric lymphadenitis, and inflammatory bowel disease. Pelvic ultrasound may detect thickened adnexal structures and is the imaging study of choice to exclude other possible diagnoses. Minimum clinical criteria for diagnosis of PID are lower abdominal tenderness with uterine, adnexal, or cervical motion tenderness. Additional criteria that support the diagnosis are fever, mucopurulent cervix discharge, elevated white blood cell (WBC) count, elevated inflammatory markers, and documented infection with *N. gonorrhoeae* or *C. trachomatis*. Adolescents should be hospitalized for treatment if there is uncertainty about the diagnosis; pregnancy; no clinical response to oral therapy within 72 hours; inability to adhere to or tolerate oral therapy; a tubo-ovarian abscess; or severe illness with high fever, nausea, and vomiting. The recommended parenteral treatment for hospitalized patients is cefotetan or cefoxitin, plus doxycycline orally. The recommended ambulatory treatment of PID for younger persons is ceftriaxone (250 mg) in a single intramuscular (IM) dose, plus doxycycline orally for 14 days, with or without metronidazole for 14 days. Follow-up examination should be performed within 72 hours.

GONORRHEA (NEISSERIA GONORROHOEAE)

*N. gonorrhoeae*, a gram-negative coccus, is often seen microscopically as diplococci. Gonorrhea is a common STI among adolescents. The highest incidence in the United States is in 15- to 24-year-old females and 20- to 24-year-old males, and incidence rates differ by race. The organism causes infection at the site of acquisition, which commonly results in mucopurulent cervicitis and urethritis (see Table 116-1), but infection of the rectum and pharynx can also occur. Disseminated gonococcal infections can occur with hematogenous spread and results in petechial or purpuric acral skin lesions, asymmetric arthralgia, tenosynovitis or septic arthritis, and, occasionally, endocarditis or meningitis. Perinatal transmission of maternal infection can lead to neonatal sepsis and meningitis (see Chapter 65) and ophthalmia neonatorum (see Chapter 119).

Treatment regimens should be effective against *N. gonorrhoeae* and *C. trachomatis* because of the high frequency of coinfection. Increasing rates of resistance to fluoroquinolones limit treatment options. A single IM dose of ceftriaxone (250 mg) is recommended for uncomplicated gonococcal infections of the cervix, urethra, and rectum. Hospitalization and treatment with ceftriaxone are recommended for disseminated gonococcal infections. For all gonococcal infections, azithromycin or doxycycline also should be administered unless chlamydial infection is excluded.

CHLAMYDIA (CHLAMYDIA TRACHOMATIS)

Chlamydiae are obligate intracellular bacteria with a biphasic life cycle, existing as relatively inert elementary bodies in their extracellular form and as reticulate bodies when phagocytosed and replicating within a phagosome. Reticulate bodies divide by binary fission and, after 48 to 72 hours, reorganize into elementary bodies that are released from the cell. *Chlamydia* infects nonciliated squamous columnar cells and the transitional epithelial cells that line the mucosa of the urethra, cervix, rectum, and conjunctiva.

*C. trachomatis* serovars D through K cause urethritis, cervicitis, PID, inclusion conjunctivitis in newborns, and infant pneumonia. *C. trachomatis* serovars L1–3 cause lymphogranuloma venereum, an infrequent STI characterized by unilateral, painful inguinal lymphadenitis. *C. trachomatis* serovars A, B, Ba, and C produce trachoma (hyperendemic blinding), which eventually leads to blindness from extensive local scarring.

*Chlamydia* is the most frequently diagnosed bacterial STI in adolescents and accounts for most cases of nongonococcal urethritis and cervicitis (see Table 116-1). There is a 5:1 female-to-male ratio. Males often have dysuria and a mucopurulent discharge, although approximately 25% may be asymptomatic. Women are more often asymptomatic (approximately 70%) or may have minimal symptoms including dysuria, mild abdominal pain, or vaginal discharge. Prepubertal girls may have vaginitis. At least 30% of persons with gonococcal cervicitis, urethritis, proctitis, or epididymitis have coinfection. Increasing rates of resistance to fluoroquinolones limit treatment options. A single IM dose of ceftriaxone (250 mg) is recommended for uncomplicated gonococcal infections of the cervix, urethra, and rectum. Hospitalization and treatment with ceftriaxone are recommended for disseminated gonococcal infections. For all gonococcal infections, azithromycin or doxycycline also should be administered unless chlamydial infection is excluded.

**Chapter 116 ♦ Sexually Transmitted Infections**
These tests usually remain positive lifelong even if the infection is not treated. Only culture should be used for medicolegal purposes to confirm infection. A single oral dose of azithromycin (1 g) or doxycycline for 7 days is recommended, which can be combined with a single dose of ceftriaxone (250 mg) to treat concomitant gonorrhea infection.

**SYPHILIS (TREPONEMA PALLIDUM)**

Syphilis is caused by *T. pallidum*, a long, slender, coiled spirochete. It cannot be cultivated routinely in vitro but can be observed by dark-field microscopy. Untreated infection progresses through several clinical stages (see Table 116-2). **Primary syphilis** is manifested as a single, painless genital ulcer, or chancre, usually on the genitalia, that appears 3 to 6 weeks after inoculation. **Secondary syphilis** follows 6 to 8 weeks later and is manifested as fever, generalized lymphadenopathy, and a disseminated maculopapular rash that also is present on the palms and soles. Plaquelike skin lesions, condylomata lata, and mucous membrane lesions occur and are infectious. **Tertiary syphilis** is a slowly progressive disease that involves the cardiovascular, neurologic, and musculoskeletal systems and is not seen in children. **Latent syphilis** is an asymptomatic infection detected by serologic testing. Early latent syphilis indicates acquisition within the preceding year; all other cases of latent syphilis are designated either late latent syphilis or latent syphilis of unknown duration. Infection can be passed from pregnant women and infect their infants resulting in congenital syphilis (see Chapter 66).

The diagnosis of syphilis is based on serologic testing. **Non-treponemal antibody tests**, the Venereal Disease Research Laboratory (VDRL) test, and the rapid plasma reagin (RPR) test are screening tests and can be quantified as titers that increase with increasing duration of infection and decrease in response to therapy. A nonquantitative VDRL test can be performed on cerebrospinal fluid but is insensitive. Rheumatic disease and other infectious diseases may cause false positive results. Confirmatory, specific **treponemal antibody tests**, the microhemagglutination assay—*T. pallidum* (MHA-TP) and fluorescent treponemal antibody-absorption (FTA-ABS) are more specific and are used to confirm the diagnosis of syphilis. These tests usually remain positive lifelong even if the infection is treated and cured. Dark-field examination of chancres, mucous membranes, or cutaneous lesions may reveal motile organisms.

The treatment of choice for all stages of syphilis is parenteral penicillin G. Primary syphilis, secondary syphilis, and early latent syphilis are treated with a single IM dose of benzathine penicillin G. Tertiary, late latent, and latent syphilis of unknown duration are treated with three doses at 1-week intervals. Neurosyphilis is treated with intravenous aqueous crystalline penicillin G for 10 to 14 days. A systemic, febrile **Jarisch-Herxheimer reaction** occurs in 15% to 20% of syphilitic patients treated with penicillin.

**HERPES SIMPLEX VIRUS (HSV) INFECTION**

HSV-1 and HSV-2 are large, double-stranded DNA viruses of the herpesvirus family with a linear genome contained within an icosahedral capsid. There is significant DNA homology between types 1 and 2. The virus initially infects mucosal surfaces and enters cutaneous neurons where it migrates along the axons to sensory ganglia. As viral replication occurs in the ganglia, infectious virus moves along the axon to infect and destroy epithelial cells. Infection may disseminate to other organs in immunocompromised patients. Virus latency is maintained in the ganglia where it undergoes periodic reactivation and replication triggered by undefined events. Although either virus can be found in any site, HSV-1 more commonly occurs in the central nervous system, eyes, and mouth, whereas HSV-2 more commonly involves the genitalia. Reinfection can occur with exposure to the other type or even a second strain of the same type.

**Primary genital herpes** is characterized by multiple painful, grouped vesicles or ulcerative and crusted external genital lesions on an erythematous base (see Table 116-2). In females the cervix is also involved. Symptoms may include regional lymphadenopathy, discharge, and dysuria. Primary illness lasts 10 to 20 days with recurrences in 50% to 80% of patients. **Secondary, recurrent, or reactivation eruptions** are not as dramatic and are not associated with systemic symptoms. In primary infection, viral shedding lasts 1 to 2 weeks, and the entire course from vesicle and ulcer onset resolves over 16 to 20 days. In recurrent disease, virus shedding lasts for less than 7 days, and the course resolves over 8 to 10 days. Many persons experience five to eight recurrences per year. Some primary and many recurrent episodes are asymptomatic.

Viral cultures and PCR are the preferred methods of diagnosis; culture typically shows cytopathic effect in 1 to 3 days and seldom takes longer than 5 days. PCR assays have increased sensitivity over culture. Viral shedding is intermittent after primary infection, so both culture and PCR can fail to detect latent infection. Serologic testing is useful for primary infection only (to show seroconversion between acute and convalescent sera), and positive serologies persist lifelong. Titers are not helpful in guiding management of recurrences.

Oral famciclovir and valacyclovir are effective treatments in reducing the severity and duration of symptoms in primary cases and may reduce recurrences. Once-daily suppressive
therapy reduces the frequency of genital herpes recurrences by 70% to 80% among patients who have frequent recurrences (more than six recurrences per year). Local hygiene and sitz baths may relieve discomfort. The use of condoms provides some protection against sexual transmission of HSV.

**TRICHOMONIASIS (TRICHOMONAS VAGINALIS)**

Trichomoniasis is caused by the protozoan *T. vaginalis* and often is associated with other STIs such as gonorrhea and *Chlamydia*. Infection is asymptomatic in as many as 90% of men and 85% of women. Symptomatic males can have urethritis. Symptomatic females have vaginitis with thin, malodorous, frothy yellow-green discharge, vulvar irritation, and cervical “strawberry hemorrhages” (see Table 116-3). Diagnosis is based on visualization of motile, flagellated protozoans in the urine or in a saline wet mount, which has a sensitivity of only 60% to 70% among symptomatic women. Culture is the most sensitive method of diagnosis. The diagnosis of both sexual partners with oral metronidazole or tinidazole in a single dose is recommended.

**GENITAL WARTS (HUMAN PAPILLOMAVIRUSES)**

HPV, the cause of genital warts (condylomata acuminata), is the most common STI in the United States with the highest prevalence rates among 15- to 24-year-olds. Most HPV infections are asymptomatic or subclinical. HPV types 6 and 11 cause 90% of genital warts and are nononcogenic. HPV types 16 and 18 are associated with 70% of cases of cervical cancer. HPV types 31, 33, and 35 are also oncogenic. Types 6 and 11 cause 90% of genital warts and are nononcogenic. HPV types 16 and 18 are associated with 70% of cases of cervical cancer. HPV types 31, 33, and 35 are also oncogenic.

- In children beyond the newborn period and without hemoglobinopathies, bone infections occur almost exclusively in the metaphysis of long bones due to sluggish blood flow through tortuous vascular loops unique to this site. Preceding nonpenetrating trauma is often reported and may lead to local bone injury that predisposes to infection. Bone infections in children with sickle cell disease occur in the diaphyseal portion of the long bones, probably as a consequence of antecedent focal infarction. In children younger than 12 to 18 months of age, capillaries perforate the epiphyseal growth plate, permitting spread of infection across the epiphysis leading to suppurative arthritis, whereas in older children, infection is contained in the metaphysis because these vessels no longer cross the epiphyseal growth plate (Figs. 117-1AB).

**OSTEOMYELITIS**

**ETIOLOGY**

Acute hematogenous osteomyelitis is the most common manifestation of osteomyelitis in children and evolves secondary to bacteremia. Subacute osteomyelitis usually follows local inoculation by penetrating trauma and is not associated with systemic symptoms, and chronic osteomyelitis results from an untreated or inadequately treated (usually subacute) osteomyelitis.

In children beyond the newborn period and without hemoglobinopathies, bone infections occur almost exclusively in the metaphysis of long bones due to sluggish blood flow through tortuous vascular loops unique to this site. Preceding nonpenetrating trauma is often reported and may lead to local bone injury that predisposes to infection. Bone infections in children with sickle cell disease occur in the diaphyseal portion of the long bones, probably as a consequence of antecedent focal infarction. In children younger than 12 to 18 months of age, capillaries perforate the epiphyseal growth plate, permitting spread of infection across the epiphysis leading to suppurative arthritis, whereas in older children, infection is contained in the metaphysis because these vessels no longer cross the epiphyseal plate (Figs. 117-1AB).

*Staphylococcus aureus* is responsible for more than 80% of acute skeletal infections. Other common causes include Group A streptococcus and *Streptococcus pneumoniae*. *Neisseria meningitidis*, *Mycobacterium tuberculosis*, *Bartonella henselae*, *Actinomyces* spp., and anaerobes are less common causes. Group B streptococcus and enteric gram-negatives are other major causes in neonates. Sickle cell disease and other hemoglobinopathies predispose to osteomyelitis caused by *Salmonella* and *S. aureus*. *Pasteurella multocida* osteomyelitis may
follow cat or dog bites. The use of polymerase chain reaction testing reveals that a significant proportion of culture negative osteomyelitis is due to *Kingella kingae*. Conjugate vaccine has reduced greatly the incidence of *Haemophilus influenzae* type b infections.

Subacute focal bone infections caused by *Pseudomonas aeruginosa* and *S. aureus* usually occur in ambulatory persons who sustain puncture wounds of the foot. *Pseudomonas chondritis* is strongly associated with puncture wounds through sneakers, which harbor *Pseudomonas* in the foam insole. *S. aureus* is the most common cause of chronic osteomyelitis. Chronic recurrent multifocal osteomyelitis is an autoinflammatory syndrome characterized by recurrent episodes of fever, bone pain, and radiographic findings of osteomyelitis. Bones uncommonly involved in acute hematogenous osteomyelitis such as the clavicle, scapula, or small bones of the hands or feet are often affected, pathogens are not identified on culture, and histopathology demonstrates plasmacytic infiltrates.

**EPIDEMIOLOGY**

Osteomyelitis may occur at any age but is most common in children 3 to 12 years of age and affects boys twice as frequently as girls. Osteomyelitis from penetrating trauma or peripheral vascular disease is more common in adults.

**CLINICAL MANIFESTATIONS**

The most common presenting complaints are focal pain, exquisite point tenderness over the bone, warmth, erythema, and swelling. Fever, anorexia, irritability, and lethargy may accompany the focal findings. Weight bearing and active and passive motion of the affected extremity are decreased, mimicking paralysis (pseudoparalysis). Muscle spasm may make the extremity difficult to examine. The adjacent joint space may be involved in young children, suggested by pain with minimal joint range of motion (see Chapter 118).

Usually only one bone is involved. The femur, tibia, or humerus is affected in approximately two thirds of patients. Approximately 15% of cases involve the bones of the hands or feet, and 10% involve the pelvis. Vertebral osteomyelitis is notable for an insidious onset, vague symptoms, backache, occasional spinal cord compression, and, usually, little associated fever or systemic toxicity. Patients with osteomyelitis of the pelvis may present with fever, limp, and vague abdominal, hip, groin, or thigh pain. Pyomyositis of pelvic muscles may mimic osteomyelitis.

**LABORATORY AND IMAGING STUDIES**

The presence of leukocytosis is inconsistent. Blood cultures are important but are negative in many cases. Elevated acute phase reactants, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are sensitive but nonspecific findings. Serial determinations of ESR and CRP are helpful in monitoring the course of the illness and response to treatment. Direct subperiosteal or metaphyseal needle aspiration definitively establishes the diagnosis. Identification of bacteria in aspirated material by Gram stain can establish the diagnosis within hours of clinical presentation.

Plain radiographs can demonstrate soft tissue swelling such as the loss of the periosteal fat line within the first 3 days of symptoms, but bony lesions such as periosteal elevation and bone destruction are absent until after 10 to 14 days of symptoms (Fig. 117-2). *Brodie abscess* is a subacute intraosseous abscess that does not drain into the subperiosteal space and is classically located in the distal tibia. *Sequestra*, portions of
avascular bone that have separated from adjacent bone, frequently are covered with a thickened sheath, or involucrum, both of which are hallmarks of chronic osteomyelitis.

Radionuclide scanning for osteomyelitis has largely been supplanted by magnetic resonance imaging, which is sensitive to the inflammatory marrow changes even during the earliest stages of osteomyelitis. Technetium-99m bone scans are useful for identifying multifocal disease. Gallium-67 scans are often positive if the technetium-99m bone scan is negative.

**DIFFERENTIAL DIAGNOSIS**
Osteomyelitis must be differentiated from infectious arthritis (see Chapter 118), cellulitis, pyomyositis, fasciitis, diskitis, trauma, juvenile idiopathic arthritis, bone cysts, histiocytosis, and malignancy.

**TREATMENT**

Initial antibiotic therapy for osteomyelitis is based on the likely organism for the age of the child, Gram stain of bone aspirate, and associated diseases (Table 117-1). Initial therapy includes an antibiotic that targets *S. aureus* and *Kingella*, such as oxacillin or nafcillin. Clindamycin or vancomycin should be used if methicillin-resistant *S. aureus* is suspected based on patient factors or local *S. aureus* epidemiology. For patients with sickle cell disease, initial therapy should include an antibiotic with activity against *Salmonella*.

**Table 117-1 Recommended Antibiotic Therapy for Osteomyelitis in Children**

<table>
<thead>
<tr>
<th>COMMON PATHOGEN</th>
<th>RECOMMENDED TREATMENT*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACUTE HEMATOGENOUS OSTEOMYELITIS</strong></td>
<td></td>
</tr>
</tbody>
</table>
| *Staphylococcus aureus* | Methicillin-sensitive: Nafcillin (or oxacillin) or cefazolin  
Methicillin-resistant: Clindamycin or vancomycin or linezolid |
| *Streptococcus pyogenes* (group A streptococci) | Penicillin G |
| *Streptococcus pneumoniae* | Penicillin G or ceftriaxone/cefotaxime or vancomycin |
| **Subacute Focal Osteomyelitis** | |
| *Pseudomonas aeruginosa* | Ceftazidime or piperacillin-tazobactam plus an aminoglycoside |
| *Kingella kingae* | Penicillin G, oxacillin, or cefotaxime |

*Optimal specific therapy is based on susceptibilities of the organism that is isolated.

Response to intravenous (IV) antibiotics usually occurs within 48 hours. Lack of improvement after 48 hours indicates that surgical drainage may be necessary or that an unusual pathogen may be present. Surgical drainage is indicated for extensive or severe disease, if the disease is chronic or atypical, the hip joint is involved, or sequestrum or spinal cord compression is present. Antibiotics are administered for a minimum of 4 to 6 weeks. After initial inpatient treatment and adequate clinical response, including decreases in CRP or ESR, transition to home therapy with oral or IV antibiotics may be considered if adherence is ensured.
COMPLICATIONS AND PROGNOSIS

Complications of acute osteomyelitis are uncommon and usually arise because of inadequate or delayed therapy or concomitant bacteremia. Vascular insufficiency, which affects delivery of antibiotics, and trauma are associated with higher rates of complications.

Hematogenous osteomyelitis has an excellent prognosis if treated promptly and if surgical drainage is performed when appropriate. The poorest outcomes are in neonates and in infants with involvement of the hip or shoulder joints (see Chapter 118). Approximately 2% to 4% of acute infections recur despite adequate therapy, and approximately 25% of these fail to respond to extensive surgical debridement and prolonged antimicrobial therapy, ultimately resulting in bone loss, sinus tract formation, or amputation (although rare). Sequelae related to skeletal growth disturbance are most common with neonatal osteomyelitis.

PREVENTION

There are no effective means to prevent hematogenous S. aureus osteomyelitis. Universal immunization of infants with conjugate Haemophilus influenzae type b vaccine has practically eliminated serious bacterial infections from this organism, including bone and joint infections.

Children with puncture wounds to the foot should receive prompt irrigation, cleansing, debridement, removal of any visible foreign body or debris, and tetanus prophylaxis. The value of oral prophylactic antibiotics for preventing osteomyelitis after penetrating injury is uncertain.

Chapter 118

INFECTIOUS ARTHRITIS

ETIOLOGY

Infectious arthritis (suppurative or septic arthritis) is a serious bacterial infection of the joint space resulting from hematogenous dissemination of bacteria. Infectious arthritis less often results from contiguous spread of infection from surrounding soft tissues or direct inoculation into the joint (penetrating trauma). Spread of osteomyelitis into the joint space is more common in children under 18 months of age and occurs via organisms passing through transphyseal vessels to the epiphysis (see Fig. 117-1A). The bacteria causing infectious arthritis are similar to bacteria causing osteomyelitis (Table 118-1). Lyme disease also may cause arthritis (see Chapter 122).

The arthritis of disseminated gonococcal infections includes both reactive and supplicative forms in early and late gonococcal disease, respectively. With untreated genital infection, gonococccemia may occur with fever and a polyarticular, symmetric arthritis and rash, known as the arthritis-dermatitis syndrome. Bacterial cultures of the synovium are sterile at this stage, despite a relatively high prevalence of bacteremia. Monarticular arthritis of large, weight-bearing joints develops days to weeks later. Cultures of affected synovial fluid at this stage often yield the pathogen.

Reactive arthritis is immune-mediated synovial inflammation that follows a bacterial or viral infection, especially Yersinia and other enteric infections. Reactive arthritis of the hip joints in children 3 to 6 years of age is known as toxic or transient synovitis (see Chapter 200).

EPIDEMIOLOGY

Infectious arthritis occurs most commonly in children younger than 5 years of age and adolescents.

CLINICAL MANIFESTATIONS

<table>
<thead>
<tr>
<th>Escherichia coli</th>
<th>Haemophilus influenzae type b*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella pneumoniae</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td><strong>COMMON</strong></td>
<td><strong>UNCOMMON</strong></td>
</tr>
<tr>
<td>YOUNG INFANT (&lt;2 MONTHS)</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Anaerobic bacteria</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Group A streptococci</td>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Kingella kingae</td>
<td>Haemophilus influenzae type b*</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>Mycobacterium tuberculosis</td>
</tr>
<tr>
<td><strong>Reactive Arthritis</strong></td>
<td></td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td></td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td></td>
</tr>
<tr>
<td>Shigella flexneri</td>
<td></td>
</tr>
<tr>
<td>Salmonella</td>
<td></td>
</tr>
<tr>
<td>Group A streptococci</td>
<td></td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td></td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td></td>
</tr>
<tr>
<td>Rubella virus</td>
<td></td>
</tr>
</tbody>
</table>

*The incidence of invasive infections caused by H. influenzae type b has diminished greatly with universal childhood Hib vaccination.

The typical features of supplicative arthritis include monarticular involvement with erythema, warmth, swelling, and tenderness over the affected joint with a palpable effusion.

Table 118-1 Pathogenic Organisms Causing Arthritis in Children
and markedly decreased range of movement. The onset may be sudden or insidious with symptoms noted when the joint is moved only, such as during a diaper change, or if parents become aware of decreased voluntary movement of a joint or limb. Toddlers may exhibit a limp or refuse to walk. In septic arthritis of the hip, the lower limb may be preferentially held in external rotation and flexion to minimize pain from pressure on the joint capsule. Similarly the knee and elbow joints usually are held in flexion. The joints of the lower extremity are most often involved: the knees (40%), the hips (20%), and the ankles (14%). Small joints, such as those of the hand, usually are involved after penetrating trauma or closed fist injuries. Minor genital tract symptoms that have been ignored may precede development of the early arthritis-dermatitis syndrome associated with disseminated gonococcal infection. A history of febrile illness antedating the development of monarticular arthritis characterizes late gonococcal arthritis.

**LABORATORY AND IMAGING STUDIES**

Leukocytosis and an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are common. Arthrocentesis is important to distinguish among the causes of arthritis (Table 118-2). Adolescents with acute infectious arthritis should have urethral, cervical, rectal, and pharyngeal examinations and cultures or nucleic acid amplification tests performed for *Neisseria gonorrhoeae.*

Blood or joint cultures are positive in approximately 50% of cases. Joint fluid that exhibits the characteristics of pyogenic infection may not reveal bacterial pathogens, even in the absence of preceding antibiotic therapy, because of the bacteriostatic effects of synovial fluid. Gram stain, acid-fast stain, and potassium hydroxide preparation for fungi should be performed and are often informative even if the cultures are negative.

Plain radiographs typically add little information to the physical findings. Radiographs may show swelling of the joint capsule, a widened joint space, and displacement of adjacent normal fat lines. Radionuclide scans are of limited use, although magnetic resonance imaging or technetium-99m bone scans may be helpful to exclude concurrent bone infection or deep abscesses. Ultrasound is especially useful for identifying joint effusions and is the initial diagnostic procedure of choice for evaluation of suppurative infections of the hip.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of infectious arthritis in infants, children, and adolescents includes other infectious diseases, autoimmune disorders, rheumatic fever, and trauma.

Suppurative arthritis must be distinguished from Lyme disease, osteomyelitis, suppurative bursitis, fasciitis, myositis, cellulitis, and soft tissue abscesses. Psoas muscle abscess often presents with fever and pain on hip flexion and rotation. Juvenile idiopathic arthritis, Kawasaki disease, Henoch-Schönlein purpura, other rheumatic disorders, and Crohn’s disease must be differentiated from infectious arthritis. In most of these diseases, the presence of symmetric or multiple joint involvement

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>APPEARANCE</th>
<th>WBC COUNT (mm³/L)</th>
<th>PMNs (%)</th>
<th>MUCIN CLOT</th>
<th>SYNOVIAL FLUID–BLOOD GLUCOSE DIFFERENCE (mg/dL)</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear, yellow</td>
<td>0–200 (200) *</td>
<td>&lt;10</td>
<td>Good</td>
<td>No difference</td>
<td>—</td>
</tr>
<tr>
<td>Trauma</td>
<td>Clear, turbid, or hemorrhagic</td>
<td>50–4000 (600)</td>
<td>&lt;30</td>
<td>Good</td>
<td>No difference</td>
<td>Common in hemophilia</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Clear or slightly turbid</td>
<td>0–9000 (3,000)</td>
<td>&lt;20</td>
<td>Good to fair</td>
<td>No difference</td>
<td>LE cell positive, complement decreased</td>
</tr>
<tr>
<td>Rheumatoid arthritis, reactive arthritis (Reiter syndrome, inflammatory bowel disease)</td>
<td>Turbid</td>
<td>250–80,000 (19,000)</td>
<td>&gt;70</td>
<td>Poor</td>
<td>30</td>
<td>Decreased complement</td>
</tr>
<tr>
<td>Infectious pyogenic infection</td>
<td>Turbid</td>
<td>10,000–250,000 (80,000)</td>
<td>&gt;90</td>
<td>Poor</td>
<td>50–90</td>
<td>Positive culture result, positive Gram stain</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Turbid</td>
<td>2500–100,000 (20,000)</td>
<td>&gt;60</td>
<td>Poor</td>
<td>40–70</td>
<td>Positive results on culture, PPD testing, and acid-fast stain</td>
</tr>
<tr>
<td>Lyme arthritis</td>
<td>Turbid</td>
<td>500–100,000 (20,000)</td>
<td>&gt;60</td>
<td>Poor</td>
<td>70</td>
<td>History of tick bite or erythema migrans</td>
</tr>
</tbody>
</table>

*LE, Lupus erythematosus; PMN, polymorphonuclear cell; PPD, purified protein derivative of tuberculin; WBC, white blood cell.

*Average in parentheses.*
often excludes infectious arthritis. **Suppurative bursitis** with *Staphylococcus aureus* occurs most often in older boys and men and is usually a consequence of trauma or, less commonly, a complication of bacteremia.

**TREATMENT**

Initial antibiotic therapy for infectious arthritis is based on the likely organism for the age of the child and the Gram stain of joint fluid. Suppurative arthritis of the hip joint, especially, or shoulder joint necessitates prompt surgical drainage. With insertion of the joint capsule below the epiphysis in these ball-and-socket joints, increased pressure in the joint space can adversely affect the vascular supply to the head of the femur or humerus, leading to avascular necrosis. Infections of the knee may be treated with repeated arthrocenteses, in addition to appropriate parenteral antibiotics.

Several antimicrobial agents provide adequate antibiotic levels in joint spaces (Table 118-3). Initial therapy for neonates should include antibiotics with activity against *S. aureus*, group B streptococcus, and aerobic gram-negative rods, such as nafcillin and cefoxitin. Initial therapy for children 3 months to 5 years old should include antibiotics with activity against *S. aureus*. Addition of appropriate antibiotics should be considered if the child is unimmunized against *Haemophilus influenzae* type b (Hib). Confirmed methicillin-susceptible *S. aureus* infections are best treated with nafcillin or oxacillin, and methicillin-resistant *S. aureus* infections are best treated with clindamycin, if susceptible, or vancomycin otherwise.

The duration of therapy depends on clinical resolution of fever and pain and decline of the ESR and CRP. Infection with virulent organisms, such as *S. aureus*, usually necessitates treatment for at least 21 days. Treatment may be changed to oral antibiotics if adherence can be ensured. Oral agents with excellent activity against *S. aureus* that are often used to complete therapy include cephalaxin, clindamycin, amoxicillin-clavulanate, dicloxacillin, and ciprofloxacin (for patients >18 years).

**COMPLICATIONS AND PROGNOSIS**

The prognosis for the common forms of infectious arthritis encountered in infants and children is excellent. The major complications of neonatal, childhood, and gonococcal arthritis are loss of joint function resulting from damage to the articular surface. The highest incidence of these complications occurs with hip and shoulder infections, presumably resulting from avascular necrosis. The high incidence of concurrent suppurative arthritis with adjacent osteomyelitis in neonates places the epiphyseal growth plate at high risk for growth abnormalities. Neonates with osteomyelitis have an approximately 40% to 50% likelihood of growth disturbances with loss of longitudinal bone growth and ultimate limb shortening.

**PREVENTION**

There are no effective means to prevent hematogenous *S. aureus* arthritis. Universal immunization of infants with conjugate Hib vaccine has practically eliminated serious bacterial infections from this organism, including bone and joint infections.

### Table 118-3

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>COMMON PATHOGENS</th>
<th>RECOMMENDED TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (younger than 2 months of age)</td>
<td>Group B streptococci</td>
<td>Ampicillin plus aminoglycoside</td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
<td>Cefotaxime (or ceftriaxone) plus aminoglycoside</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
<td>Cefotaxime (or ceftriaxone) plus aminoglycoside</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td>Nafcillin (or oxacillin), vancomycin</td>
</tr>
<tr>
<td>Older infants and children</td>
<td><em>S. aureus</em></td>
<td>Nafcillin (or oxacillin), vancomycin</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus pneumoniae</em></td>
<td>Cefotaxime (or ceftriaxone) or vancomycin (based on susceptibilities)</td>
</tr>
<tr>
<td></td>
<td><em>Group A streptococci</em></td>
<td>Penicillin G</td>
</tr>
<tr>
<td></td>
<td><em>Kingella kingae</em></td>
<td>Penicillin G, nafcillin (or oxacillin) or cefotaxime</td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus influenzae type b</em></td>
<td>Cefotaxime or ceftriaxone</td>
</tr>
<tr>
<td></td>
<td><em>Neisseria gonorrhoeae: disseminated gonococcal infection</em></td>
<td>Ceftriaxone</td>
</tr>
</tbody>
</table>

*The incidence of invasive infections caused by *H. influenzae* type b has diminished greatly with universal childhood Hib vaccination.*

### Ocular Infections

**ETIOLOGY**

**Acute conjunctivitis** is usually a bacterial or viral infection of the eye characterized by a rapid onset of symptoms that persist for a few days. Nontypable *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* account for approximately two thirds of bacterial causes (Table 119-1). Other causes include *Neisseria gonorrhoeae* and *Pseudomonas aeruginosa*, which is associated with extended-use soft contact lenses. Viral conjunctivitis most commonly is caused by adenoviruses, which cause **epidemic keratoconjunctivitis**, and less frequently by coxsackieviruses and other enteroviruses. **Keratitis**, or inflammation of the cornea, is not commonly associated with conjunctivitis but occurs with *N. gonorrhoeae*, herpes simplex virus (HSV), and adenovirus infections.

Neonatal conjunctivitis, or **ophthalmia neonatorum**, is purulent conjunctivitis during the first month of life, usually...
acquired during birth. The common causes of neonatal conjunctivitis, in order of decreasing prevalence, are chemical conjunctivitis secondary to silver nitrate gonococcal prophylaxis, *Chlamydia trachomatis*, common bacterial causes of conjunctivitis, *Escherichia coli*, other gram-negative enteric bacilli, HSV, and *N. gonorrhoeae*.

**EPIDEMIOLOGY**

Conjunctivitis is common in young children, especially if they come in contact with other children with conjunctivitis. Pre-disposing factors for bacterial infection include nasolacrimal duct obstruction, sinus disease, ear infection, and allergic disease when children rub their eyes frequently. Conjunctivitis occurs in 1% to 12% of neonates. A mild to moderate chemical conjunctivitis commonly is present from 24 to 48 hours of age in most newborns who receive ophthalmic silver nitrate as prophylaxis. Approximately 50% of infants born vaginally to infected mothers have neonatal acquisition of *C. trachomatis*, in which the risk of chlamydial conjunctivitis (inclusion conjunctivitis) is 25% to 50%.

**CLINICAL MANIFESTATIONS**

Symptoms include redness, discharge, matted eyelids, and mild photophobia. Physical examination findings include chemosis, injection of the conjunctiva, and edema of the eyelids. Corneal involvement suggests gonococcal or herpetic infection. Herpetic corneal lesions appear as dendritic or ameboid ulcers or, more commonly, in recurrent infection, as a deep keratitis. Unilateral conjunctivitis with ipsilateral otitis media is often caused by nontypable *H. influenzae*.

The timing and manifestations of neonatal conjunctivitis are helpful in identifying the cause (Table 119-2). *N. gonorrhoeae* causes severe conjunctivitis with profuse purulent discharge. Chlamydial conjunctivitis usually occurs in the second week of life but may appear 3 days to 6 weeks after delivery. There is mild to moderate inflammation with purulent discharge issuing from one or both eyes.

**LABORATORY AND IMAGING STUDIES**

Cultures are not routinely obtained because bacterial conjunctivitis is usually self-limited or responds quickly to topical antibiotic treatment. If gonococcal conjunctivitis is suspected, especially in neonates, Gram stain and culture must be obtained. In these infants, blood and other sites of infection (such as cerebrospinal fluid) should be cultured. Additional testing for *Chlamydia*, human immunodeficiency virus (HIV), and syphilis should be performed on the mother and infant as necessary as well.

**DIFFERENTIAL DIAGNOSIS**

Distinguishing bacterial from viral conjunctivitis by presentation and appearance is difficult (see Table 119-1). Vesicular lid lesions, if present, suggest HSV. *Hyperpurulent conjunctivitis* characterized by reaccumulation of purulent discharge within minutes is characteristic of *N. gonorrhoeae* infection. The differential diagnosis is delineated in Table 119-3.

**Blepharitis** is associated with staphylococcal infections, seborrhea, and meibomian gland dysfunction. The child complains of photophobia, burning, irritation, and a foreign body sensation that causes the child to rub the eyes. Eyelid hygiene with an eyelid scrub routine is the initial step in treatment.

** Hordeola** are acute suppurative nodular inflammatory lesions of the eyelids associated with pain and redness. *Exter nal hordeola* or styes occur on the anterior eyelid, in the Zeis glands, or in the lash follicles and usually are caused by staphylococci. **Internal hordeola** occur in the meibomian glands and may be infected with staphylococci or may be sterile. If the meibomian gland becomes obstructed, the gland secrections accumulate, and a chalazion develops. Hordeola usually respond spontaneously to local treatment measures but may recur.

**Dacryocystitis** is an infection or inflammation of the lacrimal sac, which is usually obstructed, and is most commonly caused by *Staphylococcus aureus* or coagulase-negative staphylococci. A mucopurulent discharge can be expressed with
### Table 119-2: Clinical Manifestations and Treatment of Neonatal Conjunctivitis

<table>
<thead>
<tr>
<th>ETIOLOGIC AGENT</th>
<th>CASES (%)</th>
<th>DISCHARGE AND EXTERNAL EXAMINATION</th>
<th>TYPICAL AGE AT ONSET</th>
<th>DIAGNOSIS</th>
<th>ASSOCIATED MANIFESTATIONS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical: silver nitrate</td>
<td>Variable (1%), depending on use of silver nitrate</td>
<td>Watery discharge</td>
<td>1–3 days</td>
<td>No organisms on smear or culture</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Chlamydia trachomatis (inclusion conjunctivitis)</td>
<td>2–40</td>
<td>Scant discharge; mild swelling; hyperemia; follicular response; late corneal staining</td>
<td>4–19 days</td>
<td>Test of discharge with a DIF test or PCR assay</td>
<td>May presage C. trachomatis pneumonia (at 3 weeks–3 months of age)</td>
<td>Erythromycin (oral)</td>
</tr>
<tr>
<td>Bacterial: <em>Staphylococcus, Streptococcus, Pseudomonas, E. coli</em></td>
<td>30–50</td>
<td>Purulent moderate discharge; mild lid and conjunctival swelling; corneal involvement with risk for perforation</td>
<td>2–7 days</td>
<td>Gram stain; culture on blood agar</td>
<td></td>
<td>Topical therapy</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>&lt;1</td>
<td>Copious, purulent discharge; swelling of lids and conjunctvae; corneal involvement common; risk for perforation and corneal scar</td>
<td>1–7 days</td>
<td>Gram stain (gram-negative intracellular diplococci); culture on chocolate agar</td>
<td>Culture other sites including blood and CSF</td>
<td>May be associated with severe disseminated gonococcal infection Ceftriaxone Hospitalize patient</td>
</tr>
<tr>
<td>HSV</td>
<td>&lt;1</td>
<td>Clear or serosanguineous discharge; lid swelling; keratitis with cloudy cornea; dendrite formation</td>
<td>3 days–3 weeks</td>
<td>Viral culture; DIF test, PCR assay</td>
<td>May be associated with disseminated perinatal HSV infection</td>
<td>Acyclovir (intravenous) for systemic involvement</td>
</tr>
</tbody>
</table>

CSF, Cerebrospinal fluid; DIF, direct immunofluorescence; HSV, herpes simplex virus; PCR, polymerase chain reaction.

### Table 119-3: Differential Diagnosis of Ocular Infections

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>ETIOLOGIC AGENTS</th>
<th>SIGNS AND SYMPTOMS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial conjunctivitis</td>
<td><em>Haemophilus influenzae, Haemophilus aegyptius, Streptococcus pneumoniae, Neisseria gonorrhoeae</em></td>
<td>Mucopurulent unilateral or bilateral discharge, normal vision, photophobia, conjunctival injection and edema (chemosis); gritty sensation</td>
<td>Topical antibiotics, parenteral ceftriaxone for gonococcus</td>
</tr>
<tr>
<td>Viral conjunctivitis</td>
<td>Adenovirus, echovirus, coxsackievirus</td>
<td>Same as for bacterial infection; may be hemorrhagic, unilateral</td>
<td>Self-limited</td>
</tr>
<tr>
<td>Neonatal conjunctivitis</td>
<td>Chlamydia trachomatis, gonococcus, chemical (silver nitrate), <em>Staphylococcus aureus</em></td>
<td>Palpebral conjunctival follicle or papillae; same as for bacterial infection</td>
<td>Ceftriaxone for gonococcus and oral erythromycin for C. trachomatis</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>Seasonal pollens or allergen exposure</td>
<td>Itching, incidence of bilateral chemosis (edema) greater than that of erythema, tarsal papillae</td>
<td>Antihistamines, steroids, cromolyn</td>
</tr>
<tr>
<td>Keratitis</td>
<td>Herpes simplex, adenovirus, <em>S. pneumoniae, S. aureus, Pseudomonas, Acanthamoeba</em>, chemicals</td>
<td>Severe pain, corneal swelling, clouding, limbus erythema, hypopyon, cataracts; contact lens history with amebic infection</td>
<td>Specific antibiotics for bacterial/fungal infections; keratoplasty, acyclovir for herpes</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td><em>S. aureus, S. pneumoniae, Candida albicans</em>, associated surgery or trauma</td>
<td>Acute onset, pain, loss of vision, swelling, chemosis, redness; hypopyon and vitreous haze</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Anterior uveitis (iritis)</td>
<td>JIA, reactive arthritis, sarcoidosis, Behçet disease, inflammatory bowel disease</td>
<td>Unilateral/bilateral; erythema, ciliary flush, irregular pupil, iris adhesions; pain, photophobia, small pupil, poor vision</td>
<td>Topical steroids, plus therapy for primary disease</td>
</tr>
<tr>
<td>Posterior uveitis (choroiditis)</td>
<td>Toxoplasmosis, histoplasmosis, <em>Toxocara canis</em></td>
<td>No signs of erythema, decreased vision</td>
<td>Specific therapy for pathogen</td>
</tr>
</tbody>
</table>
gentle pressure on the nasolacrimal sac. Treatment usually requires probing of the nasolacrimal system to establish communication.

Endophthalmitis is an emergent, sight-threatening infection that usually follows trauma, surgery, or hematogenous spread from a distant focus. Causative organisms include coagulase-negative staphylococci, S. aureus, S. pneumoniae, Bacillus cereus, and Candida albicans. Examination is difficult because of severe blepharospasm and extreme photophobia. A hypopyon and haze may be visible on examination.

**TREATMENT**
The lids should be treated as needed with warm compresses to remove accumulated discharge. Acute bacterial conjunctivitis is frequently self-limited, but topical antibiotics hasten resolution. Antibiotics are instilled between the eyelids four times a day until the discharge and chemosis subside. Recommended treatment includes topical trimethoprim-polymyxin B solution, sulfacetamide 5% solution, or erythromycin ointment. Ciprofloxacin solution should be restricted to corneal infections and resistant gram-negative infections in hospitalized patients. Gonococcal conjunctivitis in adults is treated with a single intramuscular (IM) dose of ceftriaxone (1 g) plus azithromycin (to treat possible concomitant chlamydial infection).

The treatment of ocular infections depends on the cause. For example, Gonococcal conjunctivitis should be treated with a single dose of ceftriaxone (25 to 50 mg/kg intravenously [IV] or IM; maximum dose 125 mg). These infants should be hospitalized. Antibiotic treatment also is recommended for newborns to mothers with untreated gonorrhea. Chlamydial conjunctivitis is treated with oral erythromycin for 14 days, partly to reduce the risk of subsequent chlamydial pneumonia.

**COMPLICATIONS AND PROGNOSIS**
The prognosis for bacterial and viral conjunctivitis is excellent. The major complication is keratitis, which can lead to ulcerations and perforation, and is uncommon except with N. gonorrhoeae and HSV infections. Chlamydial conjunctivitis may progress in infants to chlamydial pneumonia, which typically develops from 4 to 12 weeks of age (see Chapter 110).

**PREVENTION**
Careful hand washing is important to prevent spread of conjunctivitis. Bacterial conjunctivitis is considered contagious for 24 hours after initiating effective treatment. Children may return to school, but treatment measures must be continued until there is complete clinical resolution.

All newborns, whether delivered vaginally or by cesarean section, should receive prophylaxis for gonococcal ophthalmia neonatorum as soon as possible after delivery. Silver nitrate ointment or tetracycline 1% ointment is frequently self-limited, but topical antibiotics hasten resolution. Unilateral, red, gritty feeling; visible or microscopic size

**Table 119-3** Differential Diagnosis of Ocular Infections—cont’d

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>ETIOLOGIC AGENTS</th>
<th>SIGNS AND SYMPTOMS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episcleritis/scleritis</td>
<td>Idiopathic autoimmune disease (e.g., SLE, Henoch-Schönlein purpura)</td>
<td>Localized pain, intense erythema, unilateral; blood vessels bigger than in conjunctivitis; scleritis may cause globe perforation.</td>
<td>Episcleritis is self-limited; topical steroids for fast relief.</td>
</tr>
<tr>
<td>Foreign body</td>
<td>Occupational or other exposure</td>
<td>Unilateral, red, gritty feeling; visible or microscopic size</td>
<td>Irrigation, removal; check for ulceration.</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>S. aureus, Staphylococcus epidermidis, seborrheic, blocked lacrimal duct; rarely molluscum contagiosum, Phthirius pubis, Pediculus capitis</td>
<td>Bilateral, irritation, itching, hyperemia, crusting, affecting lid margins</td>
<td>Topical antibiotics, warm compresses.</td>
</tr>
<tr>
<td>Dacryocystitis</td>
<td>Obstructed lacrimal sac: S. aureus, H. influenzae, S. pneumoniae</td>
<td>Pain, tenderness, erythema and exudate in areas of lacrimal sac (inferomedial to inner canthus); tearing (epiphora); possible orbital cellulitis</td>
<td>Systemic, topical antibiotics; surgical drainage.</td>
</tr>
<tr>
<td>Dacryoadenitis</td>
<td>S. aureus, S. pneumoniae, CMV, measles, EBV, enteroviruses, trauma, sarcoidosis, leukemia</td>
<td>Pain, tenderness, edema, erythema over gland area (upper temporal lid); fever, leukocytosis</td>
<td>Systemic antibiotics; drainage of orbital abscesses.</td>
</tr>
<tr>
<td>Orbital cellulitis (postseptal cellulitis)</td>
<td>Paranasal sinusitis: H. influenzae, S. aureus, S. pneumoniae, other streptococci, Trauma: S. aureus</td>
<td>Rhinorrhea, chemosis, vision loss, painful extraocular motion, proptosis, ophthalmoplegia, fever, lid edema, leukocytosis</td>
<td>Systemic antibiotics; drainage of orbital abscesses.</td>
</tr>
<tr>
<td>Periorbital cellulitis (preseptal cellulitis)</td>
<td>Trauma: S. aureus, other streptococci, Bacteremia: pneumococcus, streptococci, H. influenzae</td>
<td>Cutaneous erythema, warmth, normal vision, minimal involvement of orbit; fever, leukocytosis, toxic appearance</td>
<td>Systemic antibiotics.</td>
</tr>
</tbody>
</table>

CMV, Cytomegalovirus; EBV, Epstein-Barr virus; JIA, juvenile idiopathic arthritis; SLE, systemic lupus erythematosus.
INFECTION IN THE IMMUNOCOMPROMISED PERSON

ETIOLOGY
Many diseases or their treatments adversely affect the immune system, including genetic immunodeficiencies, human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), cancer, stem cell and organ transplantation, and immunosuppressive drugs used to treat cancer, autoimmune diseases, and transplant patients. These patients are at significant risk of life-threatening infections from invasive *endogenous infection* from bacterial or fungal flora of the oropharynx, skin, and gastrointestinal tract, acquisition of *exogenous infection* from infected persons, and reactivation of latent infections until immune function recovers (Table 120-1).

The infections seen in immunocompromised persons can often be predicted by which component of the immune system is abnormal, and the evaluation of fever in immunocompromised hosts differs. Episodes of fever and *neutropenia*, defined as an *absolute neutrophil count* of less than 500/mm³ neutrophils and bands, are especially common in cancer and transplant patients and increase risk for bacterial and fungal infections. The use of corticosteroids and potent immunosuppressive drugs that impair the activation of T lymphocytes increases the risk for pathogens normally controlled by T cell-mediated responses, such as *Pneumocystis jiroveci* and *Toxoplasma gondii*, and intracellular pathogens, such as *Salmonella*, *Listeria*, and *Mycobacterium*.

*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and coagulase-negative staphylococci are the most commonly identified bacterial pathogens in immunocompromised persons. Central indwelling catheters often are associated with infections caused by coagulase-negative staphylococci, *S. aureus*, gram-negative bacteria, *Enterococcus*, and *Candida*.

Fungal pathogens account for approximately 10% of all infections associated with childhood cancer. *Candida* causes 60% of all fungal infections, with *Aspergillus* as the second most common pathogen. Other risk factors for fungal infections include oropharyngeal and gastrointestinal mucositis.

### Table 120-1
Pathogens of Importance in Patients with Cancer (listed alphabetically)

<table>
<thead>
<tr>
<th>BACTERIA</th>
<th>FUNGI</th>
<th>PROTOZOA</th>
<th>VIRUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides fragilis</td>
<td>Aspergillus</td>
<td>Cryptosporidium parvum</td>
<td>Adenoviruses</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Blastoschizomyces capitatus</td>
<td>Cyclospora cayetanensis</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Candida spp.</td>
<td>Cystoisospora belli</td>
<td>Echoviruses</td>
</tr>
<tr>
<td>Clostridium septicum</td>
<td>Chrysosporium</td>
<td>Enterocytozoon bieneusi</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>Cryptococcus neoformans</td>
<td>Giardia lamblia</td>
<td>Hepatitis A virus</td>
</tr>
<tr>
<td>Comamonas acidivorans</td>
<td>Cunninghamella bertholletiae</td>
<td>Leishmania donovani</td>
<td>Herpes simplex viruses</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>Fusarium spp.</td>
<td>Septata intestinalis</td>
<td>Human herpes virus 6</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>Geotrichum candidum</td>
<td>Human metapneumovirus</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Malassezia furfur</td>
<td>Influenza viruses</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Mucor</td>
<td>Norovirus</td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>Pseudallescheria boydii</td>
<td>Parainfluenza viruses</td>
<td></td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Rhizopus</td>
<td>Parvovirus B19</td>
<td></td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>Scopulariopsis</td>
<td>Respiratory syncytial virus</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>Trichosporon beigeli</td>
<td>Varicella-zoster virus</td>
<td></td>
</tr>
<tr>
<td>Mycobacterium chelonae</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycobacterium haemophilum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocardia asteroides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediococcus acidilactici</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propionibacterium granulosum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas pseudomallei</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vibrio vulnificus</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
facilitating systemic fungal invasion, presence of long-term indwelling intravascular catheters, extreme prematurity, and broad-spectrum antibacterial therapy that promotes fungal colonization as a precursor to infection.

Infection with *T. gondii* represents reactivation of quiescent infection facilitated by cancer-associated or therapy-associated cellular immunodeficiency. *P. jiroveci* primarily causes pneumonitis in patients with leukemia, lymphoma, HIV or those on long-term corticosteroids, but can also cause extrapulmonary disease (sinusitis, otitis media).

Viral opportunistic infections in patients with cancer usually represent symptomatic reactivation from latency facilitated by cancer-associated or therapy-associated cellular immunodeficiency. Herpes simplex virus (HSV) can cause severe and prolonged mucocutaneous infection or disseminated disease. Cytomegalovirus (CMV) can cause focal disease in immunocompromised persons, especially in stem cell transplant patients. Manifestations of CMV disease include hepatitis, pneumonitis, esophagitis, encephalitis, and enteritis with gastrointestinal ulcerations. Reactivation of Epstein-Barr virus (EBV) is associated with posttransplant lymphoproliferative disorder. Varicella zoster virus (VZV) can cause serious primary infection in susceptible persons, often with accompanying encephalitis, hepatitis, or, most ominously, pneumonitis. Zoster also can reactivate during chemotherapy and may be disseminated.

**EPIDEMIOLOGY**

Chemotherapeutic agents target rapidly dividing cells, especially myeloproliferative cells, which cause myelosuppression. Children receiving allogeneic transplants are at greater risk for infection than children receiving autologous transplants. Prolonged time to hematologic engraftment is a significant risk factor for infection in these patients. Children receiving stem cell or organ transplants have significantly greater immunosuppression as a consequence of the myeloablative conditioning regimens. Foreign bodies (shunts, central venous catheters) interfere with cutaneous barriers against infection and together with neutropenia or immunosuppression increase the risk of bacterial or fungal infections (see Chapter 121).

The relative rate of infection in patients with cancer at admission or during hospitalization is 10% to 15%. The most frequently infected sites, in descending order, are the respiratory tract, the bloodstream, surgical wounds, and the urinary tract.

**CLINICAL MANIFESTATIONS**

Fever is the most common, and sometimes the only, presenting symptom of serious infection in cancer and transplant patients. The presence of fever with neutropenia, even in the absence of other signs or symptoms, demands prompt evaluation because of the potential for life-threatening infection. Despite being immunocompromised, these patients develop fever and some typical signs and symptoms associated with infections. All symptoms and signs should be evaluated thoroughly. However, some symptoms may be absent based on the underlying immunodeficiency. For example, in the absence of neutrophils to contain and induce localized signs of inflammation, determination of the source of infection by physical examination is often difficult. Chest findings may be absent, despite pneumonia, and revealed only by chest radiograph at presentation or when the neutrophil count recovers.

**LABORATORY TESTS AND IMAGING**

Assessing fever and neutropenia in immunocompromised persons requires blood cultures for bacterial and fungal pathogens obtained by peripheral venipuncture and from all lumens of any indwelling vascular catheters. A complete blood count with differential, C-reactive protein, complete chemistry panel, culture of urine and Gram staining/culture of potential sites of specific infection found during history and physical should be performed. Antigen tests, especially for serum cryptococcal antigen, should be considered. Chest radiographs are important to assess for the presence of pulmonary infiltrates. Specialized imaging studies, such as the CT or MRI, can be useful in selected cases, such as with suspected sinusitis or intra-abdominal infection, or to further delineate the location and extent of abnormalities seen on plain radiographs. Sinus infection with bacteria, *Aspergillus*, or *Zygomycetes* is common in neutropenic hosts and may be detected only on the CT scan.

**DIFFERENTIAL DIAGNOSIS**

Initially the patient should have a complete physical examination, including careful scrutiny of the oropharynx, nares, external auditory canals, skin and axilla, groin, perineum, and rectal area. The exit site and subcutaneous tunnel of any indwelling vascular catheter should be examined closely for erythema and palpated for tenderness and expression of purulent material. Perirectal abscess is a potentially serious infection in neutropenic hosts, with tenderness and erythema that may be the only clues to infection. Any presumptive infection identified during the evaluation should direct appropriate cultures and tailor anti-infective therapy.

**TREATMENT**

Treatment should be provided as appropriate for focal infections identified by physical examination or diagnostic imaging. Select low-risk patients may be managed as outpatients. Empirical treatment of fever and neutropenia without an identified source should include an extended-spectrum penicillin or cephalosporin with activity against gram-negative bacilli, including *P. aeruginosa*, sometimes in combination with an aminoglycoside (Fig. 120-1). If the patient has an indwelling vascular catheter, vancomycin should be added because of the increasing prevalence of methicillin-resistant *S. aureus* but can be discontinued if *S. aureus* is not cultured after 48 to 72 hours. Specific antibiotic regimens should be guided by local antibiotic resistance patterns at each institution.
If no microbiologic cause is isolated, empirical broad-spectrum antibiotics are continued as long as the patient remains neutropenic, regardless of whether the fever resolves (Fig. 120-2). Antibiotic therapy should be modified as indicated by new findings or if the patient's clinical status deteriorates. Further investigation for fungal infection and empirical treatment with amphotericin B or another antifungal agent is instituted in patients who have neutropenia and persistent fever without a focus, despite broad-spectrum antibacterial therapy for approximately 5 days (see Fig. 120-2).

The use of recombinant granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor...
Figure 120-2 Continuing management of possible infection after 7 days of fever without an identified source in cancer and transplant patients. (From Conrad DA: Patients with cancer. In Jenson HB, Baltimore RS editors: Pediatric Infectious Diseases: Principles and Practice, ed 2, Philadelphia, 2002, Saunders, p 1165.)
stimulates neutrophil production by the bone marrow, reduces the duration and severity of neutropenia, and decreases the risk of infection. Some chemotherapeutic protocols for the treatment of solid tumors that result in prolonged neutropenia incorporate hematopoietic cytokine therapy as part of the treatment protocol.

**PREVENTION**

Current guidelines discourage the use of broad-spectrum prophylactic antibiotics to prevent fever and neutropenia because of lack of efficacy and concerns about development of antibiotic resistance. Administration of trimethoprim-sulfamethoxazole to prevent *P. jiroveci* infection is routine for patients undergoing intensive chemotherapy or immunosuppression for transplantation. Prophylaxis generally is begun with initiation of anticancer therapy and continued until 6 months after chemotherapy has been completed. In select populations, such as patients undergoing hematopoietic stem cell transplantation, prophylactic antifungals such as fluconazole are beneficial.

Immunocompromised susceptible persons exposed to chickenpox within 2 days before the onset of rash until 5 days after the onset of rash in the index case should receive varicella zoster immune globulin (VZIG). Modified infection after VZIG may not result in protective immunity, and persons who receive VZIG prophylaxis should be considered still at risk with any subsequent exposures.

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### Table 121-1: Organisms Causing Catheter-Related Infections

<table>
<thead>
<tr>
<th>CLASSIFICATION OF PATHOGEN</th>
<th>COMMON</th>
<th>UNCOMMON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram-positive organisms</td>
<td>Coagulase-negative staphylococci, <em>Staphylococcus aureus</em>, <em>Enterococcus</em></td>
<td>Diphtheroids, <em>Bacillus</em>, <em>Micrococcus</em></td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td><em>Escherichia coli</em>, <em>Klebsiella</em>, <em>Pseudomonas aeruginosa</em></td>
<td><em>Acinetobacter</em>, <em>Enterobacter</em>, <em>Neisseria</em></td>
</tr>
<tr>
<td>Fungi</td>
<td><em>Candida albicans</em></td>
<td><em>Malassezia furfur</em>, <em>Candida parapsilosis</em>, <em>Candida glabrata</em>, <em>Candida tropicalis</em></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Nontuberculous mycobacteria</td>
<td></td>
</tr>
</tbody>
</table>
The treatment of catheter-related infection depends on the site of the infection and the pathogen involved. Catheters that are no longer necessary should be removed if infection is suspected. Catheter-associated bacteremia can be treated with simple catheter removal, removal plus antibiotics, or, in a stable patient, an attempt of antibiotic therapy alone (Fig. 121-1). Infection with organisms of low virulence may be manifested by fever alone, and removal of the catheter frequently is followed by prompt defervescence and complete resolution of infection. Empirical initial therapy for suspected infection should include antibiotics active against gram-negative organisms such as a broad-spectrum cephalosporin, and against *S. aureus* and coagulase-negative staphylococci such as oxacillin, nafcillin, or vancomycin. Antibiotic regimens should be tailored to the specific organism identified. Eradication of infection can be accomplished without removal of the central line in 89% of uncomplicated bactemic infections, 94% of exit site infections, and 25% of tunnel infections. If the patient is not critically ill and the pathogen is likely to be susceptible to antibiotic therapy, a trial of antibiotics is given through the infected catheter. The total duration of therapy depends on the pathogen and the duration of positive cultures and is usually 10 to 14 days after sterilization of the bloodstream. Catheter removal is indicated with sepsis, septic thrombophlebitis, clinical deterioration (despite appropriate therapy), persistently positive blood culture results after 48 to 72 hours of appropriate antimicrobial therapy, embolic lesions, or fungal infection because of poor response to antifungal therapy alone (see Fig. 121-1). Infection of the pocket around an implanted port is unlikely to respond to antibiotics, and removal of the foreign body is usually necessary.

**Antibiotic-lock** is a method of sterilizing intravascular catheters by using high concentrations of antibiotics infused into the portion of the catheter between the hub and the vessel entry. The solution is allowed to dwell within the catheter segment for several hours. It also may be useful for treatment of catheter-associated infections and for prevention of infection.

Aseptic technique is essential during catheter insertion. Catheters that are placed during emergency situations should be replaced as soon as medically feasible. Care of indwelling catheters involves meticulous attention to sterile technique whenever the system is entered. Care of the catheter entry site commonly involves a topical antibiotic or disinfectant. Catheters that are no longer necessary should be removed.

**VENTILATOR-ASSOCIATED PNEUMONIA**

Intubation of the airway provides direct access to the lungs and bypasses normal host defenses. Organisms enter the lungs directly through the lumen of the tube or by descending around the tube, which may result in ventilator-associated pneumonia. Contaminated respiratory equipment, humidification systems, or condensate introduces bacteria directly into lower airways. The continuously open upper airway increases the risk of aspiration of oropharyngeal flora and reflux of gastric contents and interferes with clearance of the airway by coughing because an effective cough requires a closed glottis. Suctioning of the upper respiratory tract or mouth requires clean technique but does not require aseptic technique. Suction catheters that reach the lower airways must be sterile and usually are designed for single use.

**URINARY CATHETERS**

The most important risk factors for urinary tract infections (UTIs) are the presence of catheters, instrumentation, and anatomic abnormalities (see Chapter 114). Organisms enter the bladder through the catheter by instillation of contaminated irrigation fluids, backflow of contaminated urine from the drainage bag, or ascent of bacteria around the meatus along the outside of the catheter. Indwelling catheters facilitate direct access to the bladder and should have a closed drainage system. After simple, straight catheterization, the incidence of UTI is 1% to 2%. Organisms that cause catheter-associated UTIs include fecal flora, such as gram-negative enteric bacilli, most commonly *Escherichia coli*, and *Enterococcus*. With concomitant antibiotic treatment, resistant organisms predominate, and fungi emerge as pathogens.

The most important aspect of prevention is to minimize the duration and use of catheterization. Intermittent

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**Figure 121-1** Management of central venous catheter infection. (From De Paw BE, Verweij PE: Infections in patients with hematologic malignancies. In Mandell GL, Bennett JE, Dolin R, editors: Principles and Practice of Infectious Diseases, ed 6, Philadelphia, 2005, Churchill Livingstone, Fig. 307-1, p 3434.)
catheterization is preferred over indwelling catheter drainage whenever feasible. Insertion of catheters must be performed with aseptic technique, and the drainage system must remain closed at all times, with sterile technique used whenever the system is entered. Drainage bags always should be dependent to avoid backflow of urine into the bladder.

**PERITONEAL DIALYSIS–ASSOCIATED INFECTIONS**

Indwelling catheters used for peritoneal dialysis may develop exit site infections, tunnel infections, or lead to peritonitis. The usual route of infection is from the skin surface along the tunnel and into the peritoneum. The most common pathogens are skin flora, including *Staphylococcus*; organisms that contaminate water, such as *Pseudomonas* and *Acinetobacter*; enteric flora, such as *E. coli* and *Klebsiella*; and fungi, such as *C. albicans*. Peritonitis may present with fever, vague abdominal pain, and cloudy dialysate. The diagnosis is established on clinical manifestations and confirmed by culture of the dialysate. Prevention of infection requires careful planning of the location of the exit site to minimize contamination, aseptic insertion of the catheter, meticulous care of the catheter site, securing of the catheter to avoid tension and motion, and aseptic technique during dialysis.

**CENTRAL NERVOUS SYSTEM SHUNTS**

Important risk factors of health care–associated central nervous system infections are surgery, ventriculoperitoneal shunts, and cerebrospinal fluid (CSF) leaks. Infection of ventriculoperitoneal shunts results from contamination of the system at the time of placement or from hematogenous seeding. Externalized ventricular drains and subdural bolts allow direct access of skin flora to the CSF. For these devices, the rates of infection increase with the duration of catheterization, especially beyond 5 days.

The most common pathogens causing shunt infections are coagulase-negative staphylococci and *S. aureus*. After skull fracture or cranial surgery, a CSF fistula leak may facilitate ascending infection from the nasopharynx, especially with *Streptococcus pneumoniae*, which frequently colonizes the nasopharynx. Patients with shunt infections may present with only fever and headache, or may present with typical signs and symptoms of meningitis (see Chapter 100). Infections caused by coagulase-negative staphylococci typically present with insidious onset of fever, malaise, headache, and vomiting. Empirical therapy is with vancomycin, with additional antibiotics if gram-negative bacteria are suspected.

Antibiotics frequently are used perioperatively during placement of shunts and other neurosurgical procedures. There is no proof that antibiotics decrease infection rates in these clean procedures. External ventricular drains should be maintained as closed systems with aseptic technique and removed as soon as possible. Drainage bags always should be dependent to avoid backflow.

**Zoonoses** are infections that are transmitted in nature between vertebrate animals and humans. Many zoonotic pathogens are maintained in nature by means of an *enzootic cycle*, in which mammalian hosts and arthropod vectors infect each other. Humans frequently are only incidentally infected. Of the more than 150 different human zoonotic diseases that have been described (Table 122-1), Lyme disease (*Borrelia burgdorferi*) accounts for 90% of reported vector-borne infections in the United States. Other common pathogens include *Rickettsia rickettsii* (Rocky Mountain spotted fever), *ehrlichiosis* (*Ehrlichia chaffeensis*), *West Nile virus*, and *anaplasmosis* (*Anaplasma phagocytophilum*). The epidemiology of zoonoses is related to the geographic distribution of the hosts and, if vector-borne, the distribution and seasonal life cycle of the vector.

Many zoonoses are spread by ticks including Lyme disease, Rocky Mountain spotted fever, *ehrlichiosis*, *tularemia*, *tick typhus*, and *babesiosis*. Mosquitoes transmit the arboviral encephalitides (see Chapter 101), *dengue fever*, *malaria*, and *yellow fever*. Preventive measures to avoid tick-borne and mosquito-borne diseases include using insect repellants that contain *DEET* (N,N-diethyl-m-toluamide) on skin and insect repellants that contain *permethrin* on clothing; avoiding tick-infested habitats (thick scrub oak, briar, poison ivy sites); avoiding excretory products of wild animals; wearing appropriate protective clothing (closed-toe shoes, long pants, etc.); and promptly removing ticks.

Ticks are best removed using blunt forceps or tweezers to grasp the tick as close to the skin as possible to pull the tick steadily outward. Squeezing, twisting, or crushing the tick should be avoided because the tick’s bloated abdomen can act like a syringe if squeezed. Transmission of infection seems to be most efficient after 30 to 36 hours of nymphal tick attachment for human granulocytic *ehrlichiosis*, after 36 to 48 hours for *B. burgdorferi*, and after 56 to 60 hours for *Babesia*. Prophylactic antimicrobial therapy after a tick bite or exposure is not recommended.

**LYME DISEASE (Borrelia burgdorferi)**

**Etiology**

Lyme disease is a tick-borne infection caused by the spirochete, *B. burgdorferi*. The vector in the eastern and midwestern United States is *Ixodes scapularis*, the black-legged tick that is commonly known as the *deer tick*. The vector on the Pacific Coast is *Ixodes pacificus*, the western black-legged tick. Ticks usually become infected by feeding on the white-footed mouse (*Peromyscus leucopus*), which is a natural reservoir for *B. burgdorferi*. The larvae are dormant over winter and emerge the following spring in the nymphal stage, the stage of the tick that is most likely to transmit the infection to humans.

**Epidemiology**

Over 20,000 cases are reported annually in the United States, with 96% of cases reported from New England, the eastern parts of the Middle Atlantic states, and the upper Midwest.
Early localized disease and early disseminated disease, including facial nerve palsy (or other cranial nerve palsy) and carditis with first-degree or second-degree heart block, is treated with doxycycline or amoxicillin for 14 to 21 days. Early disease with carditis with third-degree heart block or meningitis and late disease begins weeks to months after infection. Arthritis is the usual manifestation and may develop in 50% to 60% of untreated patients. The male to female ratio is 7:1. The knee is involved in greater than 90% of cases, but any joint may be affected. Symptoms may resolve over 1 to 2 weeks but often recur in other joints. If untreated most cases resolve, but chronic erosive arthritis persists in 10% of patients as the episodes increase in duration and severity. Cardiac abnormalities occur in approximately 10% of untreated patients. Neuroborreliosis, the late manifestations of Lyme disease involving the central nervous system (CNS), is rarely reported in children.

**Clinical Manifestations**

The geographic distribution of 24,364 confirmed cases of Lyme disease in the United States in 2011. The risk for acquiring Lyme disease varies by the distribution of *Ixodes scapularis* and *Ixodes pacificus*, the proportion of infected ticks for each species at each stage of the tick’s life cycle, and the presence of grassy or wooded locations favored by white-tailed deer. (From Centers for Disease Control and Prevention: Lyme Disease—United States, 2011, available from the CDC website: http://www.cdc.gov/lyme/stats/maps/map2011.html.)

(Fig. 122-1). In Europe most cases occur in Scandinavian countries and central Europe. Because exposure to ticks is more common in warm months, Lyme disease is noted predominantly in summer. The incidence is highest among children 5 to 10 years old, at almost twice the incidence among adolescents and adults.

**Decision-Making Algorithms**

| Arthritis | Fever and Rash |

| **Arthritis** | **Fever and Rash** |

The clinical manifestations are divided into early and late stages. Early infection may be localized or disseminated. **Early localized disease** develops 7 to 14 days after a tick bite as the site forms an erythematous papule that expands to form a red, raised border, often with central clearing. The lesion, *erythema migrans*, harbors *B. burgdorferi* and may be 15 cm wide, pruritic, or painful. Systemic manifestations may include malaise, lethargy, fever, headache, arthralgias, stiff neck, myalgias, and lymphadenopathy. The skin lesions and early manifestations resolve without treatment over 2 to 4 weeks. Not all patients with Lyme disease recall a tick bite or develop erythema migrans.

Approximately 20% of patients develop **early disseminated disease** with multiple secondary skin lesions, aseptic meningitis, pseudotumor, papilledema, cranioneuropathies including Bell palsy, polyradiculitis, peripheral neuropathy, mononeuritis multiplex, or transverse myelitis. Carditis with various degrees of heart block rarely may develop during this stage. Neurologic manifestations usually resolve by 3 months but may recur or become chronic.

**Laboratory and Imaging Studies**

Antibody tests during early, localized Lyme disease may be negative and are not useful. The diagnosis of late disease is confirmed by serologic tests specific for *B. burgdorferi*. The sensitivity and specificity of serologic tests for Lyme disease vary substantially. A positive enzyme-linked immunosorbent assay or immunofluorescence assay result must be confirmed by immunoblot showing antibodies against at least either two to three (for IgM) or five (for IgG) proteins of *B. burgdorferi* (at least one of which is one of the more specific, low-molecular-weight, outer-surface proteins).

In late disease, the erythrocyte sedimentation rate is elevated and complement may be reduced. The joint fluid shows an inflammatory response with total white blood cell count of 25,000 to 125,000 cells/mm³, often with a polymorphonuclear predominance (see Table 118-2). The rheumatoid factor and antinuclear antibody are negative, but the Venereal Disease Research Laboratory test may be falsely positive. With CNS involvement, the cerebrospinal fluid shows a lymphocytic pleocytosis with normal glucose and slightly elevated protein.

**Differential Diagnosis**

A history of a tick bite and the classic rash is helpful but is not always present. *Erythema migrans* of early, localized disease may be confused with nummular eczema, tinea corporis, granuloma annulare, an insect bite, or cellulitis. **Southern tick-associated rash illness**, which is similar to erythema migrans, occurs in southeastern and south central states and is associated with the bite of *Amblyomma americanum*, the lone star tick, and infection with *Borrelia lonestari*.

During early, disseminated Lyme disease, multiple lesions may appear as erythema multiforme or urticaria. The aseptic meningitis is similar to viral meningitis, and the seventh nerve palsy is indistinguishable from herpetic or idiopathic Bell palsy. Lyme carditis is similar to viral myocarditis. Monarticular or pauciartricular arthritis of late Lyme disease may mimic suppurative arthritis, juvenile idiopathic arthritis, or rheumatic fever (see Chapter 89). The differential diagnosis of neuroborreliosis includes degenerative neurologic illness, encephalitis, and depression.

**Treatment**

Early localized disease and early disseminated disease, including facial nerve palsy (or other cranial nerve palsy) and carditis with first-degree or second-degree heart block, is treated with doxycycline or amoxicillin for 14 to 21 days. Early disease with carditis with third-degree heart block or meningitis and
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<th>CAUSATIVE AGENT</th>
<th>COMMON ANIMAL RESERVOIRS</th>
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<tr>
<td>Anthrax</td>
<td><em>Bacillus anthracis</em></td>
<td>Cattle, goats, sheep, swine, cats, wild animals</td>
<td>Aerosol inhalation of spores in hides and other animal by-products, direct contact</td>
<td>Worldwide; rare in United States</td>
</tr>
<tr>
<td>Brucellosis</td>
<td><em>Brucella</em></td>
<td>Cattle, sheep, goats, swine, horses, dogs</td>
<td>Aerosol inhalation, direct contact, ingestion of contaminated goat cheese and milk</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Campylobacteriosis</td>
<td><em>Campylobacter jejuni</em></td>
<td>Rodents, dogs (puppies), cats, fowl (chickens), swine</td>
<td>Direct contact, ingestion of contaminated food or water</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Cat-scratch disease</td>
<td><em>Bartonella henselae</em></td>
<td>Cats, dogs</td>
<td>Bites and scratches</td>
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</tr>
<tr>
<td>Erysipeloid</td>
<td><em>Erysipelothrix rhusiopathiae</em></td>
<td>Sheep, swine, turkeys, ducks, fish</td>
<td>Direct contact</td>
<td>Worldwide</td>
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<tr>
<td>Listeriosis</td>
<td><em>Listeria monocytogenes</em></td>
<td>Cattle, fowl, goats, sheep</td>
<td>Ingestion of contaminated food, unpasteurized cheese and dairy products</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Plague</td>
<td><em>Yersinia pestis</em></td>
<td>Wild and domestic rodents, cats, dogs</td>
<td>Direct contact, flea bite</td>
<td>New Mexico, Arizona, Utah, Colorado, California</td>
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<tr>
<td>Rat-bite fever (bacillary fever)</td>
<td><em>Streptobacillus moniliformis</em></td>
<td>Mice, rats, hamsters</td>
<td>Bites, ingestion of contaminated food or water</td>
<td>Japan, Asia; rare in United States</td>
</tr>
<tr>
<td>Salmonellosis</td>
<td><em>Nontyphoidal Salmonella</em></td>
<td>Fowl, dogs, cats, reptiles, amphibians</td>
<td>Direct contact, ingestion of contaminated food or water</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Tularemia</td>
<td><em>Francisella tularensis</em></td>
<td>Rabbits, squirrels, dogs, cats</td>
<td>Aerosol inhalation, direct contact, ingestion of contaminated meat, tick bite, deerfly bite</td>
<td>California, Utah, Arkansas, Oklahoma</td>
</tr>
<tr>
<td>Yersiniosis</td>
<td><em>Yersinia enterocolitica</em>, <em>Yersinia pseudotuberculosis</em></td>
<td>Rodents, cattle, goats, sheep, swine, fowl, dogs</td>
<td>Direct contact, ingestion of contaminated food or water</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Wound infection, bacteremia</td>
<td><em>Pasteurella multocida, Capnocytophaga canimorsus</em></td>
<td>Cats, dogs, rodents</td>
<td>Direct contact, bites and scratches</td>
<td>Worldwide</td>
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<tr>
<td>Mycobacterial Diseases</td>
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<tr>
<td>Wound infection</td>
<td><em>Mycobacterium marinum, Mycobacterium fortuitum, Mycobacterium kansasi</em></td>
<td>Fish, aquarium</td>
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<td>Worldwide</td>
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<td>Spirochetal Diseases</td>
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<tr>
<td>Leptospirosis</td>
<td><em>Leptospira interrogans</em></td>
<td>Dogs, rodents, livestock</td>
<td>Direct contact, contact with water or soil contaminated by urine of infected animals</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Lyme disease</td>
<td><em>Borrelia burgdorferi</em></td>
<td>Deer, rodents</td>
<td>Tick bite (<em>Ixodes scapularis, Ixodes pacificus</em>)</td>
<td>Northeast and Midwest United States, California</td>
</tr>
<tr>
<td>Rat-bite fever (Haverhill fever)</td>
<td><em>Spirillum minus</em></td>
<td>Mice, rats, hamsters</td>
<td>Bites, ingestion of contaminated food or water</td>
<td>Japan, Asia; rare in United States</td>
</tr>
<tr>
<td>Relapsing fever</td>
<td><em>Borrelia</em></td>
<td>Rodents, fleas</td>
<td>Louse bite, flea bite, transplacental transmission</td>
<td>Western and southern United States</td>
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<tr>
<td>Southern tick- associated rash illness</td>
<td><em>Borrelia lonestari</em></td>
<td>Deer, rodents</td>
<td>Tick bite (<em>I. scapularis</em>)</td>
<td>Southeastern and south-central U.S.</td>
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<tr>
<td>Disease</td>
<td>Causative Agent</td>
<td>Common Animal Reservoirs</td>
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<tr>
<td><strong>Rickettsial Diseases</strong></td>
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<tr>
<td>Spotted Fever Group</td>
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</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
<td>Rickettsia rickettsii</td>
<td>Dogs, rodents</td>
<td>Tick bite (Dermacentor variabilis, the American dog tick; Dermacentor andersoni, the wood tick; Rhipicephalus sanguineus, the brown dog tick; Amblyomma cajennense)</td>
<td>Western hemisphere</td>
</tr>
<tr>
<td>Mediterranean spotted fever (boutonneuse fever)</td>
<td>Rickettsia conorii</td>
<td>Dogs, rodents</td>
<td>Tick bite</td>
<td>Africa, Mediterranean region, India, Middle East</td>
</tr>
<tr>
<td>African tick-bite fever</td>
<td>Rickettsia africæ</td>
<td>Cattle, goats (?)</td>
<td>Tick bite</td>
<td>Sub-Saharan Africa, Caribbean</td>
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<tr>
<td>Rickettsialpox</td>
<td>Rickettsia akari</td>
<td>Mice</td>
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<tr>
<td>Murine typhus–like illness</td>
<td>Rickettsia felis</td>
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<tr>
<td>Typhus Group</td>
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<td></td>
</tr>
<tr>
<td>Murine typhus</td>
<td>Rickettsia typhi</td>
<td>Rats</td>
<td>Rat flea or cat flea feces</td>
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</tr>
<tr>
<td>Epidemic typhus</td>
<td>Rickettsia prowazekii</td>
<td>Humans</td>
<td>Louse feces</td>
<td>Africa, South America, Central America, México, Asia</td>
</tr>
<tr>
<td>Brill-Zinsser disease (recrudescent typhus)</td>
<td>R. prowazekii</td>
<td>Humans</td>
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</tr>
<tr>
<td>Flying squirrel (sylvatic typhus)</td>
<td>R. prowazekii</td>
<td>Flying squirrels</td>
<td>Lice or fleas of flying squirrel</td>
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<tr>
<td><strong>Scrub Typhus</strong></td>
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<tr>
<td>Scrub typhus</td>
<td>Orientia tsutsugamushi</td>
<td>Rodents (?)</td>
<td>Chigger bite</td>
<td>Southern Asia, Japan, Indonesia, Australia, Korea, Asiatic Russia, India, China</td>
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<tr>
<td><strong>Ehrlichiosis and Anaplasmosis</strong></td>
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<tr>
<td>Human monocytic ehrlichiosis</td>
<td>Ehrlichia chaffeensis</td>
<td>Deer, dogs</td>
<td>Tick bite (Amblyomma americanum)</td>
<td>United States, Europe, Africa</td>
</tr>
<tr>
<td>Anaplasmosis (human granulocytic ehrlichiosis)</td>
<td>Anaplasma phagocytophilum</td>
<td>Rodents, deer, ruminants</td>
<td>Tick bite (I. scapularis)</td>
<td>United States, Europe</td>
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<tr>
<td>Ehrlichiosis ewingii</td>
<td>Ehrlichia ewingii</td>
<td>Dogs</td>
<td>Tick bite</td>
<td>United States</td>
</tr>
<tr>
<td>Sennetsu ehrlichiosis</td>
<td>Neorickettsia sennetsu</td>
<td>Unknown</td>
<td>Ingestion of helminth-contaminated fish (?)</td>
<td>Japan, Malaysia</td>
</tr>
<tr>
<td><strong>Q Fever</strong></td>
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<tr>
<td>Q fever</td>
<td>Coxiella burnetii</td>
<td>Cattle, sheep, goats, cats, rabbits</td>
<td>Inhalation of infected aerosols, ingestion of contaminated dairy products, ticks (?)</td>
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<tr>
<td><strong>Viral Diseases</strong></td>
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<td>Colorado tick fever</td>
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<td>Humans</td>
<td>Mosquito bite (Aedes aegypti, Aedes albopictus)</td>
<td>Tropical areas of the Caribbean, the Americas, and Asia</td>
</tr>
</tbody>
</table>

Continued
late neurologic disease (other than facial nerve or other cranial nerve palsy) are treated with intravenous or intramuscular ceftriaxone or intravenous penicillin G for 14 to 28 days. Arthritis is treated with doxycycline (for children >9 years of age) or amoxicillin for 28 days. If there is recurrence, treatment should be with a repeated oral regimen or with the regimen for late neurologic disease.

Complications and Prognosis

Carditis, especially conduction disturbances, and arthritis are the major complications of Lyme disease. Even untreated, most cases eventually resolve without sequelae. Lyme disease is readily treatable and curable. The long-term prognosis is excellent for early and late disease. Early treatment may prevent progression to carditis and meningitis. Recurrences of arthritis are rare after recommended treatment. A community-based study of children with Lyme disease found no evidence of impairment 4 to 11 years later.

Prevention

Measures to minimize exposure to tick-borne diseases are the most reasonable means of preventing Lyme disease. Postexposure prophylaxis is not routinely recommended because the overall risk of acquiring Lyme disease after a tick bite is only 1% to 2% even in endemic areas, and treatment of the infection, if it develops, is highly effective. Nymphal stage ticks must feed for 36 to 48 hours, and adult ticks must feed for 48 to 72 hours before the risk of transmission of *B. burgdorferi* from infected ticks becomes substantial. In hyperendemic regions, prophylaxis of adults with doxycycline, 200 mg as a single dose, within 72 hours of a nymphal tick bite is effective in preventing Lyme disease.

<table>
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<tr>
<th>Disease</th>
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<td>Hantavirus</td>
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<td>Herpesvirus B</td>
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<td>Africa, Asia (and primate centers worldwide)</td>
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<tr>
<td>Lymphocytic choriomeningitis</td>
<td>Lymphocytic choriomeningitis virus</td>
<td>Rodents, hamsters, mice</td>
<td>Aerosol inhalation, direct contact, bite</td>
<td>Worldwide</td>
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<tr>
<td>Rabies</td>
<td>Rabies virus</td>
<td>Dogs, skunks, bats, raccoons, foxes, cats</td>
<td>Bites and scratches</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Vesicular stomatitis</td>
<td>Vesicular stomatitis virus</td>
<td>Horses, cattle, swine</td>
<td>Direct contact</td>
<td>Americas</td>
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</tbody>
</table>

Protozoan Diseases

African trypanosomiasis

East African sleeping sickness | *Trypanosoma brucei rhodesiense* | Wild and domestic animals | Insect bite (tsetse fly) | East Africa |

West African sleeping sickness | *Trypanosoma brucei gambiense* | Wild and domestic animals | Insect bite (tsetse fly) | West Africa |

American trypanosomiasis (Chagas disease) | *Trypanosoma cruzi* | Wild and domestic animals | Insect bite (reduviid bug); contact with fecal material of reduviid bug | South America, Central America, South Texas |

Babesiosis | *Babesia* | Cattle, wild and domestic rodents | Tick bite (*I. scapularis*), blood transfusion | Worldwide |

Leishmaniasis, mucocutaneous and cutaneous | *Leishmania* | Domestic and wild dogs | Sandfly bite | Tropics |

Leishmaniasis, visceral | *Leishmania donovani* complex | Domestic and wild dogs | Sandfly bite | Tropics |

Malaria | *Plasmodium* | Humans | Mosquito bite (*Anopheles*) | Usually imported to the United States, Southern California |

Toxoplasmosis | *Toxoplasma gondii* | Cats, livestock, pigs | Ingestion of oocysts in fecally contaminated material or ingestion of tissue cysts in undercooked meat | Worldwide |


*Many helminths are also zoonotic (see Tables 123-4 and 123-5).*
ROCKY MOUNTAIN SPOTTED FEVER (RICKETTSIA RICKETTSII)

Etiology

The cause of Rocky Mountain spotted fever is *R. rickettsii*, gram-negative coccobacillary organisms that resemble bacteria but have incomplete cell walls and require an intracellular site for replication. The organism invades and proliferates within the endothelial cells of blood vessels, causing vasculitis and resulting in increased vascular permeability, edema, and, eventually, decreased vascular volume, altered tissue perfusion, and widespread organ failure. Many tick species are capable of transmitting *R. rickettsii*. The principal ticks are the American dog tick (*Dermacentor variabilis*) in the eastern United States and Canada, the wood tick (*Dermacentor andersoni*) in the western United States and Canada, the brown dog tick (*Rhipicephalus sanguineus*) in Mexico, and *Amblyomma cajennense* in Central and South America.

Epidemiology

Rocky Mountain spotted fever is the most common rickettsial illness in the United States, occurring primarily in the eastern coastal, southeastern, and western states. Most cases occur from May to October after outdoor activity in wooded areas, with peak incidence among children 1 to 14 years of age. Approximately 40% of infected persons are unable to recall a tick bite.

Clinical Manifestations

The incubation period of Rocky Mountain spotted fever is 2 to 14 days, with an average of 7 days. The onset is nonspecific with headache, malaise, and fever. A pale, rose-red macular or maculopapular rash appears in 90% of the cases. The rash begins peripherally and spreads to involve the entire body, including palms and soles. The early rash blanches on pressure and is accentuated by warmth. It progresses over hours or days to a petechial and purpuric eruption that appears first on the feet and ankles, then the wrists and hands, and progresses centrifugally to the trunk and head. Myalgias, especially of the lower extremities, and intractable headaches are common. Severe cases progress with splenomegaly, myocarditis, renal impairment, pneumonitis, and shock.

Laboratory and Imaging Studies

Thrombocytopenia (usually <100,000 cells/mm³), anemia, hyponatremia, and elevated hepatic transaminase levels are common laboratory findings. Organisms can be detected in skin biopsy specimens by fluorescent antibodies or polymerase chain reaction, although this test is not widely available. Serologic testing is used to confirm the diagnosis, although treatment is begun before confirmation.

Differential Diagnosis

The differential diagnosis includes meningococcemia, bacterial sepsis, toxic shock syndrome, leptospirosis, ehrlichiosis, measles, enteroviruses, infectious mononucleosis, collagen vascular diseases, Henoch-Schönlein purpura, and idiopathic thrombocytopenic purpura. The diagnosis of Rocky Mountain spotted fever should be suspected with fever and petechial rash, especially with a history of a tick bite or outdoor activities during spring and summer in endemic regions. Fever, headache, and myalgias lasting more than 1 week in patients in endemic areas indicate Rocky Mountain spotted fever. Delayed diagnosis and late treatment usually result from atypical initial symptoms and late appearance of the rash.

Treatment

Therapy for suspected Rocky Mountain spotted fever should not be postponed pending results of diagnostic tests. Doxycycline is the drug of choice, even for young children, despite the theoretical risk of dental staining in children younger than 9 years of age. Fluoroquinolones also are active against *R. rickettsii* and may be an alternative treatment.

Complications and Prognosis

In severe infections, capillary leakage results in noncardiogenic pulmonary edema (acute respiratory distress syndrome), hypotension, disseminated intravascular coagulation, circulatory collapse, and multiple organ failure, including encephalitis, myocarditis, hepatitis, and renal failure.

Untreated illness may persist for 3 weeks before progressing to multisystem involvement. The mortality rate is 25% without treatment, which is reduced to 3.4% with treatment. Permanent sequelae are common after severe disease.

Prevention

Preventive measures to avoid tick-borne infections and careful removal of ticks are recommended.

EHRLICHIOSIS (EHRLICHI A CHAFFEENSIS) AND ANAPLASMOSIS (ANAPLASMA PHAGOCYTOPHILUM)

Etiology

The term *ehrlichiosis* often is used to refer to all forms of infection with *Ehrlichia*. Human monocytic *ehrlichiosis* is caused by *E. chaffeensis*, which infects predominantly mononcytic cells and is transmitted by the tick *A. americanum*. Disease may also be caused by *Ehrlichia ewingii*. Human *anaplasmosis* is caused by *A. phagocytophilum* and is transmitted by the tick *I. scapularis*.

Epidemiology

Ehrlichiosis occurs commonly in the United States. Human monocytic *ehrlichiosis* occurs in broad areas across the southeastern, south central, and Mid-Atlantic United States in a distribution that parallels that of Rocky Mountain spotted fever. *Anaplasmosis* is found mostly in the northeastern and upper midwestern United States, but infections have now been identified in northern California, the Mid-Atlantic states, and broadly across Europe.
Clinical Manifestations
Human monocytic ehrlichiosis, anaplasmosis, and *Ehrlichiosis ewingii* cause similar acute febrile illness characterized by fever, malaise, headache, myalgias, anorexia, and nausea, but often without a rash. In contrast to adult patients, nearly two thirds of children with human monocytic ehrlichiosis present with a macular or maculopapular rash, although petechial lesions may occur. Symptoms usually last for 4 to 12 days.

Laboratory and Imaging Studies
Characteristic laboratory findings include leukopenia, lymphocytopenia, thrombocytopenia, anemia, and elevated hepatic transaminases. Morulae are found infrequently in circulating monocytes of persons with human monocytic ehrlichiosis but are found in 40% of circulating neutrophils in 20% to 60% of persons with anaplasmosis (Fig. 122-2). Seroconversion or fourfold rise in antibody titer confirms the diagnosis.

Differential Diagnosis
Ehrlichiosis is clinically similar to other arthropod-borne infections, including Rocky Mountain spotted fever, tularemia, babesiosis, early Lyme disease, murine typhus, relapsing fever, and Colorado tick fever. The differential diagnosis also includes infectious mononucleosis, Kawasaki disease, endocarditis, viral infections, hepatitis, leptospirosis, Q fever, collagen vascular diseases, and leukemia.

Complications and Prognosis
Severe pulmonary involvement with acute respiratory distress syndrome has been reported in several cases. Other reported severe complications include meningoencephalitis and myocarditis. Most patients improve within 48 hours.

Prevention
Preventive measures to avoid tick-borne infections and careful removal of ticks are recommended.

PARASITIC DISEASES

Protozoal Diseases
Protozoa are the simplest organisms of the animal kingdom. They are unicellular. Most are free living, but some have a commensal or parasitic existence. Protozoal diseases include malaria, toxoplasmosis, babesiosis, and the intestinal protozoal diseases, amebiasis, cryptosporidiosis, and giardiasis.

Malaria
Etiology
Malaria is caused by obligate intracellular protozoa of the genus *Plasmodium*, including *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax*, and *P. knowlesi*. *Plasmodium* has a complex life cycle that enables survival in different cellular environments in the human host and in the mosquito vector. There are two major phases in the life cycle, an *asexual phase* (*schizogony*) in humans and a *sexual phase* (*sporogony*) in mosquitoes. The *erythrocytic phase* of *Plasmodium* asexual development begins when the merozoites released from exoerythrocytic schizonts in the liver penetrate erythrocytes. When inside the erythrocyte, the parasite transforms into the *ring form*, which enlarges to become a *trophozoite*. These latter two forms can be identified with Giemsa stain on blood smear, which is the primary means of confirming the diagnosis of malaria.

The parasites usually are transmitted to humans by female *Anopheles* mosquitoes. Malaria also can be transmitted through blood transfusion via contaminated needles and transplacentally to a fetus.

Epidemiology
Malaria is a worldwide problem with transmission in more than 100 countries with a combined population of more than 1.6 billion people. Malaria is an important cause of fever and morbidity in the tropical world. The principal areas of transmission are sub-Saharan Africa, southern Asia, Southeast Asia, Mexico, Haiti, the Dominican Republic, Central and South America, Papua New Guinea, and the Solomon Islands. Approximately 1000 to 2000 imported cases are recognized annually in the United States, with most cases occurring among infected foreign civilians from endemic areas who travel to the United States and among U.S. citizens who travel to endemic areas without appropriate chemoprophylaxis.
Clinical Manifestations

The clinical manifestations of malaria range from asymptomatic infection to fulminant illness and death, depending on the virulence of the infecting malaria species and the host immune response. The incubation period ranges from 6 to 30 days, depending on the Plasmodium species (Table 123-1). The most characteristic clinical feature of malaria, which is seldom noted with other infectious diseases, is febrile paroxysms alternating with periods of fatigue but otherwise relative wellness. The classic symptoms of the febrile paroxysms of malaria include high fever, rigors, sweats, and headache. Paroxysms coincide with the rupture of schizonts that occur every 48 hours with P. vivax and P. ovale (tertian periodicity) and every 72 hours with P. malariae (quartan periodicity).

Short-term relapse describes the recurrence of symptoms after a primary attack that is due to the survival of erythrocyte forms in the bloodstream. Long-term relapse describes the renewal of symptoms long after the primary attack, usually due to the release of merozoites from an exoerythrocytic source in the liver. Long-term relapse occurs with P. vivax and P. ovale because of persistence in the liver and with P. malariae because of persistence in the erythrocyte.

Laboratory and Imaging Studies

The diagnosis of malaria is established by the identification of organisms on stained smears of peripheral blood. In nonimmune persons, symptoms typically occur 1 to 2 days before parasites are detectable on blood smear. Although P. falciparum is most likely to be identified from blood during a febrile paroxysm, the timing of the smears is less important than obtaining smears several times each day over 3 successive days. Both thick and thin blood smears should be examined. The concentration of erythrocytes on a thick smear is approximately 20 to 40 times greater than that on a thin smear. Thick smears are used to scan large numbers of erythrocytes quickly. Thin smears allow for positive identification of the malaria species and determination of the percentage of infected erythrocytes, which also is useful in following the response to therapy. Rapid diagnostic tests may emerge as point of care tests in the near future.

Differential Diagnosis

The most important aspect of diagnosing malaria in children is to consider the possibility of malaria in any child who has fever, chills, splenomegaly, anemia, or decreased level of consciousness with a history of recent travel or residence in an endemic area, regardless of the use of chemoprophylaxis. The differential diagnosis is broad and includes many infectious diseases, such as typhoid fever, tuberculosis, brucellosis, relapsing fever, infective endocarditis, influenza, poliomyelitis, yellow fever, trypanosomiasis, kala-azar, and amebic liver abscess.

Table 123-1 Characteristics of Plasmodium Species Causing Malaria

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>P. FALCIPARUM</th>
<th>P. VIVAX</th>
<th>P. OVALE</th>
<th>P. MALARIAE</th>
<th>P. KNOWLESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exoerythrocytic cycle</td>
<td>5.5–7 days</td>
<td>6–8 days</td>
<td>9 days</td>
<td>12–16 days</td>
<td>8-9 days</td>
</tr>
<tr>
<td>Erythrocytic cycle</td>
<td>48 hours</td>
<td>42–48 hours</td>
<td>49–50 hours</td>
<td>72 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Usual incubation period (range)</td>
<td>12 days (9–14 days)</td>
<td>13 days (12–17 days; may be longer)</td>
<td>17 days (16–18 days; may be longer)</td>
<td>28 days (18–40 days; may be longer)</td>
<td>~12 days</td>
</tr>
<tr>
<td>Erythrocyte preference</td>
<td>Young erythrocytes, but can infect all</td>
<td>Reticulocytes</td>
<td>Reticulocytes</td>
<td>Older erythrocytes</td>
<td>Older erythrocytes</td>
</tr>
<tr>
<td>Usual parasite load (% erythrocytes infected)</td>
<td>≥1–5</td>
<td>1–2</td>
<td>1–2</td>
<td>1–2</td>
<td>Variable</td>
</tr>
<tr>
<td>Secondary exoerythrocytic cycle (hypnozoites) and relapses</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Duration of untreated infection</td>
<td>1–2 years</td>
<td>1.5–4 years (includes liver stage)</td>
<td>1.5–4 years (includes liver stage)</td>
<td>3–50 years</td>
<td>Unknown</td>
</tr>
<tr>
<td>Severity of primary attack</td>
<td>Severe in nonimmune forms; subpatent patients—a medical emergency—failure to recognize and treat can lead to death</td>
<td>Mild to severe—danger of splenic rupture, relapse related to persistence of latent exoerythrocytic forms</td>
<td>Mild—danger of splenic rupture, relapse related to persistence of latent exoerythrocytic forms</td>
<td>Can be chronic in subclinical and subpatent forms; can cause nephritis in children</td>
<td>Variable, can be fatal</td>
</tr>
<tr>
<td>Usual periodicity of febrile attacks</td>
<td>None</td>
<td>48 hours</td>
<td>48 hours</td>
<td>72 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Duration of febrile paroxysm</td>
<td>16–36 hours (may be longer)</td>
<td>8–12 hours</td>
<td>8–12 hours</td>
<td>8–10 hours</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Treatment
Oral chloroquine is the recommended treatment except for chloroquine-resistant \textit{P. falciparum}. Either atovaquone-proguanil (Malarone) or artemether-lumefantrine (Coartem) is an appropriate first-line therapy for malaria acquired in areas of chloroquine resistance. Specific treatment should be guided by where the patient acquired the infection and the local resistance patterns. Patients with malaria usually require hospitalization and may require intensive care unit admission. Quinidine gluconate is the only drug available in the United States that is used for parenteral treatment.

Complications and Prognosis
Cerebral malaria is a complication of \textit{P. falciparum} infection and a frequent cause of death (20% to 40% of cases), especially among children and nonimmune adults. Similar to other complications, cerebral malaria is more likely to occur among patients with intense parasitemia (>5%). Other complications include splenic rupture, renal failure, severe hemolysis (blackwater fever), pulmonary edema, hypoglycemia, thrombocytopenia, and \textit{algid malaria} (sepsis syndrome with vascular collapse).

Death may occur with any of the malarial species but is most frequent with complicated \textit{P. falciparum} malaria. The likelihood of death is increased in children with preexisting health problems, such as measles, intestinal parasites, schistosomiasis, anemia, and malnutrition. Death is much more common in developing countries.

Prevention
There are two components of malaria prevention: reduction of exposure to infected mosquitoes and chemoprophylaxis. Mosquito protection is necessary because no prophylactic regimen can guarantee protection in every instance due to the widespread development of resistant organisms.

Chemoprophylaxis is necessary for all visitors to and residents of the tropics who have not lived there since infancy. Children of nonimmune women should have chemoprophylaxis from birth. Children of women from endemic areas have passive immunity until 3 to 6 months of age, after which they are increasingly likely to acquire malaria. Specific chemoprophylaxis should be guided by the distribution of resistance pattern and determined before making specific recommendations (http://www.cdc.gov/malaria/travelers/country_table/a.html). Mefloquine, doxycycline, chloroquine, and Malarone are commonly prescribed medications.

Toxoplasmosis

Toxoplasmosis is a zoonosis caused by \textit{Toxoplasma gondii}, an intracellular protozoan parasite. Infection is acquired by infectious oocysts, such as those excreted by newly infected cats, which play an important role in amplifying the organism in nature, or from ingesting cysts in contaminated, undercooked meat. Less commonly, transmission occurs transplacentally during acute infection of pregnant women. In the United States, the incidence of congenital infection is 1 to 2 per 1000 live births.

Acquired toxoplasmosis is usually asymptomatic. Symptomatic infection is typically a heterophile-negative mononucleosis syndrome that includes lymphadenopathy, fever, and hepatosplenomegaly. Disseminated infection, including myocarditis, pneumonia, and central nervous system (CNS) toxoplasmosis, is more common among immunocompromised persons, especially persons with acquired immunodeficiency syndrome (AIDS). Among women infected during pregnancy, 40% to 60% give birth to an infected infant. The later in pregnancy that infection occurs, the more likely it is that the fetus will be infected, but the less severe the illness (see Chapter 66). Serologic diagnosis can be established by a fourfold increase in antibody titer or seroconversion, a positive IgM antibody titer, or positive polymerase chain reaction for \textit{T. gondii} in peripheral white blood cells, cerebrospinal fluid (CSF), serum, or amniotic fluid.

Treatment includes pyrimethamine and sulfadiazine, which act synergistically against \textit{Toxoplasma}. Because these compounds are folic acid inhibitors, they are used in conjunction with folic acid. Spiramycin, which is not licensed in the United States, also is used in therapy of pregnant women with toxoplasmosis. Corticosteroids are reserved for patients with acute CNS or ocular infection.

Ingesting only well-cooked meat and avoiding cats or soil in areas where cats defecate are prudent measures for pregnant or immunocompromised persons. Administration of spiramycin to infected pregnant women has been associated with lower risks of congenital infection in their offspring.

HELMINTHIASES
Helminths are divided into three groups: roundworms, or nematodes, and two groups of flatworms, the trematodes (flukes) and the cestodes (tapeworms).

Hookworm Infections
Hookworm infection is caused by several species of hookworms, with \textit{Ancylostoma duodenale} and \textit{Necator americanus} being the most important (Table 123-2). There are more than 9 million humans worldwide infected with hookworms. \textit{Ancylostoma duodenale} is the predominant species in Europe, the Mediterranean region, northern Asia, and the west coast of South America. \textit{N. americanus} predominates in the Western hemisphere, sub-Saharan Africa, Southeast Asia, and the Pacific Islands. Optimal soil conditions and fecal contamination are found in many agrarian tropical countries and in the southeastern United States. Infection typically occurs in young children, especially during the first decade of life. The larvae are found in warm, damp soil and infect humans by penetrating the skin. They migrate to the lungs, ascend the trachea, are swallowed, and reside in the intestine. The worms mature and attach to the intestinal wall, where they suck blood and shed eggs.
Infections are usually asymptomatic. Intense pruritus (ground itch) occurs at the site of larval penetration, usually the soles of the feet or between the toes, and may include papules and vesicles. Migration of larvae through the lungs usually is asymptomatic. Symptoms of abdominal pain, anorexia, indigestion, fullness, and diarrhea occur with hookworm infestation. The major manifestation of infection is anemia. Examination of fresh stool for hook worm eggs is diagnostic. Therapy includes anthelmintic treatment with albendazole, mebendazole, or pyrantel pamoate and treatment for anemia. Eradication depends on sanitation of the patient’s environment and chemotherapy.

**Ascariasis**

Ascariasis is caused by *Ascaris lumbricoides*, a large nematode. It is the most prevalent helminthiasis, affecting 1 billion people (see Table 123-2). After humans ingest the eggs, larvae are released and penetrate the intestine, migrate to the lungs, ascend the trachea, and are swallowed. On entering the intestines again, they mature and produce eggs that are excreted in the stool and are deposited in the soil, where they survive for prolonged periods. Where they die and calcify.

**Visceral Larva Migrans**

Visceral larva migrans is a systemic nematodi asis caused by ingestion of the eggs of the dog tapeworm, *Toxocara canis*, or, less commonly, the cat tapeworm, *Toxocara cati*, or the raccoon tapeworm, *Baylisascaris procyonis* (see Table 123-2). These organisms also cause **ocular larva migrans**. Visceral larva migrans is most common in young children with pica who have dogs or cats as pets. Ocular toxocariasis occurs in older children. The eggs of these roundworms are produced by adult worms residing in the dog and cat intestine. Ingested eggs hatch into larvae that penetrate the gastrointestinal tract and migrate to the liver, lung, eye, CNS, and heart, where they die and calcify.

Symptoms of visceral larva migrans are the result of the number of migrating worms and the associated immune response. Light infections are often asymptomatic. Symptoms include fever, cough, wheezing, and seizures. Physical findings may include hepatomegaly, crackles, rash, and lymphadenopathy. Visual symptoms may include decreased acuity, strabismus, periorbital edema, or blindness. Eye examination...
may reveal granulomatous lesions near the macula or disc. Ocular larva migrans is characterized by isolated, unilateral ocular disease and no systemic findings. Larvae probably enter the anterior vitreous of the eye from a peripheral branch of the retinal artery and elicit granulomas in the posterior and peripheral poles that cause vision loss.

Eosinophilia and hypergammaglobulinemia associated with elevated isohemagglutinin levels suggest the diagnosis, which is confirmed by serology (enzyme-linked immunosorbent assay) or, less commonly, by biopsy. This is usually a self-limited illness. In severe disease, albendazole or mebendazole is used. Deworming puppies and kittens, major excreters of eggs, decreases the risk of infection.

Enterobiasis (Pinworm)

Pinworm is caused by Enterobius vermicularis, a nematode that is distributed worldwide. Enterobiasis affects individuals at all socioeconomic levels, especially children. Crowded living conditions predispose to infection. Humans ingest the eggs carried on hands, present in house dust or on bedclothes. The eggs hatch in the stomach, and the larvae migrate to the cecum and mature. At night the females migrate to the perianal area to lay their eggs, which are viable for 2 days.

The most common symptoms are nocturnal anal pruritus (pruritus ani) and sleeplessness, presumably resulting from the migratory female worms. Vaginitis and salpingitis may develop secondary to aberrant worm migration. The eggs are detected by microscopically examining adhesive cellophane tape pressed against the anus in the morning to collect eggs. Less commonly, a worm may be seen in the perianal region. Treatment is with albendazole (400 mg), mebendazole (100 mg), or pyrantel pamoate (11 mg/kg, maximum 1 g) each given as a single oral dose and repeated in 2 weeks.

Schistosomiasis

Schistosomiasis (bilharziasis) is caused by flukes that parasitize the bloodstream, including Schistosoma haematobium, Schistosoma mansoni, Schistosoma japonicum, and, rarely, Schistosoma intercalatum and Schistosoma mekongi (Table 123-3). Schistosomiasis affects more than 2 million people, mainly children and young adults with a peak age range of 10 to 20 years. Humans are infected by cercariae in contaminated water that emerge in an infectious form from snails and penetrate intact skin. Each adult worm migrates to specific sites: S. haematobium to the bladder plexus and S. intercalatum and S. mekongi to the mesenteric vessels. The eggs are deposited by the adult flukes in urine (S. haematobibium) or stool (S. mansoni
and *S. japonicum*). *S. haematobium* is prevalent in Africa and the Middle East; *S. mansoni* in Africa, the Middle East, the Caribbean, and South America; *S. japonicum* in China, the Philippines, and Indonesia; *S. mekongi* in the Far East; and *S. intercalatum* in West Africa.

The manifestations of schistosomiasis result from eggs that are trapped at the site of deposition or at metastatic locations. Within 3 to 12 weeks of infection, while the worms are maturing, a syndrome of fever, malaise, cough, abdominal pain, and rash can occur. This syndrome is followed by a resultant inflammatory response that leads to further symptoms. *Kata-yama fever* is an acute condition, with fever, weight loss, hepatosplenomegaly, and eosinophilia. Eggs may be found in the urine (*S. haematobium*) or stool (*S. mansoni* and *S. japonicum*) of infected individuals. Sanitary measures, molluscicides, and therapy for infected individuals may help control the illness.

### Echinococcosis

Echinococcosis includes **hydatid or unilocular cyst disease**, caused by *Echinococcus granulosus* (the minute dog tapeworm) or *Echinococcus vogeli*, and **alveolar cyst disease**, caused by *Echinococcus multilocularis* (Table 123-4). Dogs become infected with tapeworms by eating infected sheep or cattle viscera and excrete eggs in their stools. Humans acquire echinococcosis by ingesting eggs and become an intermediate host. The eggs hatch in the intestinal tract, and the larva (*oncospheres*) penetrate the mucosa and enter the circulation to pass to the liver and other visceral organs, forming cysts 2 cm in diameter.

*E. granulosus* has a worldwide distribution and is endemic in sheep-raising and cattle-raising areas of Australia, South America, South Africa, the former Soviet Union, and the Mediterranean region. The prevalence is highest in children. Symptoms caused by *E. granulosus* result from space-occupying cysts. Pulmonary cysts may cause hemoptysis, cough, dyspnea, and respiratory distress. Brain cysts appear as tumors; liver cysts cause problems as they compress and obstruct blood flow. Ultrasonography identifies cystic lesions, and the diagnosis is confirmed by serologic testing. Large or asymptomatic granulosa cysts are removed surgically. Treatment with albendazole has shown some benefit.

### Neurocysticercosis

Neurocysticercosis is caused by infection with the larval stages (*cysticerci*) of the pork tapeworm, *Taenia solium*, and is the most frequent helminthic infection of the CNS (see Table 123-4). Humans are infected after consuming cysticerci in raw or undercooked larva-containing pork. *T. solium* is endemic in Asia, Africa, and Central and South Americas.

Cysts typically enlarge slowly, causing no or minimal symptoms for years or decades until the organism begins to die. The cyst then begins to swell, and leakage of antigen incites an inflammatory response, resulting in the presenting signs of focal or generalized seizures and calcified cerebral cysts identified by computed tomography or magnetic resonance imaging. The CSF shows lymphocytic or eosinophilic pleocytosis. The diagnosis is confirmed by serologic testing. Neurocysticercosis is treated with albendazole or praziquantel, corticosteroids for concomitant cerebral inflammation from cyst death, and anticonvulsant drugs.

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**Table 123-4** Major Pediatric Syndromes Caused by Parasitic Cestodes

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>ETIOLOGIC AGENT</th>
<th>TRANSMISSION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinococcosis</td>
<td>Ingestion of <em>Echinococcus</em></td>
<td>Surgical resection plus albendazole</td>
<td></td>
</tr>
<tr>
<td>Unilocular</td>
<td><em>Echinococcus granulosus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echinococcosis</td>
<td><em>Echinococcus granulosus var. canadensis</em></td>
<td></td>
<td>Expectant observation</td>
</tr>
<tr>
<td>Alveolar echinococcosis</td>
<td><em>Echinococcus multilocularis</em></td>
<td></td>
<td>Surgical resection is only reliable means of treatment; some reports suggest adjunct use of albendazole or mebendazole</td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td>Larval stage of <em>Taenia solium</em> (cysticerci)</td>
<td>Ingestion of infected raw/undercooked pork</td>
<td>Albendazole or praziquantel</td>
</tr>
<tr>
<td>Adult tapeworm infections</td>
<td><em>T. solium</em> (pork tapeworm)</td>
<td>Ingestion of contaminated raw/undercooked pork</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Hymenolepis diminuta</em></td>
<td>Fecal-oral transmission</td>
<td>Praziquantel</td>
<td></td>
</tr>
<tr>
<td><em>Hymenolepis nana</em></td>
<td>Fecal-oral</td>
<td>Praziquantel</td>
<td></td>
</tr>
</tbody>
</table>

**ETIOLOGY**

*Mycobacterium tuberculosis* are pleomorphic, weakly gram-positive curved rods. Mycobacteria are **acid fast**, which is the capacity to form stable mycolate complexes with arylmethylene dyes. Mycobacteria grow slowly; culture from clinical specimens on solid synthetic media usually takes 3 to 6 weeks. Drug-susceptibility testing requires an additional 4 weeks. Growth can be detected in 1 to 3 weeks in selective liquid media using radiolabeled nutrients. Polymerase chain reaction (PCR) of clinical specimens allows rapid diagnosis in many laboratories.
EPIDEMIOLOGY
An estimated 10 to 15 million persons in the United States have latent tuberculosis infection (infection with M. tuberculosis and no disease). Without treatment, tuberculosis disease develops in 5% to 10% of immunologically normal adults with tuberculosis infection at some time during their lives; the risk is higher in infants. An estimated 8 million new cases of tuberculosis occur each year among adults worldwide. Three million deaths are attributed to the disease annually. In developing countries, 1.3 million new cases of the disease occur in children under 15 years of age, and 450,000 children die each year of tuberculosis. Most children with tuberculosis infection and disease acquire M. tuberculosis from an infectious adult.

Transmission of M. tuberculosis is from person to person, usually by respiratory droplets that become airborne when the ill individual coughs, sneezes, laughs, sighs, or breathes. Infected droplets dry and become droplet nuclei, which may remain suspended in the air for hours, long after the infectious person has left the environment.

Several patient-related factors are associated with an increased chance of transmission. Of these a positive acid-fast smear of the sputum most closely correlates with infectivity. Children with primary pulmonary tuberculosis disease rarely, if ever, infect other children or adults. Tubercle bacilli are relatively sparse in the endobronchial secretions of children with primary tuberculosis, and a significant cough is usually lacking. When young children cough, they rarely produce sputum, lacking the tussive force necessary to project and suspend infectious particles of the requisite size. Hospitalized children with suspected pulmonary tuberculosis are placed initially in respiratory isolation. Most infectious patients become noninfectious within 2 weeks of starting effective treatment, and many become noninfectious within several days.

In North America, tuberculosis rates are highest in foreign-born persons from high-prevalence countries, residents of prisons, residents of nursing homes, homeless persons, users of illegal drugs, persons who are poor and medically indigent, health care workers, and children exposed to adults in high-risk groups. Among U.S. urban dwellers with tuberculosis, persons with acquired immunodeficiency syndrome (AIDS) and racial minorities are overrepresented. Most children are infected with M. tuberculosis from household contacts, but outbreaks of childhood tuberculosis centered in elementary and high schools, nursery schools, family day care homes, churches, school buses, and stores still occur. A high-risk adult working in the area has been the source of the outbreak in most cases.

Latent tuberculosis describes the asymptomatic stage of infection with M. tuberculosis. The tuberculin skin test (TST) is positive, but the chest radiograph is normal, and there are no signs or symptoms of illness. Tuberculosis disease occurs when there are clinical signs and symptoms or an abnormal chest radiograph. The term tuberculosis usually refers to the disease. The interval between latent tuberculosis and the onset of disease may be several weeks or many decades in adults. In young children, tuberculosis usually develops as an immediate complication of the primary infection, and the distinction between infection and disease may be less obvious.

Primary pulmonary tuberculosis in older infants and children is usually an asymptomatic infection. Often the disease is manifested by a positive TST with minimal abnormalities on the chest radiograph, such as an infiltrate with hilar lymphadenopathy or Ghon complex. Hilar lymphadenopathy may compress the bronchi or trachea, malaise, low-grade fever, erythema nodosum, or symptoms resulting from lymph node enlargement may occur after the development of delayed hypersensitivity.

Lymphadenopathy is common in primary pulmonary disease. Hilar lymphadenopathy may compress the bronchi or trachea. The most common extrathoracic sites of lymphadenitis are the cervical, supraclavicular, and submandibular areas (scrofula).

Progressive primary disease is characterized by a primary pneumonia that develops shortly after initial infection. Progression to pulmonary disease, disseminated miliary disease, or progression of central nervous system (CNS) granulomas to meningitis occurs most commonly in the first year of life.

Tuberculous pleural effusion, which may accompany primary infection, generally represents the immune response to the organisms and most commonly occurs in older children or adolescents. Pleurocentesis reveals lymphocytes and an increased protein level, but the pleural fluid usually does not contain bacilli.

Reactivation pulmonary tuberculosis, common in adolescents and typical in adults, usually is confined to apical segments of upper lobes or superior segments of lower lobes. There is usually little lymphadenopathy and no extrathoracic infection because of established hypersensitivity. This is a manifestation of a secondary expansion of infection at a site seeded years previously during primary infection. Advanced disease is associated with cavitation and endobronchial spread of bacilli. Symptoms include fever, night sweats, malaise, and weight loss. A productive cough and hemoptysis often herald cavitation and bronchial erosion.

Miliary tuberculosis refers to widespread hematogenous dissemination to multiple organs. The lesions are of roughly the same size as a millet seed, from which the name miliary is derived. Miliary tuberculosis is characterized by fever, general malaise, weight loss, lymphadenopathy, night sweats, and hepatosplenomegaly. Diffuse bilateral pneumonitis is common, and meningitis may be present. The chest radiograph reveals bilateral miliary infiltrates, showing overwhelming infection. The TST may be nonreactive as a result of anergy. Liver or bone marrow biopsy is useful for the diagnosis.

Tuberculous meningitis most commonly occurs in children under 5 years old and often within 6 months of primary infection. Tubercle bacilli that seed the meninges during the primary infection replicate, triggering an inflammatory response. This condition may have an insidious onset, initially
characterized by low-grade fever, headache, and subtle personality change. Progression of the infection results in basilar meningitis with impingement of the cranial nerves and is manifested by meningeal irritation and, eventually, increased intracranial pressure, deterioration of mental status, and coma. Computed tomography (CT) scans show hydrocephalus, edema, periventricular lucencies, and infarctions. Cerebrospinal fluid (CSF) analysis reveals pleocytosis (50 to 500 leukocytes/mm³), which early in the course of disease may be either lymphocytes or polymorphonuclear leukocytes. Glucose is low, and protein is significantly elevated. Acid-fast bacilli are not detected frequently in the CSF by either lymphocytes or polymorphonuclear leukocytes. Glucose is low, and protein is significantly elevated. Acid-fast bacilli are not detected frequently in the CSF by either routine or fluorescent staining procedures. Although culture is the standard for diagnosis, PCR for M. tuberculosis is useful to confirm meningitis.

**Skeletal tuberculosis** results from either hematogenous seeding or direct extension from a caseous lymph node. This is usually a chronic disease with an insidious onset that may be mistaken for chronic osteomyelitis caused by Staphylococcus aureus. Radiographs reveal cortical destruction. Biopsy and culture are essential for proper diagnosis. Tuberculosis of the spine, Pott’s disease, is the most common skeletal site followed by the hip as well as fingers and toes (dactylitis).

Other forms of tuberculosis include abdominal tuberculosis that occurs from swallowing infected material. This is a relatively uncommon complication in developed nations where dairy herds are inspected for bovine tuberculosis. Tuberculous peritonitis is associated with abdominal tuberculosis and presents as fever, anorexia, ascites, and abdominal pain. Urogenital tuberculosis is a late reactivation complication and is rare in children. Symptomatic illness presents as dysuria, frequency, urgency, hematuria, and sterile pyuria.

**LABORATORY AND IMAGING STUDIES**

**Tuberculin Skin Test**

Two types of tests are used to detect the immune response to M. tuberculosis and are used to screen patients for latent tuberculosis and investigation of active tuberculosis. The TST response to tuberculin antigen is a manifestation of a T cell–mediated delayed hypersensitivity. The Mantoux test, an intradermal injection of 5 TU (tuberculin units) of purified protein derivative standard (PPD-S), usually on the volar surface of the forearm, is the standard TST. It is usually positive 2 to 6 weeks after onset of infection (occasionally 3 months) and at the time of symptomatic illness. This test is preferred in children less than 5 years of age. It may also be used in other settings such as contact investigations or in older patients. Only persons at high risk should be offered a Mantoux test (Table 124-1). False-negative responses may occur early in the illness, with use of inactivated antigen (as a result of poor storage practice or inadequate administration), or as a result of immunosuppression (secondary to underlying illness, AIDS, malnutrition, or overwhelming tuberculosis). Tests with questionable results should be repeated after several weeks of therapy and adequate nutrition. Because of poor nutrition, a high proportion of internationally adopted children arriving in the United States have an initial false-positive TST. All internationally adopted children with an initially negative TST should have a repeat TST after 3 months in the United States. The TST is interpreted based on the host status and size of induration (Table 124-2).

<table>
<thead>
<tr>
<th>Table 124-1</th>
<th>Tuberculin Skin Test (TST) Recommendations for Infants, Children, and Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHILDREN FOR WHOM IMMEDIATE TST OR IGRA IS INDICATED:</strong></td>
<td></td>
</tr>
<tr>
<td>• Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)</td>
<td></td>
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<tr>
<td>• Children with radiographic or clinical findings suggesting tuberculosis disease</td>
<td></td>
</tr>
<tr>
<td>• Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries of the former Soviet Union, including international adoptees)</td>
<td></td>
</tr>
<tr>
<td>• Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries</td>
<td></td>
</tr>
<tr>
<td><strong>CHILDREN WHO SHOULD HAVE ANNUAL TST OR IGRA:</strong></td>
<td></td>
</tr>
<tr>
<td>• Children infected with HIV infection (TST only)</td>
<td></td>
</tr>
<tr>
<td><strong>CHILDREN AT INCREASED RISK OF PROGRESSION OF LTBI TO TUBERCULOSIS DISEASE:</strong></td>
<td></td>
</tr>
<tr>
<td>Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, and congenital or acquired immunodeficiencies deserve special consideration. Without recent exposure, these people are not at increased risk of acquiring tuberculosis infection. Underlying immune deficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered. An initial TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged steroid administration, use of tumor necrosis factor-alpha antagonists, or other immunosuppressive therapy in any child requiring these treatments.</td>
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</tr>
</tbody>
</table>

A whole blood test of interferon-gamma (INF-γ) release assay (IGRA), a cytokine elaborated by lymphocytes in response to tuberculosis antigens, is the recommended diagnostic test for persons older than 5 years of age in the United States. It has similar sensitivity as the TST but improved specificity because it is unaffected by prior bacille Calmette-Guérin vaccination.

**Culture**

The ultimate diagnostic confirmation relies on culture of the organism, a process that usually is more successful with tissue, such as pleura or pericardial membrane from biopsy, rather than pleural or pericardial fluid. Sputum is an excellent source for diagnosis in adults but is difficult to obtain in young children. Induced sputum or gastric fluid obtained via an indwelling nasogastric tube with samples taken before or immediately on waking contains swallowed sputum and provides appropriate samples in young children. Large volumes of fluid (CSF, pericardial fluid) yield a higher rate of recovery of organisms,
but slow growth of the mycobacteria makes culture less helpful in very ill children. When the organism is grown, drug susceptibilities should be determined because of the increasing incidence of resistant organisms.

Antigen detection and DNA probes have expedited diagnosis, especially with CNS disease.

**Table 124-2 Criteria for Positive Tuberculin Skin Test Results in Clinically Defined Pediatric Populations**

<table>
<thead>
<tr>
<th>POSITIVE RESULT</th>
<th>POPULATION(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induration ≥5 mm</td>
<td>Children in close contact with persons with known or suspected contagious tuberculosis disease</td>
</tr>
<tr>
<td></td>
<td>Children suspected to have tuberculosis disease</td>
</tr>
<tr>
<td></td>
<td>Findings on chest radiograph consistent with active or previously active tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Clinical evidence of tuberculosis disease†</td>
</tr>
<tr>
<td></td>
<td>Children receiving immunosuppressive therapy† or with immunosuppressive conditions, including HIV infection</td>
</tr>
<tr>
<td>Induration ≥10 mm</td>
<td>Children at increased risk for disseminated disease</td>
</tr>
<tr>
<td></td>
<td>Children &lt;4 years of age</td>
</tr>
<tr>
<td></td>
<td>Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, and malnutrition</td>
</tr>
<tr>
<td></td>
<td>Children with increased exposure to tuberculosis disease</td>
</tr>
<tr>
<td></td>
<td>Children born, or whose parents were born, in high-prevalence regions of the world</td>
</tr>
<tr>
<td></td>
<td>Children frequently exposed to adults who are HIV-infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized, or migrant farm workers</td>
</tr>
<tr>
<td></td>
<td>Children who travel to high-prevalence regions of the world</td>
</tr>
<tr>
<td>Induration ≥15 mm</td>
<td>Children ≥4 years of age without any risk factors</td>
</tr>
</tbody>
</table>

* These criteria apply regardless of previous bacille Calmette-Guérin immunization. Erythema at tuberculin skin test site does not indicate a positive test result. Tuberculin reactions should be read at 48 to 72 hours after placement.
† Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (e.g., meningitis).
‡ Including immunosuppressive doses of corticosteroids.

Diagnostic Imaging

Because many cases of pulmonary tuberculosis in children are clinically relatively silent, radiography is a cornerstone for the diagnosis of disease. All lobar segments of the lung are at equal risk of being the focus of the initial infection. In 25% of cases, two or more lobes of the lungs are involved, although disease usually occurs at one site only. Spread of infection to regional lymph nodes occurs early.

The hallmark of childhood pulmonary tuberculosis is the relatively large size and importance of the hilar lymphadenitis compared with the less significant size of the initial parenchymal focus, together historically referred to as the Ghon complex (with or without calcification of the lymph nodes). Hilar lymphadenopathy is inevitably present with childhood tuberculosis. Partial bronchial obstruction caused by external compression from the enlarging nodes can cause air trapping, hyperinflation, and lobar emphysema. Occasionally children have a picture of lobar pneumonia without impressive hilar lymphadenopathy. If the infection is progressively destructive, liquefaction of the lung parenchyma leads to formation of a thin-walled primary tuberculous cavity. Adolescents with pulmonary tuberculosis may develop segmental lesions with hilar lymphadenopathy or the apical infiltrates, with or without cavitation, that are typical of adult reactivation tuberculosis.

Radiographic studies aid greatly in the diagnosis of extrapulmonary tuberculosis in children. Plain radiographs, CT, and magnetic resonance imaging (MRI) of the tuberculous spine usually show collapse and destruction of the vertebral body with narrowing of the involved disk spaces. Radiographic findings in bone and joint tuberculosis range from mild joint effusions and small lytic lesions to massive destruction of the bone.

In tuberculosis of the CNS, CT or MRI of the brains of patients with tuberculous meningitis may be normal during early stages of the infection. As disease progresses, basilar enhancement and communicating hydrocephalus with signs of cerebral edema or early focal ischemia are the most common findings.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of tuberculosis includes a multitude of diagnoses because tuberculosis may affect any organ, and in early disease the symptoms and signs may be nonspecific. In pulmonary disease, tuberculosis may appear similar to pneumonia, malignancy, and any systemic disease in which generalized lymphadenopathy occurs. The diagnosis of tuberculosis should be suspected if the TST or IGRA is positive or if there is history of tuberculosis in a close contact.

The differential diagnosis of tuberculous lymphadenopathy includes infections caused by atypical mycobacteria, cat-scratch disease, fungal infection, viral or bacterial disease, toxoplasmosis, sarcoidosis, drug reactions, and malignancy. The diagnosis may be confirmed by fine-needle aspiration but may necessitate excisional biopsy accompanied by appropriate histologic and microbiologic studies.

**TREATMENT**

The treatment of tuberculosis is affected by the presence of naturally occurring drug-resistant organisms in large bacterial populations, even before therapy is initiated, and the fact that mycobacteria replicate slowly and can remain dormant in the body for prolonged periods. Although a population of bacilli as a whole may be considered drug susceptible, a subpopulation of drug-resistant organisms occurs at fairly predictable frequencies of $10^5$ to $10^7$, depending on the drug. Cavities may contain $10^9$ tubercle bacilli with thousands of organisms resistant to any one drug, but only rare organisms are resistant to multiple drugs.

Patients with latent tuberculosis infection have small bacterial populations and a single drug, such as isoniazid, can be
given. Therapy for latent infection is aimed at eradicating the presumably small inoculum of organisms sequestered within macrophages and suppressed by normal T cell activity. To prevent reactivation of these latent bacilli, therapy with a single agent (usually isoniazid for 9 months) is suggested. Children with primary pulmonary tuberculosis and patients with extrapulmonary tuberculosis have medium-sized populations in which significant numbers of drug-resistant organisms may or may not be present. In general these patients are treated with at least two drugs (Table 124-3) for a prolonged course, typically 6 to 9, depending on the type of disease. Isoniazid and rifampin are bactericidal for M. tuberculosis and are effective against all populations of mycobacteria. Along with pyrazinamide, they form the backbone of the antimicrobial treatment of tuberculosis. Other drugs are used in special circumstances, such as tuberculous meningitis and antibiotic-resistant tuberculosis.

A 9-month regimen of isoniazid and rifampin cures greater than 98% of cases of drug-susceptible pulmonary tuberculosis. After daily administration for the first 1 to 2 months, both drugs can be given daily or twice weekly for the remaining 7 to 8 months, with equivalent results and low rates of adverse reactions. The addition of pyrazinamide for the first 2 months of the regimen reduces the total duration of treatment to 6 months and has similar efficacy. Noncompliance, or nonadherence, is a major problem in tuberculosis control because of the long-term nature of treatment and the sometimes difficult social circumstances of the patients. As treatment regimens become shorter, adherence assumes an even greater importance. Improvement in compliance occurs with directly observed therapy, which means that the health care worker is physically present when the medications are administered, and is the standard of care in most settings.

### COMPLICATIONS AND PROGNOSIS

The prognosis of tuberculosis in infants, children, and adolescents is excellent with early recognition and effective chemotherapy. In most children with pulmonary tuberculosis, the disease completely resolves, and ultimately radiographic findings are normal. The prognosis for children with bone and joint tuberculosis and tuberculous meningitis depends directly on the stage of disease at the time antituberculosis medications are started. Tuberculosis of the spine may result in angulation or gibbus formation that requires surgical correction after the infection is cured. Most childhood tuberculous meningitis occurs in developing countries, where the prognosis is poor.

### PREVENTION

Tuberculosis control programs involve case finding and treatment, which interrupts secondary transmission of infection from close contacts. Infected close contacts are identified by positive TST reactions and can be started on appropriate treatment to prevent transmission.

Prevention of transmission in health care settings involves appropriate physical ventilation of the air around the source case. Offices, clinics, and hospital rooms used by adults with possible tuberculosis should have adequate ventilation, with air exhausted to the outside (negative-pressure ventilation). Health care providers should have annual TSTs.

The only available vaccine against tuberculosis is the bacille Calmette-Guérin vaccine. The original vaccine organism was a strain of Mycobacterium bovis attenuated by subculture every 3 weeks for 13 years. The preferred route of administration is intradermal injection with a syringe and needle because this is the only method that permits accurate measurement of an
individual dose. The official recommendation of the World Health Organization is a single dose administered during infancy. This vaccine is not routinely used in the United States. Some studies show bacille Calmette-Guérin to provide 80% to 90% protection from tuberculosis, and other studies show no protective efficacy at all. Many infants who receive bacille Calmette-Guérin vaccine never have a positive TST reaction. When a reaction does occur, the induration size is usually less than 10 mm, and the reaction wanes after several years.

**Chapter 125**

**HIV AND AIDS**

**ETIOLOGY**

The cause of acquired immunodeficiency syndrome (AIDS) is the human immunodeficiency virus (HIV), a single-stranded RNA virus of the retrovirus family that produces a reverse transcriptase enabling the viral RNA to act as a template for DNA transcription and integration into the host genome. HIV-1 causes 99% of all human cases. HIV-2, which is less virulent, causes 1% to 9% of cases in parts of Africa and is very rare in the United States.

HIV infects helper T cells (CD4 cells) and cells of monocyte-macrophage lineage via interaction of viral protein gp120 with the CD4 molecule and chemokines (CXCR4 on T cells and CCR5 on dendritic cells and macrophages) that serve as coreceptors. Interaction with these molecules facilitates membrane fusion and cell entry by the virus. HIV infection directly and indirectly depletes CD4 T cells. Because helper T cells are important for delayed hypersensitivity, T cell–dependent B cell antibody production, and T cell–mediated lymphokine activation of macrophages, their destruction produces a profound combined (B and T cell) immunodeficiency. A lack of T cell regulation and unrestrained antigenic stimulation result in polyclonal hypergammaglobulinemia with nonspecific and ineffective globulins. Other cells bearing CD4, such as microglia, astrocytes, oligodendroglia, and placental tissues also may be infected with HIV.

HIV infection is a continuously progressive process with a variable period of clinical latency before development of AIDS-defining conditions. All untreated patients have evidence of ongoing viral replication and progressive CD4 lymphocyte depletion. There are no overt manifestations of immunodeficiency until CD4 cell numbers decline to critical threshold levels. Quantitation of the viral load has become an important parameter in management.

**Horizontal transmission** of HIV is by sexual contact (vaginal, anal, or orogenital), percutaneous contact (from contaminated needles or other sharp objects), or mucous membrane exposure to contaminated blood or body fluid. Transmission by contaminated blood and blood products has been eliminated in developed countries but still occurs in developing countries. **Vertical transmission** of HIV from mother to infant may occur transplacentally in utero, during birth, or by breastfeeding. Risk factors for perinatal transmission include prematurity, rupture of membranes more than 4 hours, and high maternal circulating levels of HIV at delivery. Perinatal transmission can be decreased from approximately 25% to less than 8% with antiretroviral treatment of the mother before and during delivery and postnatal treatment of the infant. Breastfeeding by HIV-infected mothers increases the risk of vertical transmission by 30% to 50%. In untreated infants, the mean incubation interval for development of an AIDS-defining condition after vertical transmission is 5 months (range, 1 to 24 months) compared with a longer incubation period after horizontal transmission of 7 to 10 years.

**CLINICAL MANIFESTATIONS**

In adolescents and adults, primary infection results in the **acute retroviral syndrome** that develops after an incubation period of 2 to 6 weeks and consists of fever, malaise, weight loss, pharyngitis, lymphadenopathy, and often a maculopapular rash. The risk of opportunistic infections and other AIDS-defining conditions is related to the depletion of CD4 T cells. A combination of CD4 cell count and percentage and clinical manifestations is used to classify HIV infection in children (Tables 125-1 and 125-2).

Initial symptoms with vertical transmission vary and may include failure to thrive, neurodevelopmental delay, lymphadenopathy, hepatosplenomegaly, chronic or recurrent diarrhea, interstitial pneumonia, or oral thrush. These findings may be subtle and remarkable only by their persistence.

**EPIDEMIOLOGY**

Worldwide, as of 2010, approximately 34 million persons are living with HIV and 3.4 million of them are children. There were 2.7 million new infections in 2010 with approximately 390,000 new infections in children. Roughly 70% of all people living with HIV reside in sub-Saharan Africa. Worldwide, 1.8 million people died from HIV-related illnesses in 2010. In 2010 the estimated number of people over the age of 13 years and living with HIV in the United States was 1.1 million, and approximately 9800 children are infected. Vertical transmission is much less common than previously, and approximately 50 infants are born with HIV infection each year in the United States. Most pediatric cases now occur in adolescents who engage in unprotected sexual activities. Worldwide the number of deaths related to HIV and the number of children infected with HIV have steadily decreased in large part due to treatment with antiretroviral therapy.
Manifestations that are more common in children than adults with HIV infection include recurrent bacterial infections, lymphoid hyperplasia, chronic parotid swelling, lymphocytic interstitial pneumonitis, and earlier onset of progressive neurologic deterioration. Pulmonary manifestations of HIV infection are common and include Pneumocystis jiroveci pneumonia, which can present early in infancy as a primary pneumonia characterized by hypoxia, tachypnea, retractions, elevated serum lactate dehydrogenase, and fever.

In the United States, most pregnant women are screened and, if indicated, treated for HIV infection. Infants born to HIV-infected mothers receive prophylaxis and are prospectively tested for infection. The diagnosis of HIV infection in most infants born in the United States is confirmed before development of clinical signs of infection.

**LABORATORY AND IMAGING STUDIES**

HIV infection can be diagnosed definitively by 1 month of age and in virtually all infected infants by 6 months of age using viral diagnostic assays (RNA polymerase chain reaction [PCR], DNA PCR, or virus culture). Maternal antibodies may be detectable until 12 to 15 months of age, and a positive serologic test is not considered diagnostic until 18 months of age.

HIV DNA PCR is the preferred virologic method for diagnosing HIV infection during infancy and identifies 38% of infected infants at 48 hours and 96% at 28 days. Diagnostic viral testing should be performed by 48 hours of age, at 1 to 2 months of age, and at 3 to 6 months of age. An additional test at 14 days of age is often performed because the diagnostic sensitivity increases rapidly by 2 weeks of age. HIV RNA PCR has 25% to 40% sensitivity during the first weeks of life, increasing to 90% to 100% by 2 to 3 months of age. However, a negative HIV RNA PCR cannot be used to exclude infection and, thus, is not recommended as first-line testing.

HIV infection of an exposed infant is confirmed if virologic tests are positive on two separate occasions. HIV infection can be reasonably excluded in nonbreastfed infants with at least two virologic tests performed at older than 1 month of age, with one test being performed after 4 months of age, or at least two negative antibody tests performed after 6 months of age, with an interval of at least 1 month between the tests. Loss of HIV antibody combined with negative HIV DNA PCR confirms absence of HIV infection. Persistence of a positive HIV antibody test after 18 months of age indicates HIV infection.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of AIDS in infants includes primary immunodeficiency syndromes and intrauterine infections with cytomegalovirus (CMV) and syphilis. Prominence of individual symptoms, such as diarrhea, may suggest other etiologies.

**TREATMENT**

Management of HIV infection in children and adolescents is rapidly evolving and becoming increasingly complex. It should be directed by a specialist in the treatment of HIV infection. Therapy is initiated based on the severity of HIV disease, as indicated by AIDS-defining conditions, and the risk of disease progression, as indicated by CD4 cell count and plasma HIV RNA level (Table 125-3). Initiation of antiretroviral therapy while the patient is still asymptomatic may preserve immune function and prevent clinical progression but incurs the adverse effects of therapy and may facilitate emergence of drug-resistant virus. Because the risk of HIV progression is fourfold to sixfold greater in infants and very young children, treatment recommendations for children are more aggressive than for adults. All age groups show rapid increases in risk as CD4 cell percentage declines to less than 15%.

Initiation of therapy (see Table 125-3) is recommended for infants less than 12 months of age regardless of symptoms of HIV disease or HIV RNA level. Initiation of therapy is recommended for all children 1 to 5 years of age with AIDS or significant HIV-related symptoms or CD4 count below 25% (clinical category C or most clinical category B) regardless of symptoms or HIV RNA level. For children older than 5 years with AIDS or significant HIV-related symptoms, CD4 count below 350/mm³ should be treated. Indications for treatment of adolescents and adults include CD4 cell count less than 200 to 350/mm³ or plasma HIV RNA levels above 55,000 copies/mL.

Combination therapy with highly active antiretroviral therapy (HAART) is recommended based on the risk of disease progression as determined by CD4 percentage or count and plasma HIV RNA copy number; the potential benefits are substantial.
### 1994 Revised HIV Pediatric Classification System: Clinical Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CATEGORY A: MILDLY SYMPTOMATIC</strong></td>
<td>Lymphadenopathy (nodal tissue enlargement of ≥0.5 cm palpable at more than two sites; bilateral = one site)</td>
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<td></td>
<td>Hepatomegaly</td>
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<td>Splenomegaly</td>
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<td>Dermatitis</td>
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<td>Parotitis</td>
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<td></td>
<td>Recurrent or persistent upper respiratory infection, sinusitis, or otitis media</td>
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<tr>
<td><strong>CATEGORY B: MODERATELY SYMPTOMATIC</strong></td>
<td>Anemia (&lt;8 g/dL), neutropenia (&lt;1000/mm³), or thrombocytopenia (&lt;100,000/mm³) persisting ≥30 days</td>
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<td></td>
<td>Bacterial meningitis, pneumonia, or sepsis (single episode)</td>
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<td></td>
<td>Candidiasis, oropharyngeal (i.e., thrush) persisting for &gt;2 months in children younger than 6 months of age</td>
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<td>Cardiomyopathy</td>
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<td></td>
<td>Cytomegalovirus infection with onset before the age of 1 month</td>
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<td></td>
<td>Diarrhea, recurrent or chronic</td>
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<td>Hepatitis</td>
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<td></td>
<td>HSV stomatitis, recurrent (i.e., more than two episodes within 1 year)</td>
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<td></td>
<td>HSV bronchitis, pneumonitis, or esophagitis with onset before the age of 1 month</td>
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<td>Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome</td>
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<td>Leiomyosarcoma</td>
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<td></td>
<td>LIP or pulmonary lymphoid hyperplasia complex</td>
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<td>Nephropathy</td>
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<td>Nocardiosis</td>
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<td></td>
<td>Fever lasting &gt;1 month</td>
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<td>Varicella, disseminated (i.e., complicated chickenpox)</td>
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<tr>
<td><strong>CATEGORY C: SEVERELY SYMPTOMATIC</strong></td>
<td>Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)</td>
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<td></td>
<td>Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)</td>
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<td></td>
<td>Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)</td>
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<tr>
<td></td>
<td>Cryptococcosis, extrapulmonary</td>
</tr>
<tr>
<td></td>
<td>Cryptosporidiosis or isosporiasis with diarrhea persisting &gt;1 month</td>
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<tr>
<td></td>
<td>Cytomegalovirus disease with onset of symptoms before the age of 1 month (other than liver, spleen, or lymph nodes)</td>
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<td></td>
<td>Encephalopathy (at least one progressive deficit present for at least 2 months in the absence of a concurrent illness): (a) failure to attain or loss of developmental milestones/intellectual ability, verified by standard scale or tests; (b) impaired brain growth or acquired microcephaly; (c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance</td>
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<td></td>
<td>Herpes simplex virus infection (mucocutaneous ulcer persisting for &gt;1 month; bronchitis, pneumonitis, or esophagitis affecting a child younger than 1 month of age)</td>
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<tr>
<td></td>
<td>Histoplasmosis, disseminated (other than or in addition to lungs or cervical or hilar lymph nodes)</td>
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<td></td>
<td>Kaposi sarcoma</td>
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<td></td>
<td>Lymphoma (primary tumor, in brain; Burkitt lymphoma; immunoblastic or large cell lymphoma of B cell or unknown immunologic phenotype)</td>
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<td></td>
<td>Mycobacterium tuberculosis, disseminated or extrapulmonary</td>
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<tr>
<td></td>
<td>Mycobacterium, other species or unidentified species, disseminated (other than or in addition to lungs, skin, or cervical or hilar lymph nodes)</td>
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<tr>
<td></td>
<td>Mycobacterium avium complex or Mycobacterium kansasii, disseminated (other than or in addition to lungs, skin, or cervical or hilar lymph nodes)</td>
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<tr>
<td></td>
<td>Pneumocystis jiroveci (carinii) pneumonia</td>
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<td></td>
<td>Progressive multifocal leukoencephalopathy</td>
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<tr>
<td></td>
<td>Salmonella (nontyphoid) septicemia, recurrent</td>
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<td></td>
<td>Toxoplasmosis of the brain with onset before the age of 1 month</td>
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<td></td>
<td>Wasting syndrome in the absence of a concurrent illness could explain the following findings: (a) persistent weight loss &gt;10% of baseline or (b) downward crossing of at least two percentile lines on the weight-for-age chart or (c) below the 5th percentile on the weight-for-height chart on two consecutive measurements, ≥30 days apart, plus (1) chronic diarrhea (i.e., two or more loose stools per day for &gt;30 days) or (2) documented fever (for ≥30 days, intermittent or constant)</td>
</tr>
</tbody>
</table>

and risks of therapy; and the ability of the caregiver to adhere to administration of the therapeutic regimen. Effective combination therapy significantly reduces viral loads and leads to the amelioration of clinical symptoms and opportunistic infections. Combination therapy that includes either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor (PI) plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone is recommended for initial treatment of all HIV infected children. The goal of therapy is to reduce the plasma HIV RNA to below the level of detection and normalize or preserve the patient’s immune status. The most recent specific recommendations for treatment regimens (http://aidsinfo.nih.gov/guidelines/) should be consulted before initiating therapy for any patient.

The ability of HIV to develop resistance to antiretroviral agents rapidly and the development of cross-resistance to several classes of agents simultaneously are major problems. Determination of HIV RNA, CD4 cell count, and HIV phenotype and genotype is essential for monitoring and modifying antiretroviral treatment.

Routine immunizations are recommended to prevent vaccine-preventable infections but may result in suboptimal immune responses. In addition to heptavalent pneumococcal conjugate vaccine, 23-valent pneumococcal polysaccharide vaccine is recommended for HIV-infected children at 2 years of age and adolescents and adults with CD4 counts at or above 200/mm³. Because of the risk of fatal measles in children with AIDS, children without severe immunosuppression should receive their first dose of MMR at 12 months of age and may receive the booster as soon as 4 weeks later. Varicella zoster virus (VZV) vaccine should be given only to asymptomatic, nonimmunosuppressed children beginning at 12 months of age as two doses of vaccine at least 3 months apart. Inactivated split influenza virus vaccine should be administered annually to all HIV-infected children at or after 6 months of age. HIV-infected children exposed to varicella or measles should receive varicella zoster immune globulin or immunoglobulin prophylaxis.

### COMPLICATIONS

The approach to the numerous opportunistic infections in HIV-infected patients involves treatment and prophylaxis for infections likely to occur as CD4 cells are depleted. With potent antiretroviral therapy and immune reconstitution, routine prophylaxis for common opportunistic infections depends on the child’s age and CD4 count. Infants born to HIV-infected mothers receive prophylaxis for P. jiroveci pneumonia with trimethoprim-sulfamethoxazole (TMP-SMZ) beginning at 4 to 6 weeks of age and continued for the first year of life or discontinued if HIV infection is subsequently excluded. TMP-SMZ prophylaxis for P. jiroveci pneumonia for older children and adolescents is provided if CD4 cell counts are less than 200/mm³ or there is history of oropharyngeal candidiasis. Clarithromycin prophylaxis for Mycobacterium avium-complex infection is provided if CD4 cell counts are below 50/mm³.

P. jiroveci pneumonia is treated with high-dose TMP-SMZ and corticosteroids. Oral and gastrointestinal candidiasis is common in children and usually responds to imidazole therapy. VZV infection may be severe and should be treated with acyclovir or other antivirals. Recurrent herpes simplex virus (HSV) infections also may require long-term antiviral prophylaxis. Other common infections in HIV-infected patients include toxoplasmosis, CMV, Epstein-Barr virus infection, salmonellosis, and tuberculosis.

Children and adults with HIV are prone to malignancies, especially non-Hodgkin lymphomas, with the gastrointestinal tract being the most common site. Leiomyosarcomas are the second most common tumors among HIV-infected children. Kaposi sarcoma, caused by HHV-8, is distinctly rare in children with HIV. It was once common among adults with AIDS and is now infrequent with HAART.

### PROGNOSIS

The availability of HAART has improved the prognosis for HIV and AIDS dramatically. Risk of death is directly related to the degree of immunosuppression, viral load, and young age.
Children less than 1 year of age with very low CD4 percentiles and high viral loads have the poorest prognosis.

**PREVENTION**

Identification of HIV-infected women before or during pregnancy is crucial to providing optimal therapy for infected women and their infants and to preventing perinatal transmission. Prenatal HIV counseling and testing with consent should be provided for all pregnant women in the United States.

The rate of vertical transmission is reduced to less than 8% by chemoprophylaxis with a regimen of zidovudine to the mother (100 mg five times/24 hours orally) started by 4 weeks gestation, continued during delivery (2 mg/kg loading dose intravenously followed by 1 mg/kg/hour intravenously), and then administered to the newborn for the first 6 weeks of life (2 mg/kg every 6 hours orally). Other regimens incorporating single-dose nevirapine for infants have been shown to be similarly effective and are used in developing countries. The current recommendations for the United States include a 6-week prophylactic with zidovudine for the infant in combination with maternal intrapartum therapy. The maternal regimen includes continuation of antiretroviral therapy (if appropriate) and intravenous zidovudine if the mother’s viral load is >400 copies/mL or is unknown (http://aidsinfo.nih.gov/contentfiles/lvguidelines/peri_recommendations.pdf). Scheduled cesarean section at 38 weeks to prevent vertical transmission is recommended for women with HIV RNA levels greater than 1000 copies/mL, but it is unclear whether cesarean section is beneficial when viral load is less than 1000 copies/mL or when membranes have already ruptured.

Preventing HIV infection in adults decreases the incidence of infection in children. Adult prevention results from behavior changes such as safe-sex practices, decrease in intravenous drug use, and needle exchange programs. Prevention of pediatric AIDS includes avoidance of pregnancy and breastfeeding (in developed countries) in high-risk women. Screening of blood donors has almost eliminated the risk of HIV transmission from blood products. HIV infection almost never is transmitted in a casual or nonsexual household setting.

**Suggested Reading**


ASSESSMENT

HISTORY
After identifying the major gastrointestinal (GI) symptom, onset and progression should be determined (improved, unchanged, worsening). Characterization of signs and symptoms should identify factors such as triggers; actions that alleviate the symptom; timing, frequency and duration of symptoms; relationship to meals and defecation; and associated symptoms (e.g., fever or weight loss). Other key history includes exposures to others (family, school contacts), travel, environmental exposure, and impact of illness on the child (school absences).

PHYSICAL EXAMINATION
The history may suggest a diagnosis and direct the evaluation, which should include a full examination as well as a thorough abdominal examination. Extraintestinal disorders may produce GI manifestations (e.g., emesis with group A streptococcal pharyngitis, abdominal pain with lower lobe pneumonia). The examination should begin with a careful external inspection for abdominal distention, bruising or discoloration, abnormal veins, jaundice, surgical scars, and ostomies. Abnormalities of intensity and pitch of bowel sounds can occur with bowel obstruction. When palpating for tenderness, the examiner should note location, facial expression, guarding, and rebound tenderness. Palpation can also detect enlargement of the liver or spleen as well as feces and masses. If detected, organomegaly should be measured (with a tape measure), noting abnormal firmness or contour. A rectal examination, including inspection for fissures, skin tags, abscesses, and fistulous openings, should be performed for children with history suggesting constipation, GI bleeding, abdominal pain, chronic diarrhea, and suspicion of inflammatory bowel disease (IBD). Digital rectal examination should include assessment of anal sphincter tone, anal canal size and elasticity, tenderness, extrinsic masses, presence of fecal impaction, and caliber of the rectum. Stool should be tested for occult blood.

SCREENING TESTS
A complete blood count may provide evidence for inflammation (white blood cell [WBC] and platelet count), poor nutrition or bleeding (hemoglobin, red blood cell volume, reticulocyte count), and infection (WBC number and differential, presence of toxic granulation). Serum electrolytes, blood urea nitrogen (BUN), and creatinine help define hydration status. Tests of liver dysfunction include total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase for evidence of hepatocellular injury, and \( \gamma \)-glutamyltransferase or alkaline phosphatase for evidence of bile duct injury. Hepatic synthetic function can be assessed by coagulation factor levels, prothrombin time, and albumin level. Pancreatic enzyme tests (amylase, lipase) provide evidence of pancreatic injury or inflammation. Urinalysis can gauge dehydration and identify a possible source of protein loss.

DIAGNOSTIC IMAGING
Radiology
Consultation with a radiologist is often advisable to discuss appropriate imaging, decide what variants of the technique to use, and learn how to prepare the patient for the study. A plain abdominal x-ray to document excessive retained stool when history is consistent with constipation and encopresis is not necessary, as examination alone can confirm the diagnosis.

Endoscopy
Endoscopy permits the direct visualization of the interior of the gut. Video endoscopes may be used even in very small infants by pediatric gastroenterologists. Wireless capsule endoscopy (Fig. 126-1) enables visualization of lesions beyond the reach of conventional endoscopes. Consultation with a pediatric gastroenterologist for endoscopy is recommended for further evaluation of suspected esophageal or gastric inflammation unresponsive to medications and to confirm the diagnosis of eosinophilic esophagitis or celiac disease, evaluate gastrointestinal bleeding, evaluate suspected inflammatory bowel disease, and screen for polyp disorders. In addition, a trained endoscopist can remove esophageal and gastric foreign bodies and place feeding tubes.

COMMON MANIFESTATIONS OF GASTROINTESTINAL DISORDERS
Abdominal Pain
Bladder pain often is referred to the region below the right and pancreas pain is referred to the epigastric region. Gallbladder referred pain is called somatoparietal pain. Becomes severe and localizes to the right lower quadrant. This process extends to the overlying parietal peritoneum, the pain becomes more uncomfortable sensations, whereas more intensive stimulation of these fibers results in pain. Overactive sensation may be the basis of some kinds of abdominal pain, such as irritable bowel syndrome and functional abdominal pain. In contrast to visceral pain, somatic pain results when overlying body structures are injured. Somatic structures include the parietal peritoneum, fascia, muscles, and skin of the abdominal wall. In contrast to pain emanating from visceral injury, somatic nociceptive fibers are myelinated and are capable of rapid transmission of well-localized painful stimuli. When intra-abdominal processes cause inflammation or injury to the parietal peritoneum or abdominal wall structures, poorly localized visceral pain becomes well-localized somatic pain. For example, in acute appendicitis, the initial activation of visceral nociceptive fibers yields poorly localized discomfort in the mid-abdomen. When the inflammatory process extends to the overlying parietal peritoneum, the pain becomes severe and localizes to the right lower quadrant. This is called somatoparietal pain.

Referred pain is a painful sensation in a body region distant from the true source of pain. The location of referred pain is predictable based on the locus of visceral injury. Stomach pain is referred to the epigastric and retrosternal regions, and liver and pancreas pain is referred to the epigastric region. Gallbladder pain often is referred to the region below the right scapula. Somatic pathways stimulated by small bowel visceral afferents affect the periumbilical area, and colonic injury results in infraumbilical referred pain.

Acute Abdominal Pain

Distinguishing Features
Acute abdominal pain can signal the presence of a dangerous intra-abdominal process (e.g., appendicitis or bowel obstruction) or may originate from extraintestinal sources (e.g., lower lobe pneumonia or urinary tract stone). Not all episodes of acute abdominal pain require emergency intervention. Appendicitis and volvulus, for example, must be ruled out as quickly as possible. Few patients presenting with acute abdominal pain actually have a surgical emergency, but they must be separated from cases that can be managed conservatively.

Initial Diagnostic Evaluation

Table 126-1 lists a diagnostic approach to acute abdominal pain in children. Events that occur with a discrete, abrupt onset, such as passage of a stone, perforation of a viscus, or infarction, result in a sudden onset of pain. Gradual onset of pain is common with infectious or inflammatory causes, such as appendicitis and IBD.

A standard group of laboratory tests usually is performed for acute abdominal pain (see Table 126-1). An abdominal x-ray series evaluates for bowel obstruction or nephrolithiasis. Ultrasound or computed tomography (CT) can visualize the appendix if appendicitis is suspected but the diagnosis remains in doubt. If the initial evaluation suggests intussusception, a barium or pneumatic (air) enema may be used to diagnose and treat this condition (see Chapter 129).

Differential Diagnosis

Table 126-2 lists the differential diagnosis of acute abdominal pain in children. The urgent task of the clinician is to rule out surgical emergencies. In young children, malrotation with volvulus, incarcerated hernia, congenital anomalies, and intussusception are common concerns. In older children and teenagers, appendicitis is more common. An acute surgical abdomen is characterized by signs of peritonitis, including tenderness, abdominal wall rigidity, guarding, and absent or diminished bowel sounds. Helpful characteristics of onset, location, referral, and quality of pain are noted in Table 126-3.

Functional Abdominal Pain and Irritable Bowel Syndrome

Recurrent abdominal pain is a common problem, affecting more than 10% of all children. The peak incidence occurs between ages 7 and 12 years. Although the differential diagnosis of recurrent abdominal pain is fairly extensive (Table 126-4), most children do not have a serious (or even identifiable) underlying illness causing the pain.
### Table 126-1: Diagnostic Approach to Acute Abdominal Pain

<table>
<thead>
<tr>
<th>HISTORY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Sudden or gradual, prior episodes, association with meals, history of injury</td>
</tr>
<tr>
<td>Nature</td>
<td>Sharp versus dull, colicky or constant, burning</td>
</tr>
<tr>
<td>Location</td>
<td>Epigastric, periumbilical, generalized, right or left lower quadrant, change in location over time</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td>Fever, vomiting (bilious?), diarrhea (bloody?), abdominal distention</td>
</tr>
<tr>
<td>Extraintestinal symptoms</td>
<td>Cough, dyspnea, dysuria, urinary frequency, flank pain</td>
</tr>
<tr>
<td>Course of symptoms</td>
<td>Worsening or improving, change in nature or location of pain, aggravating and alleviating factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHYSICAL EXAMINATION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>General position</td>
<td>Growth and nutrition, general appearance, hydration, degree of discomfort, body position</td>
</tr>
<tr>
<td>Abdominal</td>
<td>Tenderness, distention, bowel sounds, rigidity, guarding, mass</td>
</tr>
<tr>
<td>Genitalia</td>
<td>Testicular torsion, hernia, pelvic inflammatory disease, ectopic pregnancy</td>
</tr>
<tr>
<td>Surrounding structures</td>
<td>Breath sounds, rales, rhonchi, wheezing, flank tenderness, tenderness of abdominal wall structures, ribs, costochondral joints</td>
</tr>
<tr>
<td>Rectal examination</td>
<td>Perianal lesions, stricture, tenderness, fecal impaction, blood</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LABORATORY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, C-reactive protein, ESR</td>
<td>Evidence of infection or inflammation</td>
</tr>
<tr>
<td>AST, ALT, GGT, bilirubin</td>
<td>Biliary or liver disease</td>
</tr>
<tr>
<td>Amylase, lipase</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Urinary tract infection; bleeding due to stone, trauma, or obstruction</td>
</tr>
<tr>
<td>Pregnancy test (older females)</td>
<td>Ectopic pregnancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RADIOLOGY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain flat and upright abdominal films</td>
<td>Bowel obstruction, appendiceal fecalith, free intraperitoneal air, kidney stones</td>
</tr>
<tr>
<td>CT scan</td>
<td>Intra-abdominal or pelvic abscess, appendicitis, Crohn's disease, pancreatitis, gallstones, kidney stones</td>
</tr>
<tr>
<td>Barium enema</td>
<td>Intussusception, malrotation</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Gallstones, appendicitis, intussusception, pancreatitis, kidney stones</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Suspected peptic ulcer or esophagitis</td>
</tr>
<tr>
<td>Upper endoscopy</td>
<td></td>
</tr>
</tbody>
</table>

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CT, computed tomography; ESR, erythrocyte sedimentation rate; GGT, γ-glutamyltransferase.

### Table 126-2: Differential Diagnosis of Acute Abdominal Pain

<table>
<thead>
<tr>
<th>TRAUMATIC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal hematoma</td>
<td></td>
</tr>
<tr>
<td>Ruptured spleen</td>
<td></td>
</tr>
<tr>
<td>Perforated viscus</td>
<td></td>
</tr>
<tr>
<td>Traumatic pancreatitis</td>
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</table>

<table>
<thead>
<tr>
<th>FUNCTIONAL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td></td>
</tr>
<tr>
<td>Mittelschmerz (ovulation)</td>
<td></td>
</tr>
<tr>
<td>Infantile colic</td>
<td></td>
</tr>
<tr>
<td>Abdominal migraine</td>
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</table>

<table>
<thead>
<tr>
<th>INFECTIOUS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendicitis</td>
<td></td>
</tr>
<tr>
<td>Viral or bacterial gastroenteritis/adenitis</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td></td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td></td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td></td>
</tr>
<tr>
<td>Cholecystitis</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>Bacterial typhlitis</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GENITAL</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Testicular torsion</td>
<td></td>
</tr>
<tr>
<td>Ovarian torsion</td>
<td></td>
</tr>
<tr>
<td>Ruptured ovarian cyst</td>
<td></td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>GENETIC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickle cell crisis</td>
<td></td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
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<table>
<thead>
<tr>
<th>METABOLIC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic ketoacidosis</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>INFLAMMATORY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>OBSTRUCTIVE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intussusception</td>
<td></td>
</tr>
<tr>
<td>Malrotation with volvulus</td>
<td></td>
</tr>
<tr>
<td>Ileus</td>
<td></td>
</tr>
<tr>
<td>Incarcerated hernia</td>
<td></td>
</tr>
<tr>
<td>Postoperative adhesion</td>
<td></td>
</tr>
</tbody>
</table>

Continued
The Digestive System

Differential Diagnosis

Children with functional abdominal pain characteristically have pain almost daily. The pain is not associated with meals or relieved by defecation and is often associated with a tendency toward anxiety and perfectionism. Symptoms often result from stress at school or in novel social situations. The pain often is worst in the morning and often prevents or delays children from attending school. Irritable bowel syndrome (IBS) is a subset of functional abdominal pain, characterized by onset of pain at the time of a change in stool frequency or consistency, a stool pattern fluctuating between diarrhea and constipation, and relief of pain with defecation. Symptoms in IBS are linked to gut motility. Pain is commonly accompanied in both groups of children by school avoidance, secondary gains, anxiety about imagined causes, lack of coping skills, and disordered peer relationships (Table 126-5).

Distinguishing Features

One needs to distinguish between functional pain/IBS and more serious underlying disorders. Warning signs for underlying illness are listed in Table 126-6. If present, further investigation is necessary. Some laboratory evaluation is warranted.

Table 126-3

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ONSET</th>
<th>LOCATION</th>
<th>REFERRAL</th>
<th>QUALITY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional/irritable bowel syndrome</td>
<td>Recurrent</td>
<td>Periumbilical, splenic and hepatic flexures</td>
<td>None</td>
<td>Dull, crampy, intermittent; duration 2 h</td>
<td>Family stress, school phobia, diarrhea and constipation, hypersensitive to pain from distention</td>
</tr>
<tr>
<td>Esophageal reflux</td>
<td>Recurrent, after meals, at bedtime</td>
<td>Substernal</td>
<td>Chest</td>
<td>Burning</td>
<td>Sour taste in mouth; Sandifer syndrome</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>Recurrent, before meals, at night</td>
<td>Epigastric</td>
<td>Back</td>
<td>Severe burning, gnawing</td>
<td>Relieved by food, milk, antacids; family history important; GI bleeding</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Acute</td>
<td>Epigastric-hypogastric</td>
<td>Back</td>
<td>Constant, sharp, boring</td>
<td>Nausea, emesis, marked tenderness</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>Acute or gradual</td>
<td>Periumbilical—lower abdomen</td>
<td>Back</td>
<td>Alternating cramping (colic) and painless periods</td>
<td>Distention, obstipation, bilaus emesis, increased bowel sounds</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Acute</td>
<td>Periumbilical or epigastric; localizes to right lower quadrant</td>
<td>Back or pelvis if retrocecal</td>
<td>Sharp, steady</td>
<td>Nausea, emesis, local tenderness, ± fever, avoids motion</td>
</tr>
<tr>
<td>Meckel diverticulum</td>
<td>Recurrent</td>
<td>Periumbilical—lower abdomen</td>
<td>None</td>
<td>Sharp</td>
<td>Hematochezia; painless unless intussusception, diverticulitis, or perforation</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Recurrent</td>
<td>Depends on site of involvement</td>
<td></td>
<td>Dull cramping, tenesmus</td>
<td>Fever, weight loss, ± hematochezia</td>
</tr>
<tr>
<td>Intussusception</td>
<td>Acute</td>
<td>Periumbilical—lower abdomen</td>
<td>None</td>
<td>Cramping, with painless periods</td>
<td>Guarded position with knees pulled up, currant jelly stools, lethargy</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>Recurrent with milk products</td>
<td>Lower abdomen</td>
<td>None</td>
<td>Cramping</td>
<td>Distention, gaseousness, diarrhea</td>
</tr>
<tr>
<td>Urilithiasis</td>
<td>Acute, sudden</td>
<td>Back</td>
<td>Groin</td>
<td>Severe, colicky pain</td>
<td>Hematuria</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Acute, sudden</td>
<td>Back</td>
<td>None</td>
<td>Dull to sharp</td>
<td>Fever, costochondral tenderness, dysuria, urinary frequency, emesis</td>
</tr>
<tr>
<td>Cholecystitis and cholelithiasis</td>
<td>Acute</td>
<td>Right upper quadrant</td>
<td>Right shoulder</td>
<td>Severe, colicky pain</td>
<td>Hemolysis ± jaundice, nausea, emesis</td>
</tr>
</tbody>
</table>

even in the absence of warning signs. The initial evaluation recommended in Table 126-7 is a sensible approach, avoiding unnecessary testing and providing ample sensitivity for most serious underlying disorders. While waiting for laboratory and ultrasound results, a 3-day trial of a lactose-free diet can evaluate for lactose intolerance. If tests are normal and no warning signs are present, testing should be stopped. If there are warning signs, progression of symptoms, or laboratory abnormalities that suggest a specific diagnosis, additional investigation may be warranted.

Treatment of Recurrent Abdominal Pain
A child who is repeatedly kept home from school because of pain receives reinforcement in the form of being excused from responsibilities and withdraws from full social functioning. This tends to both increase anxiety and prolong the course. To break the cycle of pain and disability, the child with functional pain must be assisted in returning to normal activities immediately. Instead of being sent home from school with stomachaches, a child may be allowed to take a short break from class until symptoms abate. The child and parents should be informed that pain is likely to be worse on the day the child returns to school as anxiety worsens dysmotility and enhances pain perception. Medications may be helpful. Fiber supplements may help to manage symptoms of IBS. Probiotics and peppermint oil can be beneficial in treating IBS. In difficult and persistent cases, cognitive behavioral

<table>
<thead>
<tr>
<th>Table 126-4</th>
<th>Differential Diagnosis of Recurrent Abdominal Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional abdominal pain*</td>
<td>Irritable bowel syndrome*</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Gallstones</td>
</tr>
<tr>
<td>Peptic disease</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>Esophagitis</td>
</tr>
<tr>
<td>Lactose intolerance*</td>
<td>Fructose malabsorption</td>
</tr>
<tr>
<td>Inflammatory bowel disease*</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Constipation*</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>Congenital intestinal malformation</td>
</tr>
<tr>
<td>Maldigestion</td>
<td>Duplicating cyst</td>
</tr>
<tr>
<td>Stricture or web</td>
<td>Celiac disease*</td>
</tr>
<tr>
<td>Abdominal migraine</td>
<td>Eosinophilic esophagitis*</td>
</tr>
</tbody>
</table>

*Common.

<table>
<thead>
<tr>
<th>Table 126-5</th>
<th>Rome III Criteria for Pediatric Functional Gastrointestinal Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Diagnostic Criteria for Childhood Functional Abdominal Pain</td>
<td></td>
</tr>
<tr>
<td>Must include all of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Episodic or continuous abdominal pain</td>
<td></td>
</tr>
<tr>
<td>2. Insufficient criteria for other functional gastrointestinal diseases</td>
<td></td>
</tr>
<tr>
<td>3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms.</td>
<td></td>
</tr>
<tr>
<td>*Criteria fulfilled at least once per week for at least 2 months before diagnosis</td>
<td></td>
</tr>
<tr>
<td>B. Diagnostic Criteria for Childhood Functional Abdominal Pain Syndrome</td>
<td></td>
</tr>
<tr>
<td>Must include functional abdominal pain at least 25% of the time and 1 or more of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Some loss of daily functioning</td>
<td></td>
</tr>
<tr>
<td>2. Additional somatic symptoms such as headache, limb pain, or difficulty sleeping</td>
<td></td>
</tr>
<tr>
<td>*Criteria fulfilled at least once per week for at least 2 months before diagnosis</td>
<td></td>
</tr>
<tr>
<td>C. Diagnostic Criteria for Irritable Bowel Syndrome</td>
<td></td>
</tr>
<tr>
<td>Must include all of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:</td>
<td></td>
</tr>
<tr>
<td>a. improved with defecation</td>
<td></td>
</tr>
<tr>
<td>b. onset associated with change in frequency of stool</td>
<td></td>
</tr>
<tr>
<td>c. onset associated with a change in form (appearance) of stool</td>
<td></td>
</tr>
<tr>
<td>2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject’s symptoms.</td>
<td></td>
</tr>
<tr>
<td>*Criteria fulfilled at least once per week for at least 2 months before diagnosis</td>
<td></td>
</tr>
<tr>
<td>D. Diagnostic Criteria for Abdominal Migraine</td>
<td></td>
</tr>
<tr>
<td>Must include all of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 hour or more.</td>
<td></td>
</tr>
<tr>
<td>2. Intervening periods of usual health lasting weeks to months.</td>
<td></td>
</tr>
<tr>
<td>3. The pain interferes with normal activities.</td>
<td></td>
</tr>
<tr>
<td>4. The pain is associated with 2 or more of the following:</td>
<td></td>
</tr>
<tr>
<td>a. anorexia</td>
<td></td>
</tr>
<tr>
<td>b. nausea</td>
<td></td>
</tr>
<tr>
<td>c. vomiting</td>
<td></td>
</tr>
<tr>
<td>d. headache</td>
<td></td>
</tr>
<tr>
<td>e. photophobia</td>
<td></td>
</tr>
<tr>
<td>f. pallor</td>
<td></td>
</tr>
<tr>
<td>5. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process considered that explains the subject’s symptoms.</td>
<td></td>
</tr>
<tr>
<td>*Criteria fulfilled 2 or more times in the preceding 12 months.</td>
<td></td>
</tr>
<tr>
<td>E. Diagnostic Criteria for Cyclic Vomiting Syndrome</td>
<td></td>
</tr>
<tr>
<td>Must include all of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Two or more periods of intense nausea and unremitting vomiting or retching lasting hours to days.</td>
<td></td>
</tr>
<tr>
<td>2. Return to usual state of health lasting weeks to months.</td>
<td></td>
</tr>
<tr>
<td>F. Functional Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Must include all of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Daily painless, recurrent passage of three or more large, unformed stools.</td>
<td></td>
</tr>
<tr>
<td>2. Symptoms lasting more than 4 weeks.</td>
<td></td>
</tr>
<tr>
<td>3. Onset of symptoms that begins between 6 and 36 months of age.</td>
<td></td>
</tr>
<tr>
<td>4. Passage of stools that occur during waking hours.</td>
<td></td>
</tr>
<tr>
<td>5. There is no failure to thrive if caloric intake is adequate.</td>
<td></td>
</tr>
</tbody>
</table>

*Courtesy of the Rome Foundation.*
therapy, amitriptyline, or a selective serotonin reuptake inhibitor may be helpful. When significant anxiety or social dysfunction persists, a mental health professional should be consulted.

**Vomiting**

**Vomiting** is a coordinated, sequential series of events that leads to forceful oral emptying of gastric contents. It is a common problem in children and has many causes. Vomiting should be distinguished from **regurgitation** of stomach contents, also known as gastroesophageal reflux (GER), chalasia, or "spitting up." Although the end result of vomiting and regurgitation is similar, they have completely different characteristics. Vomiting is usually preceded by nausea and is accompanied by forceful gagging and retching. Regurgitation, on the other hand, is effortless and not preceded by nausea.

**Differential Diagnosis**

In neonates with true vomiting, congenital obstructive lesions should be considered. Allergic reactions to formula in the first 2 months of life may present with vomiting. **Infantile GER** ("spitting up") occurs in most infants and can be large in volume, but is effortless and these infants do not appear ill. **Pyloric stenosis** occurs in the first months of life and is characterized by steadily worsening, forceful vomiting that occurs immediately after feedings. A visibly distended stomach, often with visible peristaltic waves, is often seen before vomiting. Pyloric stenosis is more common in male infants; the family history may be positive. Other obstructive lesions, such as intestinal duplication cysts, atresias, webs, and midgut malrotation, should be considered. Metabolic disorders (e.g., organic acidemias, galactosemia, urea cycle defects, adrenogenital syndromes) may present with vomiting in infants. In older children with acute vomiting, viruses and food poisoning are common. Other infections, especially streptococcal pharyngitis, urinary tract infections, and otitis media, commonly result in vomiting. When vomiting is chronic, central nervous system (CNS) causes (increased intracranial pressure, migraine) must be considered. **Cyclic vomiting syndrome** or migraine may be the etiology of recurrent vomiting. When abdominal pain or bilious emesis accompanies vomiting, evaluation for bowel obstruction, peptic disorders, and appendicitis must be immediately initiated.

**Distinguishing Features**

**Table 126-8** lists common diagnoses that must be considered and their important historical features. Given the frequency of viral gastroenteritis as the etiology, it is important to be alert for unusual features that suggest another diagnosis. Viral gastroenteritis usually is not associated with severe abdominal pain or headache and does not recur at frequent intervals.

**Physical examination** should include assessment of the child’s hydration status, including examination of capillary refill, moistness of mucous membranes, and skin turgor (see Chapter 38). The chest should be auscultated for evidence of rales or other signs of pulmonary involvement. The abdomen must be examined carefully for distention, organomegaly, bowel sounds, tenderness, and guarding. A rectal examination and testing stool for occult blood should be considered. **Laboratory evaluation** of vomiting should include serum electrolytes, tests of renal function, complete blood count, amylase, lipase, and liver function tests. Additional testing may be required immediately when history and examination suggest a specific etiology. Ultrasound is useful to look for pyloric stenosis, gallstones, renal stones, hydronephrosis, biliary obstruction, pancreatitis, malrotation, intussusception, and other anatomic

---

**Table 126-6**  Warning Signs of Underlying Illness in Recurrent Abdominal Pain

<table>
<thead>
<tr>
<th>Warning Sign</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal screening laboratory study (anemia, hypoalbuminemia, inflammatory markers)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Bilious emesis</td>
<td></td>
</tr>
<tr>
<td>Growth failure</td>
<td></td>
</tr>
<tr>
<td>Pain awakening child from sleep</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Location away from periumbilical region</td>
<td></td>
</tr>
<tr>
<td>Blood in stools or emesis</td>
<td></td>
</tr>
<tr>
<td>Delayed puberty</td>
<td></td>
</tr>
<tr>
<td>Nocturnal diarrhea</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Perianal disease</td>
<td></td>
</tr>
<tr>
<td>Family history of inflammatory bowel disease, celiac disease, or peptic ulcer disease</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 126-7**  Suggested Evaluation of Recurrent Abdominal Pain

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INITIAL EVALUATION</strong></td>
<td>Complete history and physical examination</td>
</tr>
<tr>
<td></td>
<td>Ask about “warning signs” (see Table 126-6)</td>
</tr>
<tr>
<td></td>
<td>Determine degree of functional impairment (e.g., missing school)</td>
</tr>
<tr>
<td></td>
<td>CBC</td>
</tr>
<tr>
<td></td>
<td>ESR</td>
</tr>
<tr>
<td></td>
<td>Amylase, lipase</td>
</tr>
<tr>
<td></td>
<td>Urinalysis</td>
</tr>
<tr>
<td></td>
<td>Abdominal ultrasound—examine liver, bile ducts, gallbladder, pancreas, kidneys, ureters (move to follow up)</td>
</tr>
<tr>
<td></td>
<td>Trial of 3-day lactose-free diet</td>
</tr>
<tr>
<td></td>
<td><strong>FOLLOW-UP EVALUATION</strong></td>
</tr>
<tr>
<td></td>
<td>CT scan of the abdomen and pelvis with oral, rectal, and intravenous contrast</td>
</tr>
<tr>
<td></td>
<td>Celiac disease serology—endomysial antibody or tissue transglutaminase antibody</td>
</tr>
<tr>
<td></td>
<td>Barium upper GI series with small bowel follow-through</td>
</tr>
<tr>
<td></td>
<td>Endoscopy of the esophagus, stomach, and duodenum</td>
</tr>
<tr>
<td></td>
<td>Colonoscopy</td>
</tr>
</tbody>
</table>

CBC, Complete blood count; CT, computed tomography; ESR, erythrocyte sedimentation rate; GI, gastrointestinal.

*Consider using one or more of these to investigate warning signs, abnormal laboratory tests, or specific or persistent symptoms.*
abnormalities. CT may be indicated to rule out appendicitis or to observe structures that cannot be visualized well by ultrasound. Barium studies can show obstructive or inflammatory lesions of the gut and can be therapeutic, as in the use of contrast enemas for intussusception (see Chapter 129).

**Treatment** needs to address the consequences and the causes of the vomiting. Dehydration must be treated with fluid resuscitation. This can be accomplished in most cases with oral fluid-electrolyte solutions, but intravenous (IV) fluids may be required. Electrolyte imbalances should be corrected by appropriate choice of fluids. Underlying causes should be treated when possible.

The use of **antiemetic medications** is controversial. These drugs should not be prescribed until the etiology of the vomiting is known, and then only for severe symptoms. Phenothiazines, such as prochlorperazine, may be useful for reducing symptoms in food poisoning and motion sickness. Their side-effect profile must be considered carefully, however, and the dose prescribed should be conservative. Anticholinergics (e.g., scopolamine) and antihistamines (e.g., dimenhydrinate) are useful for the prophylaxis and treatment of motion sickness. Drugs that block serotonin 5-HT₃ receptors, such as ondansetron and granisetron, are frequently used for viral gastroenteritis and can improve tolerance of oral rehydration therapy. They are helpful for chemotherapy-induced vomiting, often combined with dexamethasone. No antiemetic should be used in patients with surgical emergencies or when a specific treatment of the underlying condition is possible. Correction of dehydration, ketosis, and acidosis is helpful to reduce vomiting in most patients with viral gastroenteritis.
Acute and Chronic Diarrhea

Diarrhea is a major cause of childhood morbidity and mortality worldwide. Deaths from diarrhea are rare in industrialized countries, but are common elsewhere. **Acute diarrhea** is a major problem when it occurs with malnutrition or in the absence of basic medical care (see Chapter 30). In North America, most acute diarrhea is viral and is self-limited, requiring no diagnostic testing or specific intervention. Bacterial agents tend to cause much more severe illness and typically are seen in food-associated outbreaks or in regions with poor public sanitation. Bacterial enteritis should be suspected when there is **dysentery** (bloody diarrhea with fever) and whenever severe symptoms are present. These infections can be diagnosed by stool culture or other assays for specific pathogens. **Chronic diarrhea** lasts more than 2 weeks and has a wide range of possible causes, including serious and benign conditions that are more difficult to diagnose.

Parents use the word diarrhea to describe loose or watery stools, excessively frequent stools, or stools that are large in volume. Constipation with overflow incontinence can be mislabeled as diarrhea. A more exact definition of diarrhea is excessive daily stool liquid volume (>10 mL stool/kg body weight/day). Stool texture, volume, and frequency help to characterize the episode of diarrhea.

### Differential Diagnosis

Diarrhea may be classified by etiology or by physiologic mechanisms (secretory or osmotic). Etiologic agents include viruses, bacteria or their toxins, chemicals, parasites, malabsorbed substances, and inflammation. **Table 126-9** lists common causes of diarrhea in childhood. **Secretory diarrhea** occurs when the intestinal mucosa directly secretes fluid and electrolytes into the stool and is the result of inflammation (e.g., inflammatory bowel disease, chemical stimulus). Secretion also is stimulated by mediators of inflammation and by various hormones, such as vasoactive intestinal peptide secreted by a neuroendocrine tumor. Cholera is a secretory diarrhea stimulated by the enterotoxin of *Vibrio cholerae*, which causes increased levels of cAMP within enterocytes and leads to secretion into the small-bowel lumen.

**Osmotic diarrhea** occurs after malabsorption of an ingested substance, which "pulls" water into the bowel lumen. A classic example is the diarrhea of lactose intolerance. Osmotic diarrhea also can result from generalized malabsorption, such as that seen with pancreatic insufficiency or with intestinal injury. Certain nonabsorbable laxatives, such as polyethylene glycol and milk of magnesia, also cause osmotic diarrhea. Fermentation of malabsorbed substances (e.g., lactose) often occurs, resulting in gas, cramps, and acidic stools. A common cause of chronic loose stools in early childhood is **functional diarrhea**, commonly known as **toddler’s diarrhea**. This condition is defined by frequent watery stools in the setting of normal growth and

<table>
<thead>
<tr>
<th>Table 126-9</th>
<th>Differential Diagnosis of Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFANT</strong></td>
<td><strong>CHILD</strong></td>
</tr>
<tr>
<td><strong>ACUTE</strong></td>
<td>Gastroenteritis*</td>
</tr>
<tr>
<td>Common</td>
<td>Systemic infection</td>
</tr>
<tr>
<td></td>
<td>Antibiotic associated (?)</td>
</tr>
<tr>
<td>Rare</td>
<td>Primary disaccharidase deficiency</td>
</tr>
<tr>
<td></td>
<td>Adrenogenital syndrome</td>
</tr>
<tr>
<td><strong>CHRONIC</strong></td>
<td>Postinfectious secondary lactase deficiency</td>
</tr>
<tr>
<td>Common</td>
<td>Cow's milk/soy protein intolerance</td>
</tr>
<tr>
<td></td>
<td>Chronic nonspecific diarrhea of infancy</td>
</tr>
<tr>
<td></td>
<td>(toddler’s diarrhea)</td>
</tr>
<tr>
<td></td>
<td>Celiac disease</td>
</tr>
<tr>
<td></td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>AIDS enteropathy</td>
</tr>
<tr>
<td>Rare</td>
<td>Primary immune defects</td>
</tr>
<tr>
<td></td>
<td>Familial villous atrophy (?)</td>
</tr>
<tr>
<td></td>
<td>Congenital chlorideorrhea</td>
</tr>
<tr>
<td></td>
<td>Acrodermatitis enteropathica</td>
</tr>
<tr>
<td></td>
<td>Lymphangiectasia</td>
</tr>
<tr>
<td></td>
<td>Abetalipoproteinemia</td>
</tr>
<tr>
<td></td>
<td>EOSINOPHILIC gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>short bowel syndrome</td>
</tr>
<tr>
<td></td>
<td>Intractable diarrhea syndrome</td>
</tr>
<tr>
<td></td>
<td>Autoimmune enteropathy</td>
</tr>
<tr>
<td></td>
<td>Factitious</td>
</tr>
</tbody>
</table>

AIDS, Acquired immunodeficiency syndrome.
Gastroenteritis includes viral (rotavirus, norovirus, astrovirus) and bacterial (Salmonella, Shigella, Escherichia coli, Clostridium difficile, Yersinia, Campylobacter, other) agents.
weight gain and is caused by excessive intake of sweetened liquids, overwhelming the disaccharide absorptive capacity of the intestine. Diarrhea typically improves tremendously when the child’s beverage intake is reduced or changed.

**Distinguishing Features**

**Diarrhea**

Stools are isosmotic, even in osmotic diarrhea, because of the relatively free exchange of water across the intestinal mucosa. Osmoles present in the stool are a mixture of electrolytes and other osmotically active solutes. To determine whether the diarrhea is osmotic or secretory, the osmotic gap is calculated:

\[
\text{Osmotic gap} = 290 - 2 ([\text{Na}^+] + [\text{K}^+])
\]

Assuming the stool is isosmotic (an osmolarity of 290 mOsm/L), the measured stool sodium and potassium (and their associated anions, accounting for an equal amount) accounts for much of the osmolality. Secretory diarrhea is characterized by an osmotic gap of less than 50. A number significantly higher than 50 defines osmotic diarrhea and indicates that malabsorbed substances other than electrolytes account for fecal osmolarity.

Another way to differentiate between osmotic and secretory diarrhea is to stop all feedings (in hospitalized patients receiving intravenous fluids). If the diarrhea stops completely while the child is NPO (nothing by mouth), the patient has osmotic diarrhea. A child with a pure secretory diarrhea would continue to have massive stool output. Neither method for classifying diarrhea works perfectly, because most diarrheal illnesses are a mixture of secretory and osmotic components. Viral enteritis damages the intestinal lining, causing malabsorption and osmotic diarrhea. The associated inflammation results in release of mediators that cause excessive secretion. A child with viral enteritis may have decreased stool volume while NPO, but the secretory component of the diarrhea persists until the inflammation resolves.

The history should include the onset of diarrhea, number and character of stools, estimates of stool volume, and presence of other symptoms, such as blood in the stool, fever, and weight loss. Recent travel and exposures should be documented, dietary factors should be investigated, and a list of medications recently used should be obtained. Factors that seem to worsen or improve the diarrhea should be determined. Physical examination should be thorough, evaluating for abdominal distention, tenderness, quality of bowel sounds, presence of blood in the stool or a large fecal mass on rectal examination, and anal sphincter tone.

Laboratory testing should include stool culture and complete blood count if bacterial enteritis is suspected. If diarrhea occurs after a course of antibiotics, a Clostridium difficile toxin assay should be ordered; if stools are reported to be oily or fatty, fecal fat content or fecal elastase to test for pancreatic insufficiency should be measured. Tests for specific diagnoses should be sent when appropriate (e.g., serum antibody tests for celiac disease; colonoscopy for suspected ulcerative colitis). A trial of lactose restriction for several days or lactose breath hydrogen testing is helpful in the evaluation of lactose intolerance.

**Constipation and Encopresis**

Constipation is a common problem in childhood. When a child is thought to be constipated, his parents may be concerned about straining with defecation, hard stool consistency, large stool size, decreased stool frequency, fear of passing stools, or any combination of these. Physicians define constipation as two or fewer stools per week or passage of hard, pellet-like stools for at least 2 weeks. A common pattern of constipation is functional constipation, which is characterized by two or fewer stools per week, voluntary withholding of stool, and infrequent passage of large-diameter, often painful stools. Children with functional fecal retention often exhibit “retentive posturing” (standing or sitting with legs extended and stiff or crossed legs) and have associated fecal incontinence caused by leakage of retained stool (encopresis).

**Differential Diagnosis**

The differential diagnosis is listed in Table 126-10. Functional constipation commonly occurs during toilet training, when the child is unwilling to defecate on the toilet. Retained stool becomes harder and larger over time, leading to painful defecation. This aggravates voluntary withholding of stool, with perpetuation of the constipation.

Hirschsprung disease is characterized by delayed meconium passage in newborns, abdominal distention, vomiting, occasional fever, and foul-smelling stools. This condition is caused by failure of ganglion cells to migrate into the distal bowel, resulting in spasm and functional obstruction of the aganglionic segment. Only about 6% of infants with Hirschsprung disease pass meconium in the first 24 hours of life, compared with 95% of normal infants. Most affected babies rapidly become ill with symptoms of enterocolitis or obstruction. Affected older children do not pass large-caliber stools because of rectal spasm, and they do not have encopresis. Other causes of constipation include spinal cord abnormalities, hypothyroidism, drugs, cystic fibrosis, and anorectal malformations (see Table 126-10). A variety of systemic disorders affecting metabolism or muscle function can result in constipation. Children with developmental disabilities have a great propensity for constipation because of diminished capacity to cooperate with toileting, reduced effort or control of pelvic floor muscles during defecation, and diminished perception of the need to pass stool.

**Distinguishing Features**

Table 126-10 includes typical characteristics of the common causes of constipation. Congenital malformations usually cause...
symptoms from birth. Functional constipation is overwhelmingly the most common diagnosis in older patients. Constipation in older children often begins after starting school, when free and private access to toilets may be restricted. Use of some drugs, especially opiates and some psychotropic medications, is also associated with constipation.

For a few specific causes of constipation, directed diagnostic testing can make the diagnosis. A narrowed, aganglionic distal bowel and dilated proximal bowel on barium enema suggests Hirschsprung disease. Rectal suction biopsy confirms the absence of ganglion cells in the rectal submucosal plexus, with hypertrophy of nerve fibers. Lack of internal anal sphincter relaxation can be shown by anorectal manometry in Hirschsprung’s disease. Rectal suction biopsy confirms the absence of ganglion cells on rectal suction biopsy specimen, absent relaxation of the internal sphincter, “transition zone” from narrow distal bowel to dilated proximal bowel on barium enema.

Evaluation and Treatment of Functional Constipation
In most cases of constipation, the history is consistent with functional constipation—absence of neonatal constipation, active fecal retention, and infrequent, large stools with soiling. In these patients, no testing other than a good physical examination is necessary. Young children with painful defecation must have a prolonged course of stool softener therapy to alleviate fear of defecation. The child should be asked to sit on the toilet for a few minutes on awakening in the morning and immediately after meals, when the colon is most active and it is easiest to pass a stool. Use of a positive reinforcement system for taking medication and sitting on the toilet is helpful for younger children. The stool softener chosen should be non–habit forming, safe, and palatable. Polyethylene glycol and milk of magnesia are the most commonly used agents.

**Gastrointestinal Bleeding**

**Gastrointestinal Bleeding**
GI tract bleeding can be an emergency when large-volume bleeding is present, but even the presence of small amounts of blood in stool or emesis is sufficient to cause concern. Evaluation of bleeding should include confirmation that blood truly is present, estimation of the amount of bleeding, stabilization of the patient’s intravascular blood volume, localization of the source of bleeding, and appropriate treatment of the underlying cause. When bleeding is massive, it is crucial that the

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**Table 126-10: Common Causes of Constipation and Characteristic Features**

<table>
<thead>
<tr>
<th>CAUSES OF CONSTIPATION</th>
<th>CLINICAL FEATURES</th>
</tr>
</thead>
</table>
| Hirschsprung disease                      | History: Failure to pass stool in first 24 h, abdominal distention, vomiting, symptoms of enterocolitis (fever, foul-smelling diarrhea, megacolon). Not associated with large-caliber stools or encopresis.  
  Examination: Snug anal sphincter, empty, contracted rectum. May have explosive release of stool as examiner’s finger is withdrawn.  
  Laboratory: Absence of ganglion cells on rectal suction biopsy specimen, absent relaxation of the internal sphincter, “transition zone” from narrow distal bowel to dilated proximal bowel on barium enema. |
| Functional constipation                    | History: No history of significant neonatal constipation, onset at potty training, large-caliber stools, retentive posturing, may have encopresis.  
  Examination: Normal or reduced sphincter tone, dilated rectal vault, fecal impaction, soiled underwear, palpable fecal mass in left lower quadrant.  
  Laboratory: No abnormalities, barium enema would show dilated distal bowel. |
| Anorectal and colonic malformations        | History: Constipation from birth due to abnormal anatomy.  
  Examination: Anorectal abnormalities are shown easily on physical examination.  
  Laboratory: Anteriorly displaced anus is found chiefly in females, with a normal-appearing anus located close to the posterior fourchette of the vagina.  
  Laboratory: Barium enema shows the anomaly. |
| Multisystem disease                        | History: Presence of other symptoms or prior diagnosis.  
  Examination: Specific abnormalities may be present that directly relate to the underlying diagnosis.  
  Laboratory: Tests directed at suspected disorder confirm the diagnosis. |
| Spinal cord abnormalities                  | History: History of swelling or exposed neural tissue in the lower back, history of urinary incontinence.  
  Examination: Lax sphincter tone due to impaired innervation, visible or palpable abnormality of lower back usually (but not always) present.  
  Laboratory: Bony abnormalities often present on plain x-ray. Magnetic resonance imaging (MRI) of spinal cord reveals characteristic abnormalities. |
| Drugs                                      | History: Recent use of drugs known to cause constipation.  
  Examination: Features suggest functional constipation.  
  Laboratory: No specific tests available. |
| Narcotics                                  |                                                                                                                                                  |
| Psychotropics                              |                                                                                                                                                  |

---
patient receive adequate resuscitation with fluid and blood products before moving ahead with diagnostic testing.

Differential Diagnosis
GI bleeding has different causes at different ages (Table 126-11).

Distinguishing Features
Red substances in foods, beverages, or medications (such as cefdinir) occasionally can be mistaken for blood. A test for occult blood is worth performing whenever the diagnosis is in doubt. The GI tract may not be the source of the observed fecal blood. A history of cough and examination of the mouth, nostrils, and lungs is needed to exclude these as a source of hematemesis. Blood in the toilet or diaper may be coming from the urinary tract, vagina, or even a severe diaper rash. If the bleeding is GI, it is important to determine the source as high in the GI tract or distal to the ligament of Treitz. Vomited blood is always proximal. Rectal bleeding may be coming from anywhere in the gut. When dark clots or melena are seen mixed with stool, a higher location is suspected, whereas bright red blood on the surface of stool probably is coming from lower in the colon. When upper GI tract bleeding is suspected, a nasogastric tube may be placed and gastric contents aspirated for evidence of recent bleeding.

The location and hemodynamic significance of the bleeding can also be assessed by history and examination. The parents should be asked to quantify the bleeding. Details of associated symptoms should be sought. Assessment of the vital signs including orthostatic changes when bleeding volume is large, pulses, capillary refill and assessment of pallor of the mucous membranes provides valuable information. Laboratory assessment and imaging studies should be ordered as indicated (Table 126-12).

| Table 126-11 Causes and Distinguishing Characteristics of Gastrointestinal Bleeding |
|---------------------|-----------------------------|--------------------------|
| **AGE**             | **TYPE OF BLEEDING**        | **CHARACTERISTICS**       |
| NEWBORN             |                             |                          |
| Ingested maternal blood* | Hematemesis or rectal, large | Apt test indicates adult hemoglobin is present, cracked maternal nipples, amount |
| Peptic disease      | Hematemesis, amount varies  | Blood found in stomach on lavage |
| Coagulopathy        | Hematemesis or rectal, bruising, other sites | History of home birth (no vitamin K) |
| Allergic colitis*   | Streaks of bloody mucus in stool | Eosinophils in feces and in rectal mucosa |
| Necrotizing enterocolitis | Rectal | Sick infant with tender and distended abdomen |
| Duplication cyst    | Hematemesis                 | Cystic mass in abdomen on imaging study |
| Volvulus            | Hematemesis, hematochezia   | Acute tender distended abdomen |
| INFANCY TO 2 YEARS OLD |                   |                          |
| Peptic disease      | Usually hematemesis, rectal possible | Epigastric pain, coffee-ground emesis |
| Esophageal varices  | Hematemesis                 | History or evidence of liver disease |
| Intussusception*    | Rectal bleeding             | Crampy pain, distention, mass |
| Meckel diverticulum* | Rectal                     | Massive, bright red bleeding; no pain |
| Bacterial enteritis* | Rectal                     | Bloody diarrhea, fever |
| NSAID injury        | Usually hematemesis, rectal possible | Epigastric pain, coffee-ground emesis |
| >2 YEARS OLD        |                             |                          |
| Peptic disease      | See above                   | See above                |
| Esophageal varices  | See above                   | See above                |
| NSAID injury*       | See above                   | See above                |
| Inflammatory bowel disease | Usually rectal        | Crampy pain, poor weight gain, diarrhea |
| Bacterial enteritis* | See above                   | See above                |
| Pseudomembranous colitis | Rectal                   | History of antibiotic use, bloody diarrhea |
| Juvenile polyp      | Rectal                      | Painless, bright red blood in stool; not massive |
| Meckel diverticulum* | See above                   | See above                |
| Nodular lymphoid hyperplasia | Rectal           | Streaks of blood in stool, no other symptoms |
| Mallory-Weiss syndrome* | Hematemesis          | Bright red or coffee-ground, follows retching |
| Hemolytic uremic syndrome | Rectal                  | Thrombocytopenia, anemia, uremia |
| Hemorrhoids         | Rectal                      | Dilated external veins, blood with wiping |

NSAID, Nonsteroidal anti-inflammatory drug.
*Common
Treatment of GI bleeding should begin with an initial assessment, rapid stabilization, and a logical sequence of diagnostic tests. When a treatable cause is identified, specific therapy should be started. In many cases, the amount of blood is small, and no resuscitation is required. For children with large-volume bleeds, the ABCs of resuscitation (airway, breathing, circulation) should be addressed first (see Chapters 38 and 40). Oxygen should be administered and the airway protected with an endotracheal tube if massive hematemesis is present.
Fluid boluses and transfusion with packed red blood cells as required should be administered through two large-bore IVs. Frequent reassessment should continue to ensure maintenance of physiological stability (Fig. 126-2).

Chapter 127

ORAL CAVITY

EFFECTS OF SYSTEMIC DISEASE ON THE ORAL CAVITY

Medications taken for a variety of conditions may cause oral abnormalities. Drugs with anticholinergic properties diminish saliva production and increase the risk of dental caries and parotitis. Tetracyclines taken before the eruption of the permanent teeth stain the enamel. Excessive fluoride in vitamin preparations or in drinking water can result in mottled teeth. Gingival hypertrophy may be caused by cyclosporine, phenytoin, and calcium channel blockers.

Gastroesophageal reflux disease (GER) can lead to substantial enamel erosion and caries. Neonatal hyperbilirubinemia can result in bluish discoloration of the deciduous teeth. Renal failure is associated with mottled enamel of the permanent teeth. Congenital syphilis causes marked abnormalities in the shape of teeth, especially incisors and molars. Celiac disease can result in enamel defects. Crohn’s disease is associated with oral aphthous ulcers. Abnormal pigmentation of the lips and buccal mucosa is seen with Peutz-Jeghers syndrome and Addison disease. Candidiasis is seen commonly with immunodeficiency disorders and diabetes. Leukemic infiltrates result in gum hyperplasia and bleeding; treatment of neoplastic conditions can cause severe mucositis. Some tumors, including lymphoma, may present as mass lesions of the buccal cavity.

Osteogenesis imperfecta is associated with abnormal dentin and risk of caries. Children with ectodermal dysplasias commonly have malformed or missing teeth. Pierre Robin syndrome is associated with micrognathia and cleft palate. Disorders resulting in facial dysmorphism can have a profound effect on dental occlusion and mandibular function. Examples include mandibulofacial dysostosis, Crouzon syndrome, conditions associated with dwarfism, and others.

DECIDUOUS AND PRIMARY TEETH

Most infants are born without teeth. Natal teeth are present at birth, are usually supernumerary, and may be poorly attached. Usually, no treatment is necessary, but removal by a dentist may be needed if they are causing difficulties with feeding or injuries to the tongue. Table 127-1 presents the ages when normal deciduous teeth are acquired. The lower central incisors are typically the first to erupt, followed by the upper central incisors, lateral incisors, first molars, and bicuspids. Delayed eruption may occur in association with hypopituitarism, hypothyroidism, osteopetrosis, Gaucher disease, Down syndrome, cleft cranial dysplasia, and rickets. Deciduous teeth begin to be replaced by the permanent teeth at around age 6 years. The sequence of replacement is similar to that of the appearance of deciduous teeth.

DENTAL CARIES

Etiology

Dental caries, commonly referred to as “cavities,” occurs as a result of interactions between the tooth enamel, dietary carbohydrates, and oral flora. There is increased susceptibility if the enamel is abnormal or hypoplastic. Bacteria (Streptococcus mutans) that can adhere to and colonize the teeth, survive at low pH, and produce acids during fermentation of carbohydrates cause dental caries. The diet has a significant role. A classic example is “bottle mouth,” or baby bottle caries. This condition results when infants are allowed to have a bottle in the mouth for prolonged periods, especially during sleep, and with sweet beverages or milk in the bottle. Bacteria then have continuous substrate for acid production and can destroy multiple teeth, especially the upper incisors. Sticky sweet foods, such as candy, have the same effect.

Epidemiology and Treatment

Risk of caries is associated with lack of dental care and poor socioeconomic status and, predictably, is greatest in developing countries. Baby bottle caries is seen in 50% to 70% of low-income infants. Treatment of caries is with dental restorative surgery. The carious portion is removed and filled with silver amalgam or plastic. If the damage is severe, a protective crown may be required; extraction of the tooth may be necessary when not salvageable. If not properly treated, dental decay results in inflammation and infection of the dental pulp and surrounding alveolar bone, which can lead to abscess and facial space infections.

Prevention

Avoiding inappropriate use of bottles and excessive sweets is a commonsense remedy for baby bottle caries. Oral hygiene
The Digestive System

Section 17

THRUSH

Epidemiology

Oropharyngeal Candida albicans infection, or thrush, is common in healthy neonates. The organism may be acquired in the birth canal or from the environment. Persistent infection is common in breastfed infants as a result of colonization or infection of the mother’s nipples. Thrush in healthy older patients can occur, but should suggest the possibility of an immunodeficiency, broad-spectrum antibiotic use, or diabetes.

Clinical Manifestations

Thrush is easily visible as white plaques, often with a “fuzzy” appearance, on oral mucous membranes. When scraped with a tongue depressor, the plaques are difficult to remove, and the underlying mucosa is inflamed and friable. Clinical diagnosis is usually adequate, but may be confirmed by fungal culture or potassium hydroxide smear. Oropharyngeal candidiasis is sometimes painful (especially if associated with esophagitis) and can interfere with feeding.

Treatment

Thrush is treated with topical nystatin or an azole antifungal agent such as fluconazole. When the mother’s breasts are infected and painful, consideration should be given to treating her at the same time. Because thrush is commonly self-limited in newborns, withholding therapy in asymptomatic infants and treating only persistent or severe cases is a reasonable approach.

CLEFT LIP AND PALATE

Epidemiology

Cleft lip and palate occur separately or together and affect approximately 1 in 700 infants. It is more common in Asians (1:500) and least common in Africans (1:2500). Clefting occurs with two possible patterns: isolated soft tissue cleft palate or cleft lip with or without associated clefts of the hard palate. Isolated cleft palate is associated with a higher risk of other congenital malformations. The combined cleft lip/palate type has a male predominance.

Etiology

Cleft lip is due to hypoplasia of the mesenchymal tissues with subsequent failure of fusion. There is a strong genetic component; the risk is highest in children with affected first-degree relatives. Monozygotic twins are affected with only 60% concordance, suggesting other nongenomic factors. Environmental factors during gestation also increase risk, including drugs (phenytoin, valproic acid, thalidomide), maternal alcohol and tobacco use, dioxins and other herbicides, and possibly high altitude. Chromosomal and nonchromosomal syndromes are associated with clefting, as are specific genes in some families.

Clinical Manifestations and Treatment

Cleft lip can be unilateral or bilateral and associated with cleft palate and defects of the alveolar ridge and dentition. When present, palatal defects allow direct communication between the nasal and oral cavities, creating problems with speech and feeding. Management includes squeeze-bottle feedings, special nipples, nipples with attached shields to seal the palate, and gastrostomy in severe cases. Surgical closure of the cleft lip is usually done by 3 months of age. Closure of the palate follows, usually before 1 year of age. Missing teeth are replaced by prostheses. Cosmetic results are often good, but depend on the severity of the defect.

Complications

Speech is nasal as a result of the cleft palate. Surgical treatment is effective, but sometimes does not restore palatal function completely. Speech therapy or, occasionally, the use of a speech-assisting appliance may help. Frequent episodes of otitis media are common, as are defects of teeth and the alveolar ridge.

ESOPHAGUS AND STOMACH

GASTROESOPHAGEAL REFLUX

Etiology and Epidemiology

Gastroesophageal reflux (GER) is defined as the effortless retrograde movement of gastric contents upward into the esophagus or oropharynx. In infancy, GER is not always an abnormality. Physiologic GER (“spitting up”) is normal in infants younger than 8 to 12 months old. Nearly half of all infants are reported to spit up at 2 months of age. Infants who regurgitate meet the criteria for physiologic GER so long as they maintain adequate
Clinical Manifestations

The presence of GER is easy to observe in an infant who spits up. In older children, the refluxate is usually kept down by reswallowing, but GER may be suspected by associated symptoms, such as heartburn, cough, epigastric abdominal pain, dysphagia, wheezing, aspiration pneumonia, hoarse voice, failure to thrive, and recurrent otitis media or sinusitis. In severe cases of esophagitis, there may be laboratory evidence of anemia and hypoalbuminemia secondary to esophageal bleeding and inflammation.

When esophagitis develops as a result of acid reflux, esophageal motility and LES function are impaired further, creating a cycle of reflux and esophageal injury.

Laboratory and Imaging Studies

A clinical diagnosis is often sufficient in children with classic effortless regurgitation and no complications. Diagnostic studies are indicated if there are persistent symptoms or complications or if other symptoms suggest the possibility of GER in the absence of regurgitation. A child with recurrent pneumonia, chronic cough, or apneic spells without overt emesis may have occult GER. A barium upper GI series helps to rule out gastric outlet obstruction, malrotation, or other anatomic contributors to GER. Because of the brief nature of the examination, a negative barium study does not rule out GER. Another study, 24-hour esophageal pH probe monitoring, uses a pH electrode placed transnasally into the distal esophagus, with continuous recording of esophageal pH. Data are gathered for 24 hours and analyzed for the number and temporal pattern of acid reflux events. Esophageal impedance monitoring records the migration of electrolyte-rich gastric fluid in the esophagus. Endoscopy is useful to evaluate for esophagitis, esophageal stricture, and anatomic abnormalities.

Treatment

In otherwise healthy young infants, no treatment is necessary. For infants with complications of GER, an H2 blocker or proton-pump inhibitor may be offered (Table 128-1), but these have shown little benefit in infants with uncomplicated GER and/or fussiness. Prokinetic drugs, such as metoclopramide, occasionally are helpful by enhancing gastric emptying and increasing LES tone, but they are seldom very effective and may lead to complications. When severe symptoms persist despite medication, or if life-threatening aspiration is present, surgical intervention may be required. Fundoplication procedures, such as the Nissen operation, are designed to enhance the antireflux anatomy of the LES. In children with a severe neurologic defect who cannot tolerate oral or gastric tube feedings, placement of a feeding jejunostomy may be considered as an alternative to fundoplication. In older children, lifestyle changes should be discussed, including cessation of smoking, weight loss, not eating before bed or exercise, and limiting intake of caffeine, carbonation, and high-fat foods. However, proton pump inhibitor therapy is more effective in reducing symptoms and healing.

EOSINOPHILIC ESOPHAGITIS (EOE)

Etiology and Epidemiology

This chronic immune-mediated disorder is characterized by infiltration of eosinophils into mucosa of the esophagus. It is thought to be triggered by non-IgE-mediated allergic reactions to ingested foods or aeroallergens. EoE may have a familial connection; no specific gene has yet been identified. Incidence appears to be increasing with estimated prevalence of more than 4 per 10,000 children. It may be more common in males than females.

Clinical Manifestations

The presentation of EoE often varies with age. In young children, it may present with oral aversion, vomiting, and failure to thrive. In school-age children, it may present with vague abdominal pain or vomiting. In adolescents and adults, it presents with dysphagia and food impactions. These symptoms are attributed to the inflammatory response in the esophagus leading to edema and poor esophageal motility.

Laboratory and Imaging Studies

Diagnosis requires multilevel esophageal biopsies via flexible endoscopy with the finding of more than 15 eosinophils per high-power field (Fig. 128-1). Treatment with high-dose proton pump inhibitor therapy is recommended to exclude the possibility that findings are secondary to severe acidic esophageal injury. Gross findings at endoscopy include normal appearance, esophageal furrowing, trachealization, and eosinophilic abscesses (Fig. 128-2). A barium study may reveal
The Digestive System

a food impaction in an acutely symptomatic patient or esophageal stricture in someone with chronic disease.

**Treatment and Prognosis**

Exposure to identified causative antigens needs to be eliminated. Identification can be difficult, as typical allergy testing (skin prick, RAST, and immunocap assays) only identifies IgE-mediated antigens. Atopic patch testing may be more reliable but is not standardized and can be difficult to perform. One approach is to eliminate cow’s milk, soy, wheat, eggs, peanuts, and fish/shellfish from the diet, as these are the most common causative dietary antigens. Repeat endoscopies are often necessary to document efficacy of these eliminations. An elemental diet can also be used and is very effective, but often requires either nasogastric or gastrostomy administration because of its poor palatability.

Systemic glucocorticoids can decrease symptoms, but long-term use is discouraged secondary to complications. Swallowed “topical” glucocorticoids administered via a metered dose inhaler (fluticasone) or mixed as a slurry (budesonide)

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**Table 128-1** Treatment of Gastroesophageal Reflux

<table>
<thead>
<tr>
<th>THERAPIES</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONSERVATIVE THERAPIES</strong></td>
<td></td>
</tr>
<tr>
<td>Towel on caregiver’s shoulder</td>
<td>Cheap, effective. Useful only for physiologic reflux</td>
</tr>
<tr>
<td>Thickened feedings</td>
<td>Reduces number of episodes, enhances nutrition</td>
</tr>
<tr>
<td>Smaller, more frequent feedings</td>
<td>Can help some. Be careful not to underfeed child</td>
</tr>
<tr>
<td>Avoidance of tobacco smoke and alcohol</td>
<td>Always a good idea. May help reflux symptoms</td>
</tr>
<tr>
<td>Abstaining from caffeine</td>
<td>Inexpensive, offers some benefit</td>
</tr>
<tr>
<td>Positional therapy—upright in seat, elevate</td>
<td>Prone positioning with head of crib or bed up is helpful, but not for young infants because of risk of SIDS</td>
</tr>
<tr>
<td>Weight loss when indicated</td>
<td>Increased weight (especially abdominal) increases intra-abdominal pressure, leading to reflux</td>
</tr>
<tr>
<td><strong>MEDICAL THERAPY</strong></td>
<td></td>
</tr>
<tr>
<td>Proton-pump inhibitor</td>
<td>Effective medical therapy for heartburn and esophagitis</td>
</tr>
<tr>
<td>H$_2$ receptor antagonist</td>
<td>Reduces heartburn, less effective for healing esophagitis</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Enhances stomach emptying and LES tone. Real benefit is often minimal</td>
</tr>
<tr>
<td><strong>SURGICAL THERAPY</strong></td>
<td></td>
</tr>
<tr>
<td>Nissen or other fundoplication procedure</td>
<td>For life-threatening or medically unresponsive cases</td>
</tr>
<tr>
<td>Feeding jejunostomy</td>
<td>Useful in child requiring tube feeds. Delivering feeds downstream eliminates GERD</td>
</tr>
</tbody>
</table>

GERD, Gastroesophageal reflux disease; LES, lower esophageal sphincter; SIDS, sudden infant death syndrome.
have shown benefit. *Candida* esophagitis or oral thrush are the most common side effects.

Endoscopy can be used to relieve food impactions and to dilate esophageal strictures secondary to EoE. The prognosis for EoE is largely unknown. Symptoms tend to wax and wane over time.

**Complications**

Failure to thrive or weight loss may be seen due to difficulty in eating. Food impactions are a common complication in the older child and may require endoscopic removal. Chronic inflammation of the esophagus can predispose to esophageal strictures and possibly dysplasia.

**ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA**

**Etiology and Epidemiology**

The esophagus and trachea develop in close proximity to each other during weeks 4 to 6 of fetal life. Defects in the mesenchyme separating these two structures result in a tracheoesophageal fistula (TEF), often in association with other anomalies (renal, heart, spine, limbs). This defect occurs in about 1 in 3000 live births. TEF is not thought to be a genetic defect.

**Clinical Manifestations**

The most common forms of TEF occur with esophageal atresia; the "H-type" TEF without atresia is uncommon, as is esophageal atresia without TEF (Fig. 128-3). Associated defects include the VACTERL association—vertebral anomalies (70%), anal atresia (imperforate anus) (50%), cardiac anomalies (30%), TEF (70%), renal anomalies (50%), and limb anomalies (polydactyly, forearm defects, absent thumbs, syndactyly) (70%). A single-artery umbilical cord is often present. Infants with esophageal atresia have a history of polyhydramnios, exhibit drooling, and have mucus and saliva bubbling from the nose and mouth. Patients with a TEF are vulnerable to aspiration pneumonia. When TEF is suspected, the first feeding should be delayed until a diagnostic study is performed.

**Laboratory and Imaging Studies**

The simplest test for TEF is to gently attempt to place a 10F or larger tube via the mouth into the stomach. The passage of the tube is blocked at the level of the atresia. A chest x-ray reveals the tube coiled in the esophageal pouch. Air can be injected through the tube to outline the atretic pouch. Barium should not be used because of extreme risk of aspiration, but a tiny amount of dilute water-soluble contrast agent can be given carefully, then aspirated when the defect is clearly shown.

**Treatment and Prognosis**

The treatment of TEF is surgical. The fistula is divided and ligated. The esophageal ends are approximated and anastomosed. In some cases, primary anastomosis cannot be performed because of a long gap between the proximal and distal esophagus. Various techniques have been described to treat this problem, including pulling up the stomach, elongating the esophagus by myotomy, and simply delaying esophageal anastomosis and providing continuous suction to the upper pouch while allowing for growth.

**Complications**

The surgically reconstructed esophagus is not normal and is prone to poor motility, GER, anastomotic stricture, recurrent fistula,
and leakage. The trachea also is malformed; tracheomalacia and wheezing are common.

**ESOPHAGEAL FOREIGN BODIES**

**Etiology and Epidemiology**
Young children often place nonfood items in their mouths. When these items are swallowed, they may become lodged in the esophagus at the thoracic inlet or at the LES. The most common objects are coins. Smaller coins may pass harmlessly into the stomach, where they rarely cause symptoms. Other common esophageal foreign bodies include food items, small toys or toy parts, disk batteries, and other small household items. Children with a prior history of esophageal atresia or with poor motility secondary to GER or eosinophilic esophagitis are more prone to food impactions, which seldom occur in the normal esophagus.

**Clinical Manifestations**
Some children are asymptomatic, but most exhibit some degree of drooling, food refusal, or chest discomfort. Older children usually can point to the region of the chest where they feel the object to be lodged. Respiratory symptoms tend to be minimal, but cough or wheezing may be present, especially when the esophagus is completely blocked by a large object, such as a piece of meat, which presses on the trachea.

**Diagnosis**
Plain chest and abdominal radiographs should be taken when foreign body ingestion is suspected. Metallic objects are easily visualized. A plastic object often can be seen if the child is given a small amount of dilute x-ray contrast material to drink, although endoscopy is probably safer and more definitive.

**Treatment**
Endoscopy is ultimately necessary in most cases to remove an esophageal foreign body. Various devices can be used to remove the object, depending on its size, shape, and location. Coins usually are grasped with special-purpose forceps and removed. Nets, baskets, and snares also are available. Whenever objects that may threaten the airway are being recovered, endoscopy should be performed with endotracheal intubation and under general anesthesia. Removal is usually not necessary if the object is small and in the stomach as it will most likely pass without complication. Endoscopy is emergent for removal of any esophageal foreign body if symptomatic or if the ingested foreign body is a suspected disc battery in the esophagus or multiple magnets located in the upper tract.

**Complications**
Sharp objects may lacerate or perforate the esophagus; smooth objects present for a long time also may result in perforation due to ulceration. Corrosive objects, such as zinc-containing pennies and disc batteries, can cause considerable local tissue injury and esophageal perforation. Magnets can lead to perforation and fistula formation when they connect between adjacent loops of bowel.

**CAUSTIC INJURIES AND PILL ULCERS**

**Etiology and Epidemiology**
In adolescents, caustic ingestion injuries are usually the result of suicide attempts. In toddlers, ingestion of household cleaning products typically is accidental. Injurious agents include drain cleaners, toilet bowl cleaners, dishwasher detergents, and powerful bleaching agents. Childproof lids for commercial products offer some protection, but have not eliminated the problem. Lye-based drain cleaners, especially liquid products, cause the worst injuries because they are swallowed easily and liquefy tissue rapidly. Full-thickness burns can occur in seconds. Granular products are less likely to cause esophageal injury during accidental exposures because they burn the tongue and lips and often are expelled before swallowing. Less caustic agents, such as bleach and detergents, cause less serious injury. Pill injuries occur when certain medications (tetracyclines and nonsteroidal anti-inflammatory drugs [NSAIDs]) are swallowed without sufficient liquids, allowing prolonged direct contact of the pill with the esophageal mucosa.

**Clinical Manifestations**
Caustic burns cause immediate and severe mouth pain. The child cries out, drools, spits, and usually drops the container immediately. Burns of the lips and tongue are visible almost immediately. These burns clearly indicate the possibility of esophageal involvement, although esophageal injury can occur in the absence of oral burns. Symptoms may not be present; further evaluation by endoscopy usually is indicated with any significant history of caustic ingestion. Pill injury causes severe chest pain and often prominent odynophagia (painful swallowing) and dysphagia.

**Laboratory and Imaging Studies**
A chest x-ray should be obtained to rule out aspiration and to inspect for mediastinal air. The child should be admitted to the hospital and given intravenous (IV) fluids until endoscopy. The true extent of burns may not be endoscopically apparent immediately, but delayed endoscopy can increase the risk of perforation. Most endoscopists perform the initial endoscopy soon after injury, when the patient has been stabilized. The extent of injury and severity of the burn should be carefully determined. Risk of subsequent esophageal strictures is related to the degree of burn and whether the injury is circumferential.

**Treatment**
A nasogastric tube can be placed over a guidewire at the time of the initial endoscopy to provide a route for feeding and to stent the esophagus. Systemic steroid use has not been found to be beneficial in reducing stricture formation. Broad-spectrum antibiotics should be prescribed if infection is suspected.

**Complications**
Esophageal strictures, if they occur, usually develop within 1 to 2 months and can be treated with endoscopic
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dilation. There is a risk of perforation during dilation. When esophageal destruction is severe, surgical reconstruction of the esophagus using stomach or intestine may be necessary.

**PYLORIC STENOSIS**

*Etiology and Epidemiology*

Pyloric stenosis is an acquired condition caused by hypertrophy and spasm of the pyloric muscle, resulting in gastric outlet obstruction. It occurs in 6 to 8 per 1000 live births, has a 5-to-1 male predominance, and is more common in first-born children. Its cause is unknown.

**Clinical Manifestations**

Infants with pyloric stenosis typically begin vomiting during the first weeks of life, but onset may be delayed. The emesis becomes increasingly frequent and forceful as time passes. Vomiting differs from spitting up because of its extremely forceful and often projectile nature. The vomited material never contains bile, because the gastric outlet obstruction is proximal to the duodenum. This feature differentiates pyloric stenosis from most other obstructive lesions of early childhood. Affected infants are ravenously hungry early in the course of the illness, but become more lethargic with increasing malnutrition and dehydration. The stomach becomes massively enlarged with retained food and secretions, and gastric peristaltic waves are often visible in the left upper quadrant. A hypertrophied pylorus (the “olive”) may be palpated. As the illness progresses, very little of each feeding is able to pass through the pylorus, and the child becomes progressively thinner and more dehydrated.

**Laboratory and Imaging Studies**

Repetitive vomiting of purely gastric contents results in loss of hydrochloric acid; the classic laboratory finding is a **hypochloremic, hypokalemic metabolic alkalosis** with elevated blood urea nitrogen (BUN) secondary to dehydration. Jaundice with unconjugated hyperbilirubinemia may also occur. Plain abdominal x-rays typically show a huge stomach and diminished or absent gas in the intestine (Fig. 128-4). Ultrasound examination shows marked elongation and thickening of the pylorus (Fig. 128-5). A barium upper GI series also may be obtained whenever doubt about the diagnosis exists; this shows a “string sign” caused by barium moving through an elongated, constricted pyloric channel.
**Table 128-2**  Risk Factors for Peptic Ulcer Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
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</thead>
<tbody>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>NSAIDs, including aspirin</td>
</tr>
<tr>
<td>Tobacco use</td>
</tr>
<tr>
<td>Bisphosphonates</td>
</tr>
<tr>
<td>Potassium supplements</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Head trauma</td>
</tr>
<tr>
<td>Burn injury</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
</tbody>
</table>

NSAIDs, Nonsteroidal anti-inflammatory drugs.

**Treatment**

Treatment of pyloric stenosis includes IV fluid and electrolyte resuscitation followed by surgical pyloromyotomy. Before surgery, dehydration and hypochloremic alkalosis must be corrected, generally with an initial normal saline fluid bolus followed by infusions of half-normal saline containing 5% dextrose and potassium chloride when urine output is observed. In pyloromyotomy (often by laparoscopy), the pyloric muscle is incised longitudinally to release the constriction. Care is taken not to cut into the mucosa itself.

**PEPTIC DISEASE**

**Etiology and Epidemiology**

Acid-related injury can occur in the esophagus, stomach, or duodenum. Table 128-2 lists risk factors for peptic ulcer disease in children. *Helicobacter pylori* is responsible for more than half of ulcers in the stomach and duodenum in adults. *H. pylori* plays a significant but lesser role in childhood ulcer disease. Risk factors for acquisition of *H. pylori* are low socioeconomic status and poor sanitation, with the highest incidence in developing countries. Nonulcer dyspepsia includes upper abdominal symptoms (pain, bloating, nausea, early satiety) in the absence of gastric or duodenal ulceration. Nonulcer dyspepsia is not associated with *H. pylori* infection. GER (see Chapter 128) allows acidic gastric contents to injure the esophagus, resulting in *esophagitis*. Esophagitis is characterized by retrosternal and epigastric burning pain and is best diagnosed by endoscopy. It can range from minimal, with only erythema and microscopic inflammation on biopsy, to superficial erosions and finally to frank ulceration.

**Clinical Manifestations**

Typical symptoms are listed in Table 128-3. The presence of recurrent burning epigastric and retrosternal pain is a risk factor for esophagitis. With duodenal ulcers, pain typically occurs several hours after meals and often awakens patients at night. Eating tends to relieve the pain. Gastric ulcers differ in that pain is commonly aggravated by eating, resulting in weight loss. GI bleeding from either can occur. Many patients report symptom relief with antacids or acid blockers.

**Laboratory and Imaging Studies**

Endoscopy can be used to diagnose the underlying condition. Empiric therapy with H2 blockers or proton pump inhibitors can be used but may delay diagnosis of conditions such as *H. pylori*. For patients with chronic epigastric pain, the possibilities of inflammatory bowel disease, anatomic abnormality such as malrotation, pancreatitis, and biliary disease should be ruled out by appropriate testing when suspected (see Chapter 126 and Table 128-3 for recommended studies). Testing for *H. pylori* can be performed by biopsy during endoscopy with use of a urease test or presence histologically on tissue. If endoscopy is not done, noninvasive tests for infection can be done with reasonable accuracy with *H. pylori* fecal antigen and 13C urea breath tests (urea is metabolized into 13CO2 by the organism).

**Table 128-3**  Peptic Disorders, Symptoms, and Clinical Investigation

<table>
<thead>
<tr>
<th>SYNDROME AND ASSOCIATED SYMPTOMS</th>
<th>CLINICAL INVESTIGATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESOPHAGITIS</strong></td>
<td></td>
</tr>
<tr>
<td>Retrosternal and epigastric pain</td>
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<td>CBC, ESR, amylase, lipase, abdominal ultrasound</td>
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<td>Hematemesis</td>
<td>CBC, ESR, amylase, lipase, abdominal ultrasound</td>
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<td>Melena, hemato-positive stools</td>
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<td>Chronic vomiting</td>
<td></td>
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<td>Microcytic anemia</td>
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<td>Nocturnal pain</td>
<td></td>
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<tr>
<td>Other symptoms—same as for esophagitis and nonulcer dyspepsia</td>
<td></td>
</tr>
</tbody>
</table>

CBC, Complete blood count; ESR, erythrocyte sedimentation rate; GI, gastrointestinal.

**Treatment**

If *H. pylori* is present in association with ulcers, it should be treated with a multidrug regimen, such as omeprazole-clarithromycin-metronidazole, omeprazole-amoxicillin-clarithromycin, or omeprazole-amoxicillin-metronidazole, given twice daily for 1 to 2 weeks. Other proton-pump inhibitors may be substituted when necessary. Bismuth compounds are effective against *H. pylori* and can be considered. In North America, only the subsalicylate salt is available, the use of which raises...
some concerns about Reye syndrome and potential salicylate toxicity. Tetracycline is useful in adults, but should be avoided in children less than 8 years of age. In the absence of *H. pylori*, esophagitis and peptic ulcer disease are treated with a proton-pump inhibitor, which yields higher rates of healing than H₂ receptor antagonists. Gastric and duodenal ulcers heal in 4 to 8 weeks in at least 80% of patients. Esophagitis requires 4 to 5 months of proton-pump inhibitor treatment for optimal healing.

**CYCLIC VOMITING SYNDROME**

**Etiology and Epidemiology**

Cyclic vomiting syndrome (CVS) presents with intermittent episodes of prolonged nausea and vomiting with periods of health in between. It can occur at any age but is diagnosed most frequently in preschool to school-age children. It is thought to be a migraine variant; many patients have a positive family history of migraines, and some with CVS will eventually develop migraine headaches. Triggers to an episode often include viral illnesses, stressful or exciting events (holidays, birthdays, vacations), physical exhaustion, and menses.

**Clinical Manifestations**

Episodes can start at any time, but will often start in the early morning hours. Episodes are similar to each other in timing and duration. Repetitive vomiting can last hours to days. Patients can also have abdominal pain, diarrhea, and headaches. Those affected are typically pale, listless, and prefer to be left alone. They may have photo- or phonophobia.

**Laboratory and Imaging Studies**

There are no specific tests for CVS, which is diagnosed based on the history and the exclusion of other disorders. Diagnoses that should be considered include malrotation with intermittent volvulus, UPJ obstruction, eosinophilic esophagitis, and intracranial mass lesions, and metabolic disorders. Rome III criteria for diagnosis are outlined in Table 126-5.

**Treatment**

For the acute episode, supportive treatment includes hydration; dark, quiet environment; and antiemetics such as ondansetron. In addition, abortive therapy using antimigraine medications such as NSAIDs and triptans can be used. For those with frequent or prolonged episodes, prophylactic therapy can be used, such as cyproheptadine, tricyclic antidepressants, beta blockers, or topiramate.

**MIDGUT MALROTATION**

**Etiology and Epidemiology**

During early fetal life, the midgut is attached to the yolk sac and loops outward into the umbilical cord. Beginning at around 10 weeks’ gestation, the bowel reenters the abdomen and rotates counterclockwise around the superior mesenteric artery until the cecum arrives in the right lower quadrant. The duodenum rotates behind the artery and terminates at the ligament of Treitz in the left upper quadrant. The base of the mesentery becomes fixed along a broad attachment posteriorly, running from the cecum to the ligament of Treitz (Fig. 129-1A). When rotation is incomplete or otherwise abnormal, “malrotation” is present. Incomplete rotation occurs when the cecum stops near the right upper quadrant, and the duodenum fails to move behind the mesenteric artery; this results in an extremely narrow mesenteric root (see Fig. 129-1B) that makes the child susceptible to midgut volvulus, causing intestinal obstruction or mesenteric artery occlusion and intestinal infarction (Fig. 129-2). It is also common for abnormal mesenteric attachments (Ladd bands) to extend from the cecum across the duodenum, causing partial obstruction.

**Clinical Manifestations**

About 60% of children with malrotation present with symptoms of bilious vomiting during the first month of life. The remaining 40% present later in infancy or childhood. The emesis initially may be due to obstruction by Ladd bands without volvulus. When midgut volvulus occurs, the venous drainage of the gut is impaired; congestion results in ischemia, pain, tenderness, and often bloody emesis and stools. The bowel undergoes ischemic necrosis, and the child may appear septic. Physicians must be alert to the possibility of volvulus in patients with vomiting and fussiness or abdominal pain.

**Laboratory and Imaging Studies**

Plain abdominal x-rays generally show evidence of obstruction. Abdominal ultrasound may show evidence of malrotation. An upper gastrointestinal (GI) series shows the absence of a typical duodenal “C-loop,” with the duodenum instead remaining on the right side of the abdomen. Abnormal placement of the cecum on follow-through (or by contrast enema) confirms the diagnosis. Laboratory studies are nonspecific, showing evidence of dehydration, electrolyte loss, or evidence
The Digestive System

Figure 129-1  A, Normal rotation of the midgut. Note the long axis of mesenteric attachment (line). B, Midgut malrotation. Note the narrow mesentery, which predisposes to volvulus, and the presence of Ladd bands extending across the duodenum from the abnormally elevated cecum. (From Donellan WJ, editor: Abdominal Surgery of Infancy and Childhood, Luxembourg, 1996, Harwood Academic, pp 43/6, 43/8.)

Figure 129-2  Malrotation with volvulus. Midgut is twisted around the mesentery, with an area of darker, ischemic intestine visible. (Courtesy Robert Soper, MD.)

Treatment

Treatment is surgical. The bowel is untwisted, and Ladd bands and other abnormal membranous attachments are divided. The mesentery is spread out and flattened against the posterior wall of the abdomen by moving the cecum to the left side of the abdomen. Sutures may be used to hold the bowel in position, but postoperative adhesions tend to hold the mesentery in place, resulting in a broad attachment and eliminating the risk of recurrent volvulus. Necrotic bowel is resected and, at times, results in short gut syndrome.

INTESTINAL ATRESIA

Etiology and Epidemiology

Congenital partial or complete blockage of the intestine is a developmental defect that occurs in about 1 in 1500 live births. Atresia occurs in several forms (Fig. 129-3). One or more segments of bowel may be missing completely, there may be varying degrees of obstruction caused by webs or stenosis, or there may be obliteration of the lumen in cord-like bowel remnants. The end result is obstruction with upstream dilation of the bowel and small, disused intestine distally. When obstruction is complete or high grade, bilious vomiting and abdominal distention are present in the newborn period. In lesser cases, as in “windsock” types of intestinal webs, the obstruction is partial, and symptoms are more subtle.
Intestinal atresia presents with a history of polyhydramnios, abdominal distention and bilious vomiting in the neonatal period. If intestinal perforation is present, peritonitis and sepsis may develop.

Laboratory and Imaging Studies
Plain abdominal x-rays may localize the area of atresia and identify evidence of perforation, such as free air or calcifications typical of meconium peritonitis. Duodenal atresia appears as a double-bubble sign (gas in the stomach and enlarged proximal duodenum), with no gas distally. Atresias of the distal intestine are characterized by longer segments of dilated, air-filled bowel. Contrast studies are helpful if plain films are not sufficient. Atresia may be a complication of meconium ileus associated with cystic fibrosis. Laboratory evaluation for cystic fibrosis (see Chapter 137) is indicated in cases of small bowel atresia. A complete blood count, serum electrolytes, liver functions, and amylase should be measured to identify dehydration, pancreatitis, and other complications.

Treatment
The treatment of intestinal atresia is surgical, but surgery must be preceded by adequate hemodynamic stabilization of the patient. Intravenous (IV) fluids, nasogastric suction, and broad-spectrum antibiotics should be given.

OTHER CONGENITAL DISORDERS
Gastrochisis is an abdominal wall defect, not involving the umbilicus, through which intestinal contents have herniated. In contrast to omphalocele, the bowel is not covered by peritoneum or amniotic membrane. As a result, prolonged contact with the amniotic fluid typically causes a thick, exudative covering (a “peel”) on the exposed bowel. Gastrochisis is not associated with extraintestinal anomalies, but segments of intestinal atresia are common. After surgical reduction of the defect, return of normal bowel function may be slow and requires prolonged parenteral nutrition for infants with long atretic segments (short bowel syndrome) and infants with a thick peel.

Omphalocele is an abdominal wall defect through the umbilicus caused by failure of the intestine to return to the abdomen during fetal life. The bowel remains within the umbilical cord and is covered by peritoneum and amniotic membranes. This defect is associated with other congenital anomalies, especially cardiac defects, Beckwith-Wiedemann syndrome, and intestinal complications. Treatment is surgical closure, which sometimes must be performed in stages to fit the bowel into a congenitally small abdominal cavity.

Anorectal malformations, including imperforate anus and its variants, are embryologic defects recognized at birth by the absence of a normal anal opening. Evaluation of these infants should include observation for emergence of meconium from the urethra or fistulas on the perineum. A urinary catheter should be placed if urinary distention is present. In low lesions, a fistulous opening that drains meconium is
present on the perineum. Low lesions commonly are associated with fistulization between the bowel and bladder, vagina, or urethra. Lateral plain x-rays show the level of the defect and show gas in the bladder caused by a fistula. Initial treatment is a colostomy to divert the fecal flow, with subsequent anogenital reconstruction. The internal sphincter muscle is functionally absent in high lesions, and continence after repair is difficult to achieve. All children with imperforate anus require magnetic resonance imaging (MRI) of the lumbosacral spinal cord because of high incidence of tethered spinal cord. Urologic dysfunction is common and should be evaluated.

Hirschsprung disease is a motility defect caused by failure of ganglion cell precursors to migrate into the distal bowel during fetal life. The aganglionic distal segment does not exhibit normal motility and is functionally obstructed secondary to spasm. In 75% of cases, the involved segment is limited to the rectosigmoid; total colonic involvement is seen in 8%. Rarely, long segments of small bowel also are aganglionic. “Ultrashort” segment involves only a few centimeters of distal rectum. About 95% of normal infants pass stool spontaneously by 24 hours of age; 95% of infants with Hirschsprung disease do not. Symptoms of distal bowel obstruction occur with distention and bilious vomiting. If the diagnosis is not made quickly, enterocolitis can result, associated with a high rate of mortality. Diagnosis is based on examination and one or more diagnostic studies. Abdominal distention is present in most cases. Digital rectal examination reveals an empty rectum that clenches around the examiner’s finger, giving the impression of an elongated sphincter. When the finger is withdrawn, a powerful gush of retained stool is often expelled. A deep rectal biopsy specimen obtained surgically or by using a suction biopsy instrument is required for diagnosis. When no ganglion cells are shown in the submucosal plexus, accompanied by nerve trunk hyperplasia, the diagnosis is certain. Barium enema and anorectal manometry may be used before biopsy, but false-negative and false-positive results can occur. Therapy is surgical. When the bowel is markedly distended or inflamed, an initial colostomy usually is performed above the aganglionic segment, followed weeks later by one of several definitive repair procedures. The transanal pull-through excises the aganglionic bowel and creates a primary colorectal anastomosis without laparotomy. This procedure can be considered in patients with uncomplicated involvement limited to the rectosigmoid region.

Meckel diverticulum is a remnant of the fetal omphalomesenteric duct and is an outpouching of the distal ileum present in 1% to 2% of the population. Although most diverticula are asymptomatic throughout life, some cause massive, painless GI bleeding. Ectopic gastric tissue within the diverticulum causes ulceration of mucosa in the adjacent ileum. Meckel diverticulum may be a lead point for intussusception or may enable twisting (volvulus) of neighboring bowel around its vascular supply. Diverticulitis mimics appendicitis. Diagnosis may be made in most cases by technetium scan (Meckel scan), which labels the acid-producing mucosa. Because not all diverticula are seen, ultrasound, barium enteroclysis, or video capsule endoscopy may be useful. When the level of suspicion is high, surgical or laparoscopic investigation is warranted. The treatment is surgical excision.

The peak incidence of IBD in children is in the second decade of life. IBD includes Crohn’s disease (CD), which can involve any part of the gut, and ulcerative colitis (UC), which affects only the colon. The incidence of IBD is increasing, especially in industrialized countries, for reasons that are unclear. IBD is uncommon in tropical and Third World countries. It is more common in Jewish than in other ethnic populations. Genetic factors play a role in susceptibility, with significantly higher risk if there is a family history of IBD. Having a first-degree relative with IBD increases the risk about 30-fold. Susceptibility has been linked to some HLA subtypes, and linkage analysis has identified multiple other susceptibility loci on several chromosomes. Environmental factors (not yet identified) also seem to play a role because there is often nonconcordance among monozygotic twins. It is possible that viral infections can initiate the inflammatory process. Dietary triggers are unproven. Smoking doubles the risk of CD and halves the risk for UC.

Clinical manifestations depend on the region of involvement. UC involves only the colon, whereas CD can include the entire gut from mouth to anus. Colitis from either condition results in diarrhea, blood, and mucus in the stool; urgency; and tenesmus, a sensation of incomplete emptying after defecation. When colitis is severe, the child often awakens from sleep to pass stool. Toxic megacolon is a life-threatening complication characterized by fever, abdominal distention and pain, massively dilated colon, anemia, and low serum albumin owing to fecal protein losses. Symptoms of colitis always are present in UC and usually suggest the diagnosis early in its course. Extraintestinal manifestations of UC occur in a few patients and may include primary sclerosing cholangitis, arthritis, uveitis, and pyoderma gangrenosum (Table 129-1).

Symptoms can be subtle in CD. Small bowel involvement in CD is associated with loss of appetite, crampy postprandial pain, poor growth, delayed puberty, fever, anemia, and lethargy. Some symptoms may be present for some time before the diagnosis is made. Severe CD with fibrosis may cause partial or complete small bowel obstruction. Perineal abnormalities, including skin tags and fistulas, are another feature distinguishing CD from UC. Other extraintestinal manifestations of CD include arthritis, erythema nodosum, and uveitis or iritis.

**Laboratory and Imaging Studies**

Blood tests should include complete blood count, albumin, erythrocyte sedimentation rate, and C-reactive protein (Table 129-2). Anemia and elevated platelet counts are typical. Testing for abnormal serum antibodies can be helpful in diagnosing IBD and in discriminating between the colitis of CD and UC. Antineutrophil cytoplasmic antibody is found in about 66% of UC patients and in only a few CD
cases. **Anti–Saccharomyces cerevisiae antibody** is present in about 50% of CD patients and is uncommon in UC. More IBD-specific antibodies are being developed and include anti-OmpC, directed against an *Escherichia coli* membrane protein, and anti-CBir1, directed against bacterial flagellin, among others. Because there is overlap between CD and UC, none of these tests can discriminate absolutely between the two conditions.

In patients with suspected IBD, an **Upper GI series with small bowel follow-through** is often used to detect small bowel involvement. **Colonoscopy** is preferred over contrast enema because biopsy specimens can be obtained and because visual features can be diagnostic. Findings in UC include diffuse carpeting of the distal or entire colon with tiny ulcers and loss of hastral folds. Within the involved segment, no skip areas are present. In CD, ulcerations tend to be much larger with a linear, branching, or aphthous appearance; skip areas are usually present. **Upper endoscopy** cannot evaluate the jejunum and ileum, but is more sensitive than contrast studies in identifying proximal CD involvement. Other methods to detect small bowel involvement include **video capsule endoscopy**; computed tomography (CT) scanning, which can detect small bowel disease as well as abscesses; and **MR enterography**, which has the advantage of no radiation and good sensitivity for finding active bowel disease.

**Treatment**

**Ulcerative Colitis**

UC is treated with the aminosalicylate drugs, which deliver **5-aminosalicylic acid** (5-ASA) to the distal gut. Because it is rapidly absorbed, pure 5-ASA (mesalamine) must be specially packaged in coated capsules or pills or taken as a suppository to be effective in the colon. Other aminosalicylates (sulfasalazine, olsalazine, and balsalazide) use 5-ASA covalently linked to a carrier molecule. Sulfasalazine is the least expensive, but side effects resulting from its sulfapyridine component are common. When aminosalicylates alone cannot control the disease, steroid therapy may be required to induce remission. Whenever possible, steroids should not be used for long-term therapy. An immunosuppressive drug, such as **6-mercaptopurine** or **azathioprine**, is useful to spare excessive steroid use in difficult cases. More potent immunosuppressives, such as cyclosporine or anti–tumor necrosis factor (TNF) agents such as infliximab may be used as rescue therapy when other treatments fail. Surgical colectomy with ileoanal anastomosis is an option for unresponsive severe disease or

<table>
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<tr>
<th>Table 129-1</th>
<th>Comparison of Crohn’s Disease and Ulcerative Colitis</th>
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<tbody>
<tr>
<td><strong>FEATURE</strong></td>
<td><strong>CROHN’S DISEASE</strong></td>
</tr>
<tr>
<td>Malaise, fever, weight loss</td>
<td>Common</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>Common</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Common</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>Common</td>
</tr>
<tr>
<td>Ileal involvement</td>
<td>Common</td>
</tr>
<tr>
<td>Strictures</td>
<td>Common</td>
</tr>
<tr>
<td>Fistula</td>
<td>Common</td>
</tr>
<tr>
<td>Skip lesions</td>
<td>Common</td>
</tr>
<tr>
<td>Transmural Involvement</td>
<td>Usual</td>
</tr>
<tr>
<td>Crypt abscesses</td>
<td>Variable</td>
</tr>
<tr>
<td>Intestinal granulomas</td>
<td>Common</td>
</tr>
<tr>
<td>Risk of cancer*</td>
<td>Increased</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>Common</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>Common</td>
</tr>
<tr>
<td>Osteopenia at onset</td>
<td>Yes</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Rare</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>Rare</td>
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*Colonic cancer, cholangiocarcinoma, lymphoma in Crohn’s disease.

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<tr>
<th>Table 129-2</th>
<th>Diagnostic Studies for Inflammatory Bowel Disease</th>
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<td><strong>BLOOD TESTS</strong></td>
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<tr>
<td>CBC with WBC differential</td>
<td>Anemia, elevated platelets suggest IBD</td>
</tr>
<tr>
<td>ESR</td>
<td>Elevated in many, but not all, IBD patients</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Elevated in many, but not all, IBD patients</td>
</tr>
<tr>
<td>Albumin</td>
<td>May be low in IBD due to fecal loss</td>
</tr>
<tr>
<td>ASCA</td>
<td>Found in about 50% of CD patients and few UC patients</td>
</tr>
<tr>
<td>Atypical p-ANCA</td>
<td>Found in most UC patients and few CD patients</td>
</tr>
<tr>
<td>Anti-OmpC</td>
<td>Found in some UC and CD patients, rare in non-IBD</td>
</tr>
<tr>
<td>Anti-CBir1</td>
<td>Found in about 50% of CD patients</td>
</tr>
<tr>
<td><strong>IMAGING STUDIES</strong></td>
<td></td>
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<tr>
<td>Upper GI series with SBFT</td>
<td>Evaluate for ileal and jejunal CD</td>
</tr>
<tr>
<td>CT scan</td>
<td>Used to detect abscess, small bowel involvement</td>
</tr>
<tr>
<td>Tagged WBC scan</td>
<td>Sometimes helpful in determining extent of disease</td>
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<tr>
<td>Magnetic Resonance Enterography</td>
<td>Used to detect bowel thickening, inflammation, and strictures as well as abscesses and fistulas</td>
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<tr>
<td><strong>ENDOSCOPY</strong></td>
<td></td>
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<tr>
<td>Upper endoscopy</td>
<td>Evaluate for CD of esophagus, stomach, and duodenum; obtain tissue for histologic diagnosis</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Show presence or absence of colitis and terminal ileal CD; obtain tissue for histology</td>
</tr>
<tr>
<td>Video Capsule endoscopy</td>
<td>Emerging role in diagnosis of small bowel CD, more sensitive than upper GI series with SBFT</td>
</tr>
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</table>

**Anti-OmpC, Antibody to outer membrane protein C; ASCA, anti–Saccharomyces cerevisiae antibody; atypical p-ANCA, atypical perinuclear staining by antineutrophil cytoplasmic antibody; CBC, complete blood count; CD, Crohn’s disease; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; IBD, inflammatory bowel disease; SBFT, small bowel follow-through; WBC, white blood cell.**
Crohn’s Disease
Inflammation in CD typically responds less well to aminosalicylates; oral or IV steroids are more important in inducing remission. To avoid the need for repetitive steroid therapy, immunosuppressive drugs, usually either azathioprine or 6-mercaptopurine, are often started soon after diagnosis. CD that is difficult to control also may be treated with subcutaneous methotrexate or with agents that block the action of TNF-α. **Infliximab** is the most effective such drug and is given intravenously. Other antibodies that inhibit white blood cell (WBC) migration or action, such as natalizumab, also show promise. As with UC, surgery is sometimes necessary, usually because of obstructive symptoms, abscess, or severe, unremitting symptoms. Because surgery is not curative in CD, its use must be limited, and the length of bowel resection must be minimized.

**CELIAC DISEASE**

**Etiology and Epidemiology**
Celiac disease is an injury to the mucosa of the small intestine caused by the ingestion of gluten (a protein component) from wheat, rye, barley, and related grains. Rice does not contain gluten and can be eaten freely, as can special pure preparations of oats not contaminated by other grains. In its severe form, celiac disease causes malabsorption and malnutrition. Diagnosis was based on the presence of typical symptoms, followed by small bowel biopsy. The availability of more sensitive and specific serologic testing has revealed many patients with few or no gastrointestinal symptoms who have early, attenuated, or latent disease. Approximately 1 in 110 persons in the United States have celiac disease, but only a small proportion have been diagnosed. The disease is seen in association with type 1 diabetes, thyroiditis, Turner syndrome, and trisomy 21.

**Clinical Manifestations**

**Decision-Making Algorithms**

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Diarrhea
Pubertal Delay
Failure to Thrive

Symptoms can begin at any age when gluten-containing foods are given. Diarrhea, abdominal bloating, failure to thrive, irritability, decreased appetite, and ascites caused by hypoproteinemia are classic. Children may be minimally symptomatic or may be severely malnourished. Constipation is found in a few patients, probably because of reduced intake. A careful inspection of the child’s growth curve and evaluation for reduced subcutaneous fat and abdominal distention are crucial. Celiac disease should be considered in any child with chronic abdominal complaints. Extraintestinal manifestations include osteoporosis, pulmonary hemorrhage, seizures/encephalopathy, dermatitis herpetiformis, and erythema nodosum.

**Laboratory and Imaging Studies**
Serologic markers include IgA antiendomysial antibody and IgA tissue transglutaminase antibody. Because IgA deficiency is common in celiac disease, total serum IgA also must be measured to document the accuracy of these tests. In the absence of IgA deficiency, either test yields a sensitivity and specificity of 95%. An endoscopic **small bowel biopsy** is essential to confirm the diagnosis and should be performed while the patient is still taking gluten. The biopsy specimen shows various degrees of villous atrophy (short or absent villi), mucosal inflammation, crypt hyperplasia, and increased numbers of intraepithelial lymphocytes. When there is any question about response to treatment, a repeat biopsy specimen may be obtained several months later. Other laboratory studies should be performed to rule out complications, including complete blood count, calcium, phosphate, vitamin D, iron, total protein and albumin, and liver function tests. Mild elevations of the transaminases are common and should normalize with dietary therapy.

**Treatment**
Treatment consists of complete elimination of gluten from the diet. Consultation with a dietitian experienced in celiac disease is helpful, as is membership in a celiac disease support group. Lists of prepared foods that contain hidden gluten are particularly important for patients to use. Starchy foods that are safe include rice, soy, tapioca, buckwheat, potatoes, and (pure) oats. Many resources also are available via the Internet to help families cope with the large changes in diet that are required. Most patients respond clinically within a few weeks with weight gain, improved appetite, and improved sense of well-being. Histologic improvement lags behind clinical response, requiring several months to normalize.

**MILK AND SOY PROTEIN INTOLERANCE (ALLERGIC COLITIS)**
SEE CHAPTER 34.

**INTUSSUSCEPTION**

**Etiology and Epidemiology**
Intussusception is the “telescoping” of a segment of proximal bowel (the intussusceptum) into downstream bowel (the intussuscipiens). Most cases occur in infants 1 to 2 years old; in this age group, nearly all cases are idiopathic. Viral-induced lymphoid hyperplasia may produce a lead point in these children. In older children, the proportion of cases caused by a pathologic lead point increases. In young children, **ileocolonic** intussusception is common; the ileum invaginates into the colon, beginning at or near the ileocecal valve. When pathologic lead points are present, the intussusception may be ileoileal, jejunoileal, or jejunojejunal.

**Clinical Manifestations**

**Decision-Making Algorithms**

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Abdominal Pain
Gastrointestinal Bleeding
Irritable Infant
An infant with intussusception has sudden onset of crampy abdominal pain; the infant's knees draw up, and the infant cries out and exhibits pallor with a colicky pattern occurring every 15 to 20 minutes. Feedings are refused. As the intussusception progresses, and obstruction becomes prolonged, bilious vomiting becomes prominent, and the dilated, fatigued intestine generates less pressure and less pain. As the intussuscepted bowel is pulled further and further into the downstream intestine by motility, the mesentery is pulled with it and becomes stretched and compressed. The venous outflow from the intussuscptum is obstructed, leading to edema, weeping of fluid, and congestion with bleeding. Third space fluid losses and “currant jelly” stools result. Another unexpected feature of intussusception is lethargy. Between episodes of pain, the infant is glassy-eyed and groggy and appears to have been sedated. A sausage-shaped mass caused by the swollen, intussuscepted bowel may be palpable in the right upper quadrant or epigastrium.

**Laboratory and Imaging Studies**

The diagnosis depends on the direct demonstration of bowel within bowel. A simple way of showing this is by abdominal ultrasound. If the ultrasound is positive, or if good visualization has not been achieved, a pneumatic or contrast enema under fluoroscopy is indicated. This is a potentially useful Hay to both identify and treat intussusception. Air and barium can show the intussusception quickly and, when administered with controlled pressure, usually can reduce it completely. The success rate for pneumatic reduction is probably a bit higher than hydrostatic reduction with barium and approaches 90% if done when symptoms have been present for less than 24 hours. The pneumatic enema has the additional advantages over barium of not preventing subsequent radiologic studies and having no risk of causing barium peritonitis if perforation occurs. Nonoperative reduction should not be attempted if the patient is unstable or has evidence of pre-existing perforation or peritonitis.

**Treatment**

Therapy must begin with placement of an IV catheter and a nasogastric tube. Before radiologic intervention is attempted, the child must have adequate fluid resuscitation to correct the often severe dehydration caused by vomiting and third space losses. Ultrasound may be performed before the fluid resuscitation is complete. Surgical consultation should be obtained early as the surgeon may prefer to be present during nonoperative reduction. If pneumatic or hydrostatic reduction is successful, the child should be admitted to the hospital for overnight observation of possible recurrence (risk is 5% to 10%). If reduction is not complete, emergency surgery is required. The surgeon attempts gentle manual reduction but may need to resect the involved bowel after failed radiologic reduction because of severe edema, perforation, a pathologic lead point (polyp, Meckel diverticulum), or necrosis.

**APPENDICITIS**

**Etiology and Epidemiology**

Appendicitis is the most common surgical emergency in childhood. The prevalence of appendicitis varies by age with the peak between the ages of 10 and 12 years. It is much less common in children under the age of 5. Appendicitis begins with obstruction of the lumen, most commonly by fecal matter (fetalith), but appendiceal obstruction also can occur, secondary to hyperplasia of lymphoid tissue associated with viral infections or rarely the presence of neoplastic tissue, such as an appendiceal carcinoid tumor. Trapped bacteria proliferate and begin to invade the appendiceal wall, inducing inflammation and secretion. The obstructed appendix becomes engorged, its blood supply is compromised, and it finally ruptures. The entire process is rapid, with appendiceal rupture usually occurring within 48 hours of the onset of symptoms.

**Clinical Manifestations**

Classic appendicitis begins with visceral pain, localized to the periumbilical region. Nausea and vomiting occur soon after, triggered by the appendiceal distention. As the inflammation begins to irritate the parietal peritoneum adjacent to the appendix, somatic pain fibers are activated, and the pain localizes to the right lower quadrant. Examination of the patient reveals a tender right lower quadrant. Voluntary guarding is present initially, progressing to rigidity, then to rebound tenderness with rupture and peritonitis. These classic findings may not be present, especially in young children or if the appendix is retrocecal, covered by omentum, or in another unusual location. Clinical prediction rules have been developed for the diagnosis of appendicitis. The Alvarado/MANTRELS rule is scored by 1 point for each of the following: migration of pain to the right lower quadrant, anorexia, nausea/vomiting, rebound pain, temperature of at least 37.3°C, and WBC shift to greater than 75% neutrophils; 2 points are given for each of tenderness in the right lower quadrant and leukocytosis greater than 10,000/µL. Children with a score of 4 or less are unlikely to have appendicitis; a score of 7 or greater increases the likelihood that the patient has appendicitis. When classic history and physical examination findings are present, the patient is taken to the operating room. When doubt exists, imaging is helpful to rule out complications (right lower quadrant abscess, liver disease) and other disorders, such as mesenteric adenitis and ovarian or fallopian tube disorders. If the evaluation is negative and some doubt remains, the child should be admitted to the hospital for close observation and serial examinations.

**Laboratory and Imaging Studies**

The history and examination are often enough to make the diagnosis, but laboratory and imaging studies are helpful when the diagnosis is uncertain (Table 129-3). A WBC count greater than 10,000/mm3 is found in 89% of patients with appendicitis and 93% with perforated appendicitis. This criterion is met by 62% of abdominal pain patients without appendicitis. Urinalysis is done to rule out urinary tract infection, and x-rays of the chest or the kidney, ureter, and bladder (KUB) rule.
out lower lobe pneumonia masquerading as abdominal pain. Amylase, lipase, and liver enzymes are done to look for pancreatic or liver and gallbladder disease. The plain abdominal x-ray may reveal a calcified fecalith, which strongly suggests the diagnosis. When these studies are inconclusive, imaging is indicated with an abdominal ultrasound or CT scan, which may reveal the presence of an enlarged, thick-walled appendix with surrounding fluid. A diameter of more than 6 mm is considered diagnostic.

Treatment
Treatment of appendicitis is surgical. Simple appendectomy is curative if performed before perforation. With perforation, a course of postoperative IV antibiotics is required. Broad-spectrum coverage is necessary to cover the mixed bowel flora.

Chapter 130
LIVER DISEASE

CHOLESTASIS
Etiology and Epidemiology
Cholestasis is defined as reduced bile flow and is characterized by elevation of the conjugated, or direct, bilirubin fraction. This condition must be distinguished from ordinary neonatal jaundice, in which the direct bilirubin is never elevated (see Chapter 62). Neonatal jaundice that is secondary to unconjugated hyperbilirubinemia is the result of immature hepatocyte excretory function or hemolysis, which increases the production of bilirubin. When direct bilirubin is elevated, many potentially serious disorders must be considered (Fig. 130-1). Emphasis must be placed on the rapid diagnosis of treatable and potentially imminent lethal disorders, especially biliary atresia and metabolic disorders, such as galactosemia or tyrosinemia.

Laboratory and Imaging Studies
The laboratory approach to diagnosis of a neonate with cholestatic jaundice is presented in Table 130-1. Noninvasive studies may aid a rapid diagnosis. Early imaging studies are performed to evaluate for biliary obstruction and other anatomic lesions that may be surgically treatable. When necessary to rule out biliary atresia or to obtain prognostic information, liver biopsy is a final option (Fig. 130-2).

Treatment
Treatment of extrahepatic biliary atresia is the surgical Kasai procedure, in which the fibrotic extrahepatic bile duct remnant

Table 129-3
Diagnostic Studies in Suspected Appendicitis

<table>
<thead>
<tr>
<th>INITIAL LABORATORY TESTING</th>
<th>FOLLOW-UP STUDIES*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential</td>
<td>Abdominal ultrasound</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>CT scan of abdomen</td>
</tr>
<tr>
<td>Amylase and lipase</td>
<td></td>
</tr>
<tr>
<td>ALT, AST, GGT</td>
<td></td>
</tr>
<tr>
<td>Flat and upright abdominal radiographs (KUB)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 130-1  Differential diagnosis of jaundice in childhood. G6PD, Glucose-6-phosphate dehydrogenase; RBC, red blood cell.
Table 130-1 Laboratory and Imaging Evaluation of Neonatal Cholestasis

<table>
<thead>
<tr>
<th>EVALUATION</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INITIAL TESTS</strong></td>
<td></td>
</tr>
<tr>
<td>Total and direct bilirubin</td>
<td>Elevated direct fraction confirms cholestasis</td>
</tr>
<tr>
<td>AST, ALT</td>
<td>Hepatocellular injury</td>
</tr>
<tr>
<td>GGT</td>
<td>Biliary obstruction/injury</td>
</tr>
<tr>
<td>RBC galactose-1-phosphate uridyltransferase</td>
<td>Galactosemia</td>
</tr>
<tr>
<td>α₁-Antitrypsin level</td>
<td>α₁-Antitrypsin deficiency</td>
</tr>
<tr>
<td>Urinalysis and urine culture</td>
<td>Urinary tract infection can cause cholestasis in neonates</td>
</tr>
<tr>
<td>Blood culture</td>
<td>Sepsis can cause cholestasis</td>
</tr>
<tr>
<td>Serum amino acids</td>
<td>Aminoacidopathies</td>
</tr>
<tr>
<td>Urine organic acids</td>
<td>Organic acidurias</td>
</tr>
<tr>
<td>Very long chain fatty acids</td>
<td>Zellweger syndrome, peroxisomal disorders</td>
</tr>
<tr>
<td>Carnitine profile</td>
<td>Mitochondrial and fatty acid oxidation disorders</td>
</tr>
<tr>
<td>Sweat chloride or CF mutation analysis</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Urine culture for cytomegalovirus</td>
<td>Congenital cytomegalovirus infection</td>
</tr>
<tr>
<td><strong>INITIAL IMAGING STUDY</strong></td>
<td></td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>Choledochal cyst, gallstones, mass lesion, Caroli disease</td>
</tr>
<tr>
<td><strong>SECONDARY IMAGING STUDY</strong></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary scintigraphy</td>
<td>Evaluate for biliary atresia</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Percutaneous liver biopsy</td>
<td>Biliary atresia, idiopathic giant cell hepatitis, α₁-antitrypsin deficiency</td>
</tr>
</tbody>
</table>

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CF, cystic fibrosis; GGT, γ-glutamyltransferase; RBC, red blood cell.

Figure 130-2 Flow chart for evaluation of neonatal cholestasis.
Liver disease is removed and replaced with a roux-en-Y loop of jejunum. This operation must be performed before 3 months of age to have the best chance of success. Even so, the success rate is low; many children require liver transplantation. Some metabolic causes of neonatal cholestasis are treatable by dietary manipulation (galactosemia) or medication (tyrosinemia); all affected patients require supportive care. This includes fat-soluble vitamin supplements (vitamins A, D, E, and K) and formula containing medium-chain triglycerides, which can be absorbed without bile salt–induced micelles. Choleresic agents, such as ursodeoxycholic acid, may improve bile flow in some conditions.

**Viral Hepatitis**

SEE CHAPTER 113.

**Fulminant Liver Failure**

**Etiology and Epidemiology**

Fulminant liver failure is defined as severe liver disease with onset of hepatic encephalopathy within 8 weeks after initial symptoms, in the absence of chronic liver disease. Etiology includes viral hepatitis, metabolic disorders, autoimmune hepatitis, ischemia, neoplastic disease, and toxins (Table 130-2).

**Clinical Manifestations**

Liver failure is a multisystem disorder with complex interactions among the liver, kidneys, vascular structures, gut, central nervous system (CNS), and immune function. Hepatic encephalopathy is characterized by varying degrees of impairment (Table 130-3). Respiratory compromise occurs as severity of the failure increases and requires early institution of ventilatory support. Hypoglycemia resulting from impaired glycogenolysis and gluconeogenesis must be prevented. Renal function is impaired, and frank renal failure, or hepatorenal syndrome, may occur. This syndrome is characterized by low urine output, azotemia, and low urine sodium content. Ascites develops secondary to hypoalbuminemia and disordered regulation of fluid and electrolyte homeostasis. Increased risk of infection occurs and may cause death. Esophageal varices may cause significant hemorrhage, whereas hypersplenism from portal hypertension may produce thrombocytopenia.

**Laboratory and Imaging Studies**

Coagulation tests and serum albumin are used to follow hepatic synthetic function. These tests are confounded by administration of blood products and clotting factors. Vitamin K should be administered to maximize the liver's ability to synthesize factors II, VII, IX, and X. In addition to monitoring prothrombin time and partial thromboplastin time, many centers measure factor V serially as a sensitive index of synthetic function. Renal function tests, electrolytes, serum ammonia, blood counts, and urinalysis also should be followed. In the setting of acute liver failure, liver biopsy may be indicated to ascertain the nature and degree of injury and estimate the likelihood of recovery. In the presence of coagulopathy, biopsy must be done using a transjugular or surgical approach.

**Treatment**

Because of the life-threatening and complex nature of this condition, management must be carried out in an intensive care unit at a liver transplant center. Treatment of acute liver failure is supportive; the definitive lifesaving therapy is liver transplantation. Supportive measures are listed in Table 130-4.
Efforts are made to treat metabolic derangements, avoid hypoglycemia, support respiration, minimize hepatic encephalopathy, and support renal function.

**CHRONIC LIVER DISEASE**

**Etiology and Epidemiology**

Chronic liver disease in childhood is characterized by the development of cirrhosis and its complications, and by progressive hepatic failure. Causative conditions may be congenital or acquired. Major congenital disorders leading to chronic disease include biliary atresia, tyrosinemia, untreated galactosemia, and α₁-antitrypsin deficiency. In older children, hepatitis B or C virus, autoimmune hepatitis, Wilson disease, primary sclerosing cholangitis, cystic fibrosis, and biliary obstruction secondary to choledochal cyst are leading causes.

**Clinical Manifestations**

Chronic liver disease is characterized by the consequences of portal hypertension, impaired hepatocellular function, and cholestasis. **Portal hypertension** caused by cirrhosis results in risk of gastrointestinal bleeding, ascites, and reduced hepatic blood flow. Blood entering the portal vein from the splenic and mesenteric veins is diverted to collateral circulation that bypasses the liver, enlarging these previously tiny vessels in the esophagus, stomach, and abdomen. **Esophageal varices** are particularly prone to bleed, but bleeding also can occur from hemorrhoidal veins, engorged gastric mucosa, and gastric varices. **Ascites** develops as a result of weeping of a high-pressure ultrafiltrate from the surfaces of the viscera and is at risk of becoming infected (spontaneous bacterial peritonitis); ascites can often be massive and interfere with patient comfort and respiration. The spleen enlarges secondary to impaired splenic vein outflow, causing excessive scavenging of platelets and white blood cells; this increases the patient’s susceptibility to bleeding and infection.

**Impaired hepatocellular function** is associated with coagulopathy unresponsive to vitamin K, low serum albumin, elevated ammonia, and **hepatic encephalopathy**. The diversion...
of portal blood away from the liver via collateral circulation worsens this process. Malaise develops and contributes to poor nutrition, leading to muscle wasting and other consequences. Chronic cholestasis causes debilitating pruritus and deepening jaundice. The reduced excretion of bile acids impairs absorption of fat calories and fat-soluble vitamins, which contributes to the poor nutritional state. Deficiency of vitamin K impairs production of clotting factors II, VII, IX, and X and increases the risk of bleeding. Vitamin E deficiency leads to hematologic and neurologic consequences unless corrected.

**Laboratory and Imaging Studies**

Laboratory studies include specific tests for diagnosis of the underlying illness and testing to monitor the status of the patient. Children presenting for the first time with evidence of chronic liver disease should have a standard investigation (Table 130-5). Monitoring should include coagulation tests, electrolytes and renal function testing, complete blood count with platelet count, transaminases, alkaline phosphatase, and γ-glutamyltransferase at appropriate intervals. Frequency of testing should be tailored to the pace of the patient’s illness. Ascites fluid can be tested for infection by culture and cell count and generally is found to have an albumin concentration lower than that of serum.

**Treatment**

Treatment of chronic liver disease is complex. Supportive care for each of the many problems encountered in these patients is outlined in Table 130-6. Ultimately, survival depends on the availability of a donor liver and the patient’s candidacy for transplantation. When transplantation is not possible or is delayed, palliative procedures, such as portosystemic shunts, can be considered. The transjugular intrahepatic portosystemic shunt is an expandable stent placed between the hepatic vein and a branch of the portal vein within the hepatic parenchyma. This procedure is performed using catheters inserted via the jugular vein and is entirely nonsurgical. All portosystemic shunts carry increased risk of hepatic encephalopathy.

**SELECTED CHRONIC HEPATIC DISORDERS**

**Wilson Disease**

**Table 130-5** Laboratory and Imaging Investigation of Chronic Liver Disease

<table>
<thead>
<tr>
<th>METABOLIC TESTING</th>
<th>Serum albumin</th>
<th>AST, ALT, GGT, alkaline phosphatase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum α_1-antitrypsin level</td>
<td>Total and direct bilirubin</td>
<td></td>
</tr>
<tr>
<td>α_1-Antitrypsin phenotype if low serum level</td>
<td>Serum cholyglycine or bile acids</td>
<td></td>
</tr>
<tr>
<td>Serum ceruloplasmin</td>
<td>Serum cholesterol</td>
<td></td>
</tr>
<tr>
<td>Sweating chloride, CF gene tests if CF suspected</td>
<td>Ultrasound examination of liver and bile ducts</td>
<td></td>
</tr>
<tr>
<td>Testing for other specific conditions as indicated by clinical/laboratory findings</td>
<td>Doppler ultrasound of hepatic vessels*</td>
<td></td>
</tr>
<tr>
<td>VIRAL HEPATITIS</td>
<td>Magnetic resonance cholangiography</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Magnetic resonance angiography of hepatic vessels*</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B viral DNA, HBeAg if HBsAg positive</td>
<td>Percutaneous or endoscopic cholangiography*</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C antibody</td>
<td>Liver biopsy*</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C antibody confirmatory test if positive</td>
<td>ANATOMIC EVALUATION</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C viral RNA, genotype if antibody confirmed</td>
<td>Ultrasound of liver, pancreas, and biliary tree</td>
<td></td>
</tr>
<tr>
<td>AUTOIMMUNE HEPATITIS</td>
<td>Consider magnetic resonance cholangiography or ERCP if evidence of biliary process</td>
<td></td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Liver biopsy—as required for diagnosis or prognosis</td>
<td></td>
</tr>
<tr>
<td>Liver-kidney microsomal antibody</td>
<td>TESTS TO EVALUATION NUTRITIONAL STATUS</td>
<td></td>
</tr>
<tr>
<td>Anti-smooth muscle antibody</td>
<td>Height, weight, skinfold thickness</td>
<td></td>
</tr>
<tr>
<td>ANITIHEPATITIS</td>
<td>25-Hydroxyvitamin D level</td>
<td></td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibody</td>
<td>Vitamin A level</td>
<td></td>
</tr>
<tr>
<td>Total serum IgG (usually elevated)</td>
<td>Vitamin E level</td>
<td></td>
</tr>
<tr>
<td>TESTS TO EVALUATE LIVER FUNCTION AND INJURY</td>
<td>Prothrombin time and partial thromboplastin time before and after vitamin K administration</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time and partial thromboplastin time</td>
<td>Serum albumin and prealbumin</td>
<td></td>
</tr>
<tr>
<td>Serum ammonia</td>
<td>CBC with platelet count</td>
<td></td>
</tr>
</tbody>
</table>

*Perform when indicated to obtain specific anatomic information.

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CF, cystic fibrosis; ERCP, endoscopic retrograde cholangiopancreatography; GGT, γ-glutamyltransferase; HBeAg, hepatitis B early antigen; HBsAg, hepatitis B surface antigen.
Wilson disease is characterized by abnormal storage of copper in the liver, leading to hepatocellular injury, CNS dysfunction, and hemolytic anemia. It is an autosomal recessive trait caused by mutations in the ATP7B gene. The encoded protein of this gene functions as an ATP-driven copper pump. The diagnosis is made by identifying depressed serum levels of ceruloplasmin, elevated 24-hour urine copper excretion, the presence of Kayser-Fleisher rings in the iris, evidence of hemolysis, and elevated hepatic copper content. In any single patient, one or more of these measures may be normal. Clinical presentation also varies, but seldom occurs before age 3 years. Neurologic abnormalities may predominate, including tremor, decline in school performance, worsening handwriting, and psychiatric disturbances. Anemia may be the first noted symptom. Hepatic presentations include appearance of jaundice, spider hemangiomata, portal hypertension and its consequences, and fulminant hepatic failure. Treatment consists of administration of copper-chelating drugs (penicillamine or trientine), with monitoring of urine copper excretion. Zinc salts often replace chelating agents after chelation therapy has successfully reduced excessive body copper stores. Adequate therapy must be continued for life to prevent liver and CNS deterioration.

Autoimmune Hepatitis

Immune-mediated liver injury may be primary or occur in association with other autoimmune disorders, such as inflammatory bowel disease or systemic lupus erythematosus. Diagnosis is made on the basis of elevated serum total IgG and the presence of an autoantibody, most commonly anti-nuclear, anti-smooth muscle, or anti-liver-kidney microsomal antibody. Liver biopsy specimen shows the presence of a plasma cell–rich portal infiltrate with piecemeal necrosis. Treatment consists of corticosteroids initially, usually with the addition of an immunosuppressive drug after remission is achieved. Steroids are tapered gradually as tolerated to minimize glucocorticoid side effects. Many patients require lifelong immunosuppressive therapy, but some may be able to stop medications after several years under careful monitoring for recurrence.

Nonalcoholic Steatohepatitis

Steatohepatitis, also known as nonalcoholic fatty liver disease or nonalcoholic fatty hepatitis, is characterized by the presence of macrovesicular fatty change in hepatocytes on biopsy. Varying degrees of inflammation and portal fibrosis may be present. This disorder occurs in obese children, sometimes in association with insulin-resistant (type 2) diabetes and hyperlipidemia. Children with marked obesity, with or without type 2 diabetes, who have elevated liver enzymes and no other identifiable liver disease are likely to have this condition. Nonalcoholic fatty liver disease can progress to significant fibrosis. Treatment is with diet and exercise. Vitamin E may have some benefit. Efforts should be made to control blood glucose and hyperlipidemia and promote weight loss. In general, the rate of progression to end-stage liver disease is slow.

### Table 130-6 Management of Chronic Liver Disease

<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>CLINICAL MANIFESTATIONS</th>
<th>DIAGNOSTIC TESTING</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal variceal bleeding</td>
<td>Hematemesis, rectal bleeding, melena, anemia</td>
<td>CBC, coagulation tests, Doppler ultrasound, magnetic resonance angiography, endoscopy</td>
<td>Somatostatin (octreotide) infusion, variceal band ligation or sclerotherapy, propranolol to reduce portal pressure, acid-blocker therapy, TIPS or surgical portosystemic shunt if transplant not possible</td>
</tr>
<tr>
<td>Ascites</td>
<td>Abdominal distention, shifting dullness and fluid wave, respiratory compromise, spontaneous bacterial peritonitis</td>
<td>Abdominal ultrasound, diagnostic paracentesis; measure ascites fluid albumin (and serum albumin), cell count, WBC differential, culture fluid in blood culture bottles</td>
<td>Restrict sodium intake to 0.5-1 mEq/kg/day, restrict fluids, monitor renal function, treat peritonitis and portal hypertension. Central portosystemic shunt may be required</td>
</tr>
<tr>
<td>Nutritional compromise</td>
<td>Muscle wasting, fat-soluble vitamin deficiencies, poor or absent weight gain, fatigue</td>
<td>Coagulation studies, serum albumin, 25-hydroxyvitamin D level, vitamin E level, vitamin A level</td>
<td>Fat-soluble vitamin supplements: vitamins A, D, E, and K; use water-soluble form of vitamins. Supplemental feedings—nasogastric or parenteral if necessary</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>Irritability, confusion, lethargy, somnolence, coma</td>
<td>Serum ammonia</td>
<td>Lactulose orally or via nasogastric tube, avoid narcotics and sedatives, liver transplantation</td>
</tr>
</tbody>
</table>

CBC, Complete blood count; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cell.

*May also have peptic ulcers.
pancreas, there is destruction of pancreatic function, often before birth. Some mutations result in less severe defects in CFTR function and later onset of lung disease and pancreatic insufficiency. Less common causes of pancreatic insufficiency are Shwachman-Diamond syndrome and Pearson syndrome in developing countries and severe malnutrition in developing countries.

**Clinical Manifestations**

Children with pancreatic exocrine insufficiency have many bulky, foul-smelling stools each day, usually with visible oil or fat. They typically have voracious appetites because of massive malabsorption of calories from fat, complex carbohydrates, and proteins. Failure to thrive is uniformly present if diagnosis and treatment are not accomplished rapidly. It is important to distinguish children with malabsorption due to pancreatic disease from children with intestinal disorders that interfere with digestion or absorption. Appropriate testing should be performed to rule out conditions such as celiac disease and inflammatory bowel disease if any doubt about the state of pancreatic sufficiency exists.

**Laboratory and Imaging Studies**

Testing of pancreatic function is difficult. Direct measurement of enzyme concentrations in aspirated pancreatic juice is not routine and is technically difficult. Stools can be tested for the presence of maldigested fat, which usually indicates poor fat digestion. Measuring fecal fat can give either a qualitative assessment of fat absorption (fecal Sudan stain) or a semi-quantitative measurement (72-hour fecal fat determination) of fat maldigestion. Another way to assess pancreatic function is to test for the presence of pancreatic enzymes in the stool. Of these, measuring fecal elastase-1 by immunoassay seems to be the most accurate method of assessment. Depressed fecal elastase-1 concentration correlates well with the presence of pancreatic insufficiency.

**Treatment**

Replacement of missing pancreatic enzymes is the best available therapy. Pancreatic enzymes are available as capsules containing enteric-coated microspheres. The coating on these spheres is designed to protect the enzymes from gastric acid degradation. For children unable to swallow capsules, the contents may be sprinkled on a spoonful of soft food, such as applesauce. Excessive use of enzymes must be avoided because high doses (usually >6000 U/kg/meal) can cause colonic fibrosis. In infants, typical dosing is 2000 to 4000 U of lipase/120 mL of formula. In children younger than 4 years old, 1000 U/kg/meal is given. For older children, 500 U/kg/meal is usual. This dose may be adjusted upward as required to control steatorrhea, but a dose of 2500 U/kg/meal should not be exceeded. Use of H₂ receptor antagonists or proton-pump inhibitors can increase the efficacy of pancreatic enzymes by enhancing their release from the microspheres and reducing inactivation by acid.

**ACUTE PANCREATITIS**

**Etiology and Epidemiology**

The exocrine pancreas produces numerous proteolytic enzymes, including trypsin, chymotrypsin, and carboxypeptidase. These are produced as inactive proenzymes to protect the pancreas from autodigestion. Trypsin is activated after leaving the pancreas by enterokinase, an intestinal brush border enzyme. After activation, trypsin cleaves other proteolytic proenzymes into their active states. Protease inhibitors found in pancreatic juice inhibit early activation of trypsin; the presence of self-digestion sites on the trypsin molecule allows for feedback inactivation. Pancreatitis occurs when digestive enzymes are activated inside the pancreas, causing injury. Triggers for acute pancreatitis differ between adults and children. In the adult patient, most episodes are related to alcohol abuse or gallstones. In children, most cases are idiopathic or due to medications. Some cases are caused by pancreatic sufficient cystic fibrosis, hypertriglyceridemia, biliary microlithiasis, trauma, or viral infection. Collagen vascular disorders and parasite infestations are responsible for the remainder (Table 131-1)

**Clinical Manifestations**

Acute pancreatitis presents with relatively rapid onset of pain, usually in the epigastric region. The pain may radiate to the back and is nearly always aggravated by eating. The patient moves frequently to find a position of comfort. Nausea and vomiting occur in most cases. Pain is typically continuous and quite severe, usually requiring narcotics. Severe pancreatitis can lead to hemorrhage, visible as ecchymoses in the flanks (Grey Turner sign) or periumbilical region (Cullen sign). Rupture of a minor pancreatic duct can lead to development of a pancreatic pseudocyst, characterized by persistent severe pain and tenderness and a palpable mass. With necrosis and fluid collections, patients experiencing severe pancreatitis are prone to infectious complications, and the clinician must be alert for fever and signs of sepsis.

**Laboratory and Imaging Studies**

Acute pancreatitis can be difficult to diagnose. Elevations in total serum amylase or lipase support the diagnosis. These pancreatic enzymes are released into the blood during pancreatic injury. Nonspecific elevations of the enzymes are common, however. As acute pancreatitis progresses, the amylase level tends to decline faster than lipase, making the latter a
good choice for diagnostic testing late in the course of the disease.

Serial measurement of laboratory studies is important to monitor for severe complications. At diagnosis, baseline complete blood count, C-reactive protein, electrolytes, blood urea nitrogen, creatinine, glucose, calcium, and phosphorus should be obtained. These should be measured at least daily, along with amylase and lipase, until the patient has recovered.

Because enzyme levels are not 100% sensitive or specific, imaging studies are important for the diagnosis of pancreatitis. In acute pancreatitis, edema is present in all but the mildest cases. Ultrasound is capable of detecting this edema and should be performed as part of the overall diagnostic approach. If overlying bowel gas obscures the pancreas, a computed tomography (CT) scan allows complete visualization of the gland. CT scans should be done with oral and intravenous (IV) contrast agents to facilitate interpretation. Ultrasound and CT also can be used to monitor for the development of pseudocysts and for evidence of ductal dilation secondary to obstruction. The other important reason to perform imaging studies early in the course of pancreatitis is to rule out gallstones; the liver, gallbladder, and common bile duct all should be visualized. Magnetic resonance cholangiopancreatography may be used to detect anatomic variants causing pancreatitis.

<table>
<thead>
<tr>
<th>Table 131-1 Causes of Acute Pancreatitis in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OBSTRUCTIVE</strong></td>
</tr>
<tr>
<td>Cholelithiasis and biliary sludge</td>
</tr>
<tr>
<td>Choledochal cyst</td>
</tr>
<tr>
<td>Pancreas divisum</td>
</tr>
<tr>
<td>Anomalous junction of biliary and pancreatic ducts</td>
</tr>
<tr>
<td>Annular pancreas</td>
</tr>
<tr>
<td>Ampullary obstruction (mass, inflammation from Crohn’s disease)</td>
</tr>
<tr>
<td>Ascaris infection</td>
</tr>
<tr>
<td><strong>MEDICATIONS AND TOXINS</strong></td>
</tr>
<tr>
<td>L-Asparaginase</td>
</tr>
<tr>
<td>Valproic acid</td>
</tr>
<tr>
<td>Azathioprine and 6-mercaptopurine</td>
</tr>
<tr>
<td>Didanosine</td>
</tr>
<tr>
<td>Pentamidine</td>
</tr>
<tr>
<td>Tetracycline</td>
</tr>
<tr>
<td>Opiates</td>
</tr>
<tr>
<td>Mesalamine</td>
</tr>
<tr>
<td>Sulfasalazine</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Cannabis</td>
</tr>
<tr>
<td><strong>SYSTEMIC DISEASES</strong></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Kawasaki disease</td>
</tr>
<tr>
<td>Shock</td>
</tr>
<tr>
<td>Sickle cell disease</td>
</tr>
<tr>
<td><strong>INFECTIONOUS</strong></td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Mumps</td>
</tr>
<tr>
<td>Coxsackievirus</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Varicella zoster</td>
</tr>
<tr>
<td>Herpes simplex</td>
</tr>
<tr>
<td>Mycoplasma</td>
</tr>
<tr>
<td>Ascaris</td>
</tr>
<tr>
<td><strong>GENETIC</strong></td>
</tr>
<tr>
<td>Cystic fibrosis—CFTR mutations</td>
</tr>
<tr>
<td>Hereditary pancreatitis—SPINK and PRSS1 mutations</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>Autoimmune</td>
</tr>
</tbody>
</table>

**Treatment**

There are no proven specific therapies for acute pancreatitis. If a predisposing etiology is found, such as a drug reaction or a gallstone obstructing the sphincter of Oddi, this should be specifically treated. Initially, oral intake is prohibited, an acid-blocking drug is prescribed, and (except in mild cases) nasogastric suction is begun. Fluid resuscitation is necessary because of vomiting and third space losses. Pain relief should be provided. Meperidine, fentanyl, and hydromorphone are most commonly used. Nutritional support should be provided early in the course if the patient will be nothing by mouth (NPO) for extended periods. Feedings can begin once pain subsides or can be administered downstream from the duodenum. If this is not possible, parenteral nutrition is an option. Fewer complications and more rapid recovery occur with jejunal feedings compared with parenteral nutrition. Antibiotics should be considered if the patient is febrile, has extensive pancreatic necrosis, or has laboratory evidence of infection. A broad-spectrum antibiotic, such as imipenem, is considered the best choice.

**CHRONIC PANCREATITIS**

**Etiology and Epidemiology**

Chronic pancreatitis is defined as recurrent or persistent attacks of pancreatitis, which have resulted in irreversible morphologic changes in pancreatic structure. These include scarring of the ducts with irregular areas of narrowing and dilation (beading), fibrosis of parenchyma, and loss of acinar and islet tissue. Pancreatic exocrine insufficiency and diabetes mellitus may result from unremitting chronic pancreatitis. Most patients have discrete attacks of acute symptoms occurring repeatedly, but chronic pain may be present. The causes of chronic pancreatitis include...
hereditary pancreatitis and milder phenotypes of cystic fibrosis associated with pancreatic sufficiency. Familial disease is caused by one of several known mutations in the trypsinogen gene. These mutations obliterate autodigestion sites on the trypsin molecule, inhibiting feedback inhibition of trypsin digestion. Genetic testing is readily available for these mutations. Genetic testing for cystic fibrosis can be performed, but must include screening for the less common mutations associated with pancreatic sufficiency. Sweat chloride testing is less expensive and is abnormal in most. Less commonly, mutations in the SPINK1 gene, which codes for pancreatic trypsin inhibitor, and PRSS1, a mutation of cationic trypsinogen, are found.

Clinical Manifestations
Children with chronic pancreatitis initially present with recurring attacks of acute pancreatitis. Injury to the pancreatic ducts predisposes these children to continued attacks owing to scarring of small and large pancreatic ducts, stasis of pancreatic secretions, stone formation, and inflammation. Loss of pancreatic exocrine and endocrine tissue over time can lead to exocrine and endocrine deficiency. More than 90% of the pancreatic mass must be destroyed before exocrine deficiency becomes clinically apparent; this is a late complication that does not occur in all cases. Chronic pain is a serious problem in most affected individuals. These patients have many episodes; many do not require hospitalization.

Laboratory and Imaging Studies
Laboratory diagnosis of chronic pancreatitis is similar to acute pancreatitis but with more severe loss of pancreatic tissue it becomes less likely that the patient with elevation of amylase or lipase. Monitoring also should include looking for consequences of chronic injury, including diabetes mellitus and compromise of the pancreatic and biliary ducts. Pancreatic and biliary imaging has been accomplished by endoscopic retrograde cholangiopancreatography (ERCP). ERCP offers the possibility of therapeutic intervention to remove gallstones, dilate strictures, and place stents to enhance flow of pancreatic juice. Magnetic resonance cholangiopancreatography is an alternative to ERCP. Plain abdominal x-rays may show pancreatic calcifications. Diagnostic testing for the etiology of chronic pancreatitis should include genetic testing for hereditary pancreatitis and cystic fibrosis and sweat chloride determination.

Treatment
Treatment is largely supportive. Potential but unproven therapies include the use of daily pancreatic enzyme supplements, octreotide (somatostatin) to abort early attacks, low-fat diets, and daily antioxidant therapy. Care must be taken that extreme diets do not result in nutritional deprivation. Interventional ERCP to dilate large strictures and remove stones and surgical pancreatic drainage procedures to decompress dilated pancreatic ducts by creating a side-to-side pancreaticojejunostomy may have some value.

Etiology and Epidemiology
The peritoneum consists of a single layer of mesothelial cells that covers all intra-abdominal organs. The portion that covers the abdominal wall is derived from the underlying somatic structures and is innervated by somatic nerves. The portion covering the viscera is derived from visceral mesoderm and is innervated by nonmyelinated visceral afferents. Inflammation of the peritoneum, or peritonitis, usually is caused by infection but may result from exogenous irritants introduced by penetrating injuries or surgical procedures, radiation, and endogenous irritants such as meconium. Infectious peritonitis can be an acute complication of intestinal inflammation and perforation, as in appendicitis, or it can occur secondary to contamination of preexisting ascites associated with renal, cardiac, or hepatic disease. In this setting, when there is no other intra-abdominal source, it is referred to as spontaneous bacterial peritonitis. Spontaneous bacterial peritonitis is usually due to pneumococcus and less often to Escherichia coli.

Clinical Manifestations
Peritonitis is characterized on examination by marked abdominal tenderness. Rebound tenderness also generally is quite pronounced. The patient tends to move very little owing to intense peritoneal irritation and pain. Fever is not always present, and absence of fever should not be regarded as contradictory to the diagnosis. Patients who are taking corticosteroids for an underlying condition, such as nephrotic syndrome, are likely to have little fever and reduced tenderness.

Laboratory and Imaging Studies
Blood tests should focus on identifying the nature of the inflammation and its underlying cause. An elevated white blood cell count, erythrocyte sedimentation rate, and C-reactive protein suggest infection. In children older than 5 years, appendicitis is the leading cause. Total serum protein, albumin, and urinalysis should be ordered to rule out nephrotic syndrome. Liver function tests should be performed to rule out chronic liver disease causing ascites. The best way to diagnose suspected peritonitis is to sample the peritoneal fluid with a needle or catheter (paracentesis). Peritoneal fluid in spontaneous bacterial peritonitis has a high neutrophil count of greater than 250 cells/mm³. Other tests that should be run on the peritoneal fluid include amylase (to rule out pancreatic ascites), culture, albumin, and lactate dehydrogenase concentration. For culture, a large sample of fluid should be placed into aerobic and anaerobic blood culture bottles immediately on obtaining the sample.
Appendicitis may be identified by ultrasound or computed tomography (CT) scan. When other intra-abdominal emergencies are suspected, such as midgut volvulus, meconium ileus, peptic disease, or any other condition predisposing to intestinal perforation, specific testing should be performed.

Treatment
Peritonitis caused by an intra-abdominal surgical process, such as appendicitis or a penetrating wound, must be managed surgically. Spontaneous bacterial peritonitis should be treated with a broad-spectrum antibiotic with good coverage of resistant pneumococcus and enteric bacteria. Cefotaxime is generally effective as initial therapy while awaiting culture and sensitivity results. Anaerobic coverage with metronidazole should be added whenever a perforated viscus is suspected.

Suggested Reading
Acute and chronic respiratory diseases are common in pediatrics. Children with respiratory problems typically present with symptoms, although abnormal imaging may sometimes precede physical findings. The underlying etiology of childhood respiratory diseases includes the following: genetic (e.g., cystic fibrosis); anatomic (e.g., laryngomalacia); incomplete matura tion (e.g., premature birth); iatrogenic (e.g., oxygen toxicity); immunologic (e.g., immune deficiency); infectious (e.g., group or pneumonia); environmental (e.g., toxins or pollutants); and extrapolmonary (e.g., congenital heart disease). The optimal functioning of the entire respiratory tract allows children not only to survive, but thrive.

PULMONARY PHYSIOLOGY
Pulmonary Mechanics

The major function of the lungs is to exchange oxygen \((O_2)\) and carbon dioxide \((CO_2)\) between the atmosphere and the blood. The anatomy of the airways, mechanics of the respiratory muscles and rib cage, nature of the alveolar-capillary interface, pulmonary circulation, tissue metabolism, and neuromuscular control of ventilation all influence gas exchange.

Air enters the lungs when intrathoracic pressure is less than atmospheric pressure. During inspiration, negative intrathoracic pressure is generated by contraction and lowering of the diaphragm. The accessory muscles of inspiration (external intercostal, scalene, and sternocleidomastoid muscles) are not used during quiet breathing but are recruited during exercise or in disease states to raise and enlarge the rib cage. Exhalation is normally passive, but with active exhalation, the abdominal and internal intercostal muscles are recruited.

During normal breathing at rest, lung volumes are usually in the mid-range of inflation (Fig. 133-1). Tidal volume \((TV)\) is the amount of air inspired with each relaxed breath. The volume of gas retained in the lung at the end of a relaxed exhalation is acute and chronic respiratory diseases are common in pediatrics. Children with respiratory problems typically present with symptoms, although abnormal imaging may sometimes precede physical findings. The underlying etiology of childhood respiratory diseases includes the following: genetic (e.g., cystic fibrosis); anatomic (e.g., laryngomalacia); incomplete maturation (e.g., premature birth); iatrogenic (e.g., oxygen toxicity); immunologic (e.g., immune deficiency); infectious (e.g., group or pneumonia); environmental (e.g., toxins or pollutants); and extrapolmonary (e.g., congenital heart disease). The optimal functioning of the entire respiratory tract allows children not only to survive, but thrive.

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the **functional residual capacity** (FRC). This gas volume maintains exchange of O₂ during exhalation. **Total lung capacity** (TLC) is the volume of gas in the lungs at the end of maximal inhalation and **residual volume** (RV) is the volume of gas left in the lungs at the end of a maximal exhalation. **Vital capacity** (VC) is the maximal amount of air that can be expelled from the lungs and is the difference between TLC and RV.

**Airway resistance** is influenced by the diameter and length of the conducting airways, the viscosity of gas, and the nature of the airflow. During quiet breathing, airflow in the smaller airways may be laminar (streamlined), and resistance is inversely proportional to the fourth power of the radius of the airway. At higher flow rates, turbulent flow, especially in the larger airways, increases resistance. Relatively small changes in airway diameter can result in large changes in airway resistance. Excessive airway secretions, bronchospasm, mucosal edema and inflammation, airway stenosis, foreign bodies, loss of airway wall integrity (as with bronchiectasis), and airway compression may all produce symptomatic increases in airway resistance. In pediatrics, laryngomalacia and croup are very common causes of increased upper airway resistance; whereas asthma, bronchiolitis and cystic fibrosis (CF) are among the most common causes of increased lower airway resistance.

**Lung compliance** (change in volume for a given change in pressure) is a measure of the ease with which the lung can be inflated. Processes that decrease lung compliance (surfactant deficiency, pulmonary fibrosis, pulmonary edema) may lead to decreases in measured lung volumes. Restrictive lung diseases are characterized by normal to low FRC and RV, low TLC and VC, decreased lung compliance, and relatively normal flow rates. Restrictive lung disease can result from neuromuscular weakness, an alveolar filling process (lobar pneumonia, pulmonary edema), pleural disease (pleural effusion, inflammation, or mass), thoracic narrowing/stiffness (scoliosis, severe pectus excavatum), and abdominal distention.

### Respiratory Gas Exchange

**Alveolar ventilation** is defined as the exchange of carbon dioxide between the alveoli and external environment.

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>EXAMPLE(S)</th>
<th>Pao₂</th>
<th>Paco₂</th>
<th>Pao₂ IMPROVES WITH SUPPLEMENTAL OXYGEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilation-perfusion</td>
<td>Asthma</td>
<td>↓</td>
<td>Normal</td>
<td>Yes</td>
</tr>
<tr>
<td>mismatch</td>
<td>Bronchopulmonary dysplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atelectasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>Apnea</td>
<td>↓</td>
<td>↑</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Narcotic overdose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuromuscular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary shunt</td>
<td>Cyanotic heart disease</td>
<td>↓</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Pulmonary arteriovenous malformation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrapulmonary shunt</td>
<td>Pulmonary edema</td>
<td>↓</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>Low FIO₂</td>
<td>High altitude</td>
<td>↓</td>
<td>↑</td>
<td>Yes</td>
</tr>
<tr>
<td>Diffusion defect</td>
<td>Scleroderma</td>
<td>↓</td>
<td>Normal</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Hepatopulmonary syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary fibrosis</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

FIO₂, Fraction of inspired oxygen; Pao₂, arterial partial pressure of carbon dioxide; Paco₂, arterial partial pressure of oxygen.

Normally, about 30% of each tidal breath fills the conducting (non-gas-exchanging) airways (anatomic dead space). Because the anatomic dead space is relatively constant, increasing the tidal volume may increase the efficacy of ventilation. Conversely, if tidal volume decreases, then the dead space/tidal volume ratio increases, and alveolar ventilation decreases.

Gas exchange depends on **alveolar ventilation**, **pulmonary capillary blood flow**, and the **diffusion** of gases across the alveolar-capillary membrane. Exchange of CO₂ is determined by alveolar ventilation, whereas the exchange of O₂ is influenced primarily by the regional matching of ventilation (V) with pulmonary blood flow (Q) (V/Q matching). V/Q matching is maintained, in part, by **hypoxic pulmonary vasconstriction** (local constriction of the pulmonary vessels in areas that are hypoxenated). There are five causes of **hypoxemia** (Table 133-1). Disorders resulting in V/Q mismatching (such as pneumonia and atelectasis) are the most common causes of hypoxemia.

### Lung Defense Mechanisms

#### Cough

The lungs are constantly exposed to particles and infectious agents. The **nose** is the primary filter for large particles. The **ciliated epithelium** of the paranasal sinuses and nasal turbinates move filtered particles toward the pharynx. Particles less than 10 μm in diameter may reach the trachea and bronchi and deposit on the mucosa. Particles less than 1 μm may reach the alveoli. Ciliated cells lining the airways from the larynx to the bronchioles continuously propel a thin layer of mucus toward the mouth. **Alveolar macrophages** and **polymorphonuclear cells** engulf particles and pathogens that have been opsonized by locally secreted IgA antibodies or transudated serum antibodies.
Cough, important in protecting the lungs, is a forceful expiration that can clear the airways of debris and secretions. Cough may be voluntary or generated by reflex irritation of the nose, sinus, pharynx, larynx, trachea, bronchi, or bronchioles. Effective cough requires the ability to (1) inhale to near total lung capacity, (2) close and open the glottis, and (3) contract abdominal muscles to forcibly exhale. Loss of the ability to cough, as with neuromuscular weakness, results in poor secretion clearance and predisposes to atelectasis and pneumonia.

**HISTORY**

The complete respiratory history includes onset, duration, and frequency of respiratory symptoms (cough, noisy breathing, work of breathing/exercise tolerance, nasal congestion, sputum production), swallowing function (especially in infants), and exposure to others with respiratory illness. It is important to obtain information concerning the severity (hospitalizations, emergency department visits, missed school days) and pattern (acute, chronic, or intermittent) of symptoms. For infants, a feeding history should be obtained, including questions about coughing or choking with feeds. Family history should include questions about asthma and atopy, immune deficiencies, and CF. The environmental history queries exposure to smoke, pets, and pollutants. Travel history may also be relevant.

**PHYSICAL EXAMINATION**

Clothing should be removed from the upper half of the child’s body so that the thorax may be inspected, although maintaining modesty for adolescents should be respected. It is optimal to observe the respiratory pattern, rate, and work of breathing while the child is quiet, noting the shape and symmetry of the chest wall and the anteroposterior (AP) diameter.

Any factor that impairs respiratory mechanics is likely to increase the respiratory rate. However, nonrespiratory causes of tachypnea include fever, pain, and anxiety. Respiratory rates vary with age and activity (Table 133-2).

It is important to observe the respiratory pattern and degree of effort (work of breathing). Hyperpnea (increased depth of respiration) may be observed with fever, metabolic acidosis, pulmonary and cardiac disease, or extreme anxiety. Hyperpnea without signs of respiratory distress suggests an extrapulmonary etiology (metabolic acidosis, fever, pain). Increased work of breathing can be described as inspiratory (intercostal, supraclavicular, or substernal retractions) or expiratory (use of abdominal muscles to actively exhale). In children, increased inspiratory effort is also manifested by nasal flaring. Grunting (forced expiration against a partially closed glottis) suggests respiratory distress, but it may also be a manifestation of pain.

Causes of increased work of breathing during inspiration include extrathoracic airway obstruction (laryngomalacia, croup, subglottic stenosis) and/or decreased pulmonary compliance (pneumonia, pulmonary edema). Increased expiratory work of breathing usually indicates intrathoracic airway obstruction (see Table 133-2).

Stridor is a harsh sound caused by a partially obstructed extrathoracic airway, more commonly heard on inspiration. Wheezing is produced by partial obstruction of the lower airways, more commonly heard during exhalation. Wheezes can be monophonic and low-pitched (usually from large, central airways) or high-pitched and musical (from small peripheral airways). Secretions in the intrathoracic airways may produce wheezing but more commonly result in irregular sounds called rhonchi. Fluid or secretions in small airways may produce sounds characteristic of crumpling cellophane (crackles or rales). Having the child take a deep breath and exhale forcefully will accentuate many abnormal lung sounds. Decreased breath sounds may be due to atelectasis, lobar consolidation (pneumonia), thoracic mass, or a pleural effusion. Observation of respiratory rate, work of breathing, tracheal and cardiac deviation, and chest wall motion, combined with percussion and auscultation, helps to identify intrathoracic disease (Table 133-2).

Digital clubbing is seen in CF and in other, less common chronic pulmonary diseases (such as interstitial lung disease). It is generally not seen in asthma, so its presence should heighten concern for other diagnoses. Clubbing may also be present in nonpulmonary chronic diseases (cardiac, gastrointestinal, or hematologic) or, rarely, as a familial trait.

**Table 133-2** Breathing Patterns

<table>
<thead>
<tr>
<th>PATTERN</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal rate (breaths/min)</td>
<td>Preterm: 40–60; term: 30–40; 5 yr: 25; 10 yr: 20; 15 yr: 16; adult: 12</td>
</tr>
<tr>
<td>Obstructive</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Reduced rate, increased tidal volume, slightly prolonged expiratory phase</td>
</tr>
<tr>
<td>Severe</td>
<td>Increased rate, increased use of accessory muscles, prolonged expiratory phase</td>
</tr>
<tr>
<td>Restrictive</td>
<td>Rapid rate, decreased tidal volume</td>
</tr>
<tr>
<td>Kussmaul respiration</td>
<td>Increased rate, increased tidal volume, regular deep respiration; consider metabolic acidosis or diabetic ketoacidosis</td>
</tr>
<tr>
<td>Cheyne-Stokes respiration</td>
<td>Cyclic pattern of waxing and waning of breathing interposed by central apneas/hypopneas; consider CNS injury, depressant drugs, heart failure, uremia (rare in children)</td>
</tr>
<tr>
<td>Biot respiration</td>
<td>Ataxic or periodic breathing with a respiratory effort followed by apnea; consider brainstem injury or posterior fossa mass</td>
</tr>
<tr>
<td>Gasping</td>
<td>Slow rate, variable tidal volume; consider hypoxia, shock, sepsis, or asphyxia</td>
</tr>
</tbody>
</table>

CNS, Central nervous system.
Cough results from stimulation of irritant receptors in the airway mucosa. Acute cough generally is associated with respiratory infections or irritant exposure (smoke) and subsides as the infection resolves or the exposure is eliminated. The characteristics of the cough and the circumstances under which the cough occurs help in determining the cause. Sudden onset after a choking episode suggests foreign body aspiration. Morning cough may be due to the accumulation of excessive secretions during the night from sinusitis, allergic rhinitis, or bronchial infection. Nighttime coughing is a hallmark of asthma and can also be caused by gastroesophageal reflux disease. Cough exacerbated by lying flat may be due to postnasal drip, sinusitis, allergic rhinitis, or reflux. Recurrent coughing with exercise is suggestive of exercise-induced asthma/bronchospasm. Paroxysmal cough suggests pertussis or foreign body aspiration. A repetitive, staccato cough occurs in childhood viral infections in infants. A harsh, brassy, seal-like cough suggests croup, tracheomalacia, or psychogenic (habit) cough. The last, which is most common in teenagers, disappears during sleep. Younger children can develop a throat-clearing habit cough, which also disappears during sleep.

**Table 133-3** Physical Signs of Pulmonary Disease

<table>
<thead>
<tr>
<th>DISEASE PROCESS</th>
<th>MEDIASTINAL DEVIATION</th>
<th>CHEST MOTION</th>
<th>VOCAL FREMITUS</th>
<th>PERCUSSION</th>
<th>BREATH SOUNDS</th>
<th>ADVENTITIOUS SOUNDS</th>
<th>VOICE SIGNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>No</td>
<td>Reduced over area</td>
<td>Increased</td>
<td>Dull</td>
<td>Bronchial or reduced</td>
<td>None or crackles</td>
<td>Egophony* Pectoriloquy†</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>No</td>
<td>Hyperexpansion with limited motion</td>
<td>Normal or decreased</td>
<td>Hyperresonant</td>
<td>Normal to decreased</td>
<td>Wheezes, crackles</td>
<td>Normal to decreased</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>Shift toward affected side</td>
<td>Reduced over area</td>
<td>Decreased</td>
<td>Dull</td>
<td>Reduced</td>
<td>None or crackles</td>
<td>None</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>With tension pneumothorax: shift to the opposite side</td>
<td>Reduced over PMI</td>
<td>None</td>
<td>Resonant</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>Deviation to opposite side</td>
<td>Reduced over area</td>
<td>None or reduced</td>
<td>Dull</td>
<td>None</td>
<td>Egophony Friction rub</td>
<td>Muffled</td>
</tr>
<tr>
<td>Interstitial process</td>
<td>No</td>
<td>Reduced</td>
<td>Normal to increased</td>
<td>Normal</td>
<td>Normal</td>
<td>Inspiratory crackles</td>
<td>None</td>
</tr>
</tbody>
</table>


PMI, Point of maximum impulse.

*In egophony, e sounds like a (may be a sign of consolidation but also is associated with moderate-sized pleural effusions).

†In pectoriloquy, words/voice sounds clearer over the affected site (associated with consolidation and cavitory lesions).

**Diagnostic Measures**

**Imaging Techniques**

Chest radiographs are useful in assessing respiratory disease in children. In addition to determining lung abnormalities, they provide information about the bony thorax (rib or vertebral abnormalities), the heart (cardiomegaly, pericardial effusion), and the great vessels (right aortic arch/vascular rings, rib notching). Chest radiographs should be obtained in both the posteroanterior (PA) and lateral projections and, if possible, following a full inspiration. Estimation of lung hyperinflation based on a single PA view is unreliable; flattened diaphragms and an increased AP diameter on lateral projection is a better indicator of hyperinflation. Crowding of the blood vessels with poor inspiration can be misinterpreted as increased markings or infiltrates. External skin folds, rotation, and motion may produce distorted or unclear images. Expiratory views and fluoroscopy may detect partial bronchial obstruction due to an aspirated foreign body that results in regional hyperinflation, because the affected lung or lobe does not deflate on exhalation. Fluoroscopy can also be used to evaluate diaphragm movement.

A **barium esophagram** may be valuable in diagnosing disorders of swallowing (dysphagia) and esophageal motility, vascular rings (esophageal compression), tracheoesophageal fistulas, and, to a lesser extent, gastroesophageal reflux. When evaluating for a tracheoesophageal fistula, contrast material must be instilled under pressure via a catheter with the distal tip situated in the esophagus (see Chapter 128).

A **computed tomography (CT) scan of the chest** is the imaging test of choice for evaluating pleural masses, bronchiectasis, and mediastinal lesions as well as delineating pleural from parenchymal lesions. CT scans with intravenous contrast provide excellent information about the pulmonary vasculature and great vessels and can detect pulmonary embolism. High-resolution CT scans are used to assess lung parenchyma (congenital pulmonary malformations, interstitial lung disease) and the airways (bronchiectasis). The speed of current
CT scanners makes it possible to scan most children without sedating them. However, sedation may be required in infants and toddlers to decrease motion artifact. **Magnetic resonance imaging (MRI)**, useful in visualizing cardiac and great vessel anatomy, is less useful for evaluation of pulmonary parenchymal lesions.

**Ultrasoundography** can be used to delineate some intrathoracic masses and is the imaging procedure of choice for assessing parapneumonic effusion/empyema. It is useful for assessing diaphragmatic motion in small children.

### Measures of Respiratory Gas Exchange

A properly performed **arterial blood gas** analysis provides information about the effectiveness of both oxygenation and ventilation. However, arterial samples are more difficult to obtain, so capillary and venous blood samples are more commonly used. The $P_{CO_2}$ from a capillary sample is similar to that from arterial blood. The $P_{CO_2}$ in venous samples is approximately 6 mm Hg higher than arterial $P_{CO_2}$. The ratio of the serum bicarbonate concentration to $P_{CO_2}$ determines the pH. Capillary or venous samples should not be used to assess oxygenation.

There are both respiratory and metabolic causes of acidosis (see Chapter 37). In the presence of an alkalosis or acidosis, respiratory compensation (altering $P_{CO_2}$ to maintain a normal pH) can occur within minutes, but renal compensation (altering the serum bicarbonate level) may not be complete for several days. Recall that both the respiratory and metabolic compensation are incomplete, so pH will remain on the side of the primary insult (whether acidosis or alkalosis).

**Pulse oximetry** measures the $O_2$ saturation of hemoglobin by measuring the blood absorption of two or more wavelengths of light. It is noninvasive, easy to use, and reliable. Because of the shape of the oxyhemoglobin dissociation curve, $O_2$ saturation does not decrease much until the $P_{O_2}$ reaches approximately 60 mm Hg. Pulse oximetry may not accurately reflect true $O_2$ saturation when abnormal hemoglobin is present (carboxyhemoglobin, methemoglobin), when perfusion is poor, or if no light passes through to the photodetector (nail polish).

The measurement of $P_{CO_2}$ is accomplished most reliably by blood gas analysis. However, there are noninvasive monitors that record exhaled $P_{CO_2}$ (end-tidal $CO_2$), which is representative of alveolar $P_{CO_2}$. End-tidal $P_{CO_2}$ measurements are most commonly used in intubated and mechanically ventilated patients, but some devices can measure $P_{CO_2}$ at the nares. **Transcutaneous electrodes** can be used to monitor $P_{CO_2}$ and $P_{O_2}$ at the skin surface, but are less accurate. Noninvasive techniques of $CO_2$ measurement are best suited for detecting trends rather than for providing absolute values.

### Pulmonary Function Testing

Measurement of lung volumes and airflow rates using **spirometry** are important in assessing pulmonary disease. The patient inhales to TLC and then forcibly exhales until no more air can be expelled. During the forced expiratory maneuver, forced vital capacity (FVC), forced expired volume in the first second ($FEV_1$), and **forced expiratory flow** (FEF) rates are measured. These are compared to predicted values based on patient age, gender, and race, but rely mostly on height. Most children above 6 years of age can perform spirometry. Infant pulmonary function testing is possible, using sedation and sophisticated equipment.

Airway resistance, FRC, and RV cannot be measured with spirometry and require other techniques, such as **body plethysmography**. Helium dilution can also measure TLC and RV by determining the magnitude of dilution of inhaled helium in the air within the lung, but may underestimate air trapping.

Abnormal results on pulmonary function testing can be used to categorize **obstructive airway disease** (low flow rates and increased RV or FRC) or a **restrictive defect** (low FVC and TLC, with relative preservation of flow rates and FRC). When the $FEV_1$ and flow rates are decreased to a greater extent than the FVC, then airway obstruction is likely; however, a proportional decrease in FVC, $FEV_1$, and flow rates suggests a restrictive lung defect. The mean midexpiratory flow rate ($FEF_{25-75\%}$) is a more sensitive measure of small airways disease than the $FEV_1$, but is also more variable. Pulmonary function testing can detect reversible airway obstruction characteristic of asthma with a significant improvement in $FEV_1$ (>12%-15%) or in $FEF_{25-75\%}$ (>25%) following inhalation of a bronchodilator. Spirometry is also useful for longitudinal patient management. The **peak expiratory flow rate** (PEFR) can be obtained with a simple handheld device and may be useful for home monitoring of older children with asthma. However, it is highly dependent on patient effort, and values must be interpreted with caution. **Inhalation challenge tests** using methacholine, histamine, or cold, dry air are used to assess airway hyperreactivity, but require sophisticated equipment and special expertise and should be performed only in a pulmonary function laboratory with experienced technicians.

### Endoscopic Evaluation of the Airways

Endoscopic evaluation of the upper airways (nasopharyngoscopy) is performed with a flexible fiberoptic nasopharyngoscope to assess adenoid size, patency of the nasal passages, and abnormalities of the glottis. It is especially useful in evaluating stridor and assessing vocal cord motion/function, and it does not require sedation. Endoscopic evaluation of the subglottic space and intrathoracic airways can be done with either a flexible or rigid bronchoscope under anesthesia. **Bronchoscopy** is useful in identifying airway abnormalities (stenosis, malacia, endobronchial lesions, excessive secretions) and in obtaining airway samples for culture (bronchoalveolar lavage), especially in immunocompromised patients. Rigid bronchoscopy is the method of choice for removing foreign bodies from the airways and performing other interventions, and flexible bronchoscopy is most useful as a diagnostic tool and for obtaining lower airway cultures. Transbronchial biopsies are rarely performed in children. There are few absolute contraindications to bronchoscopy. Relative contraindications include bleeding diatheses, thrombocytopenia (<50,000/cm³), and clinical conditions when the patient is too unstable to tolerate the procedure.

### Examination of Sputum

Sputum specimens may be useful in evaluating lower respiratory tract infections, but they are difficult to obtain in young children. In addition, an expectorated specimen may not
provide a representative sample of lower airway secretions. Specimens containing large numbers of squamous epithelial cells either are not from the lower airways or are heavily contaminated with upper airway secretions and may yield misleading results. Sputum in patients with lower respiratory tract bacterial infections often contains polymorphonucleated leukocytes and one predominant organism on culture. If sputum cannot be obtained, then bronchoalveolar lavage specimens may be used for microbiologic diagnosis in selected situations. In patients with CF who cannot produce sputum, specially processed throat cultures are often used as surrogates for lower airway cultures.

**Lung Biopsy**
When less invasive methods fail to provide diagnoses in patients with pulmonary disease, a lung biopsy may be required. Concern for childhood interstitial lung disease, atypical infection (especially in an immunocompromised host), and evaluation of a mass/malformation are the most common indications for biopsy. CT-guided needle biopsy performed by an interventional radiologist is an option if limited histology is needed and the lesion is amenable to percutaneous approach (e.g., fungal nodules). Either a thoracoscopic procedure or a thoracotomy is preferred if thorough histologic evaluation is desired. Thoracotomy allows the surgeon to inspect and palpate the lung, which aids in choosing the best site for biopsy, but it is more invasive than thoracoscopy. In most cases, infants and children tolerate lung biopsy well.

**THERAPEUTIC MEASURES**

**Oxygen Administration**
Any child in respiratory distress should be treated with supplemental O2 to maintain normal O2 saturation levels. For long-term administration of O2, a nasal cannula is the most widely used device, as it enables patients to eat and speak unhindered by the O2 delivery system. Though nasal cannula is the easiest way to provide supplemental O2, the actual fraction of inspired oxygen (FIo2) delivered to the patient can be quite variable and affected by the child’s size and respiratory pattern. Humidified high flow nasal cannula (HFNC) allows the provider to more comfortably deliver higher flow rates while controlling the FIo2 and is now widely used in neonates as an alternative to noninvasive positive pressure. Supplemental O2 may also be delivered by a variety of face-mask systems ranging from a simple face mask, which can provide 30% to 40% O2, to a nonrebreather mask with reservoir that can provide nearly 100% O2.

The concentration of administered O2 should be high enough to relieve hypoxemia. The acceptable O2 saturation depends on the patient and clinical situation. Generally, supplemental O2 should be administered to achieve a goal saturation level above 90%. Normal oxygen saturation is greater than 95%. It is unnecessary to achieve 100% saturation, especially if this requires potentially toxic levels of inspired O2 for extended periods of time.

Inspired O2 concentrations less than 40% are usually safe for long-term use. Patients requiring supplemental O2 should be monitored with pulse oximetry, either intermittently or continuously, or with arterial blood gas measurements of Po2 to allow titration to the lowest possible O2 concentration.

**Aerosol Therapy**
Delivering therapeutic agents to the lower respiratory tract can be accomplished by inhalation of aerosol forms of the agents via dry powder inhaler (DPI), metered dose inhaler (MDI), or nebulizer. All of these devices are designed to generate relatively small particles that can bypass the filtering action of the upper airway and deposit in the lower airways. Many factors influence drug deposition, including patient technique, device used, age of the child, and breathing pattern. Nebulizers should be used with a face mask (infants) or mouthpiece (children and teens) to minimize loss of drug to ambient air. Plastic holding chambers (spacers) are available for all ages and should always be used with MDIs. Dry powder inhalers require a single rapid deep inhalation for optimal drug delivery, which is difficult for children under 6 years of age. MDIs and nebulizers are equally effective in delivering medications only if the technique is correct, so it is important to review this frequently and carefully with families.

**Chest Physiotherapy and Clearance Techniques**
When disease processes impair clearance of pulmonary secretions, airway clearance techniques may help maintain airway patency. One method is chest percussion, which moves secretions toward the central airways, from which they can be expectorated. Chest physiotherapy can also be performed effectively with handheld devices that generate expiratory back-pressure and vibration (TheraPEP, Flutter, and Aca-pella) and pneumatic vests. Chest physiotherapy is most beneficial in children with chronic airway secretions, especially those with CF. Children who are too weak to generate an effective cough benefit from the use of a mechanical cough assist device, used in conjunction with chest physiotherapy. Chest physiotherapy is not generally beneficial for patients with asthma or pneumonia, and its effectiveness in patients with atelectasis has not been clearly established.

**Intubation**
If the upper airway is obstructed or mechanical ventilation is needed, it may be necessary to provide the patient with an artificial airway. This is best done by placing an endotracheal tube via the mouth or nose into the trachea (intubation). Intubation alters the physiology of the respiratory tract in many ways, not all of which are beneficial. It interferes with the humidification, warming, and filtration of inspired air and prevents phonation. Intubation also stimulates secretion production. However, in acute/impending respiratory failure, intubation with an endotracheal tube is lifesaving.

Endotracheal tubes can damage the larynx and the airways if the tubes are of improper size and are not carefully maintained. The cricoid ring is the narrowest segment of a child’s airway and is completely surrounded by cartilage, which makes it vulnerable to damage, and may lead to subglottic stenosis. If the pressure created by the tube against the airway mucosa exceeds capillary filling pressure (roughly 35 cm H2O), mucosal ischemia develops, leading to necrosis. Therefore, a small air leak should be maintained around the endotracheal tube to minimize the risk of mucosal damage.

Artificial airways must be kept clear of secretions as obstruction with mucous plugs can be fatal. Providing
adequate humidification of inspired air and appropriate suctioning of the tube reduce the probability of occlusion by secretions. In addition to endotracheal tubes, the laryngeal mask airway (LMA) can be used to provide mechanical ventilation. This device consists of a tube with a soft mask at the distal end that is placed over the larynx, creating a seal without the trachea being instrumented. Although less invasive, the LMA is less secure, so it is generally limited to procedural anesthesia.

**Tracheostomy**

Tracheostomy is the surgical placement of an artificial airway into the trachea below the larynx. If prolonged intubation is anticipated, elective tracheostomy may be used to prevent laryngeal trauma, obviate the danger of accidental extubation, increase patient comfort, and facilitate nursing care. No clear guidelines are available as to how long patients can be intubated without sustaining airway damage or when a tracheostomy is indicated.

Children with severe chronic upper airway obstruction or those requiring long-term mechanical ventilation may benefit from tracheostomies. Because the tracheostomy tube hampers the ability to phonate and communicate, the child must be monitored carefully at all times. As with endotracheal tubes, tracheostomy tubes must be kept clear of secretions. Occlusion of the tube or accidental dislodgment of the tube can be fatal. Many children with tracheostomy tubes can be cared for at home provided the caregivers are well trained and adequately equipped.

**Mechanical Ventilation**

Patients who are unable to maintain adequate gas exchange may require mechanical ventilation. Most modes of mechanical ventilation involve inflation of the lungs with gas using positive pressure. The inspiratory phase is active (air is pushed in) and exhalation is passive.

**Positive-pressure ventilation** often requires an artificial airway, though it can be provided noninvasively via tight-fitting nasal or full face masks. Noninvasive ventilation is particularly useful in patients with obstructive sleep apnea and neuromuscular disease who require support only part of the day, but it can also be used to assist ventilation continuously for patients in acute respiratory failure from a variety of causes.

No method of mechanical ventilation truly simulates natural breathing. All methods have their drawbacks and complications. Positive pressure is transmitted to the entire thorax and may impede venous return to the heart during inspiration. The airways and lung parenchyma may be damaged by inflation pressures and high concentrations of inspired O2. In general, inflation pressures should be limited to those necessary to provide sufficient lung expansion for adequate ventilation and the prevention of atelectasis. Pressure-cycled and volume-cycled ventilators (conventional ventilation) are the most widely used modalities in pediatrics; however, high-frequency jet ventilation and high-frequency oscillatory ventilation are used often in neonatology and may be used in patients with severe lung disease who are failing conventional mechanical ventilation.

**CONTROL OF VENTILATION**

Ventilation is controlled primarily by central chemoreceptors located in the medulla that respond to intracellular pH and Pco2 levels (Fig. 134-1). To a lesser extent, ventilation is modulated by peripheral receptors located in the carotid and aortic bodies, which respond predominantly to Po2. The central receptors are quite sensitive. Small acute changes in Paco2 normally result in significant changes in minute ventilation. When the Pco2 is chronically elevated, the intracellular pH returns to normal levels because of compensatory increases in the bicarbonate level, and ventilatory drive is not increased. The peripheral receptors do not stimulate ventilation until the Pao2 decreases to approximately 60 mm Hg. These receptors become important in patients with chronic Paco2 elevation who may have a blunted ventilatory response to CO2.

The output of the central respiratory center also is modulated by reflex mechanisms. Full lung inflation temporarily inhibits inspiratory effort in infants (Hering-Breuer reflex) through vagal afferent fibers. Other reflexes from the airways and intercostal muscles may influence the depth and frequency of respiratory efforts (see Fig. 134-1).

**DISORDERS OF CONTROL OF BREATHING**

**Acute Life-Threatening Events**

**Etiology**

An acute life-threatening event (ALTE) is defined as any unexpected and frightening change in condition characterized by...
apnea, color change (usually blue or pale), sudden limpness, choking, or gagging. The incidence of such events is 0.05% to 1%. Specific causes can be identified in more than 50% of the cases. Gastroesophageal reflux and laryngospasm are the most common causes of ALTE, and they are associated with emesis, choking, or gagging. Central nervous system (CNS) causes (e.g., seizures, breath-holding spells, intracranial bleeding from accidental or nonaccidental trauma) account for approximately 15% of cases, and cardiovascular events and metabolic derangements account for smaller percentages. Acute infection with respiratory viruses (respiratory syncytial virus [RSV] and others), pertussis, and serious bacterial infections (sepsis, meningitis) can also cause apnea in infants.

Diagnostic Studies
In most cases, a careful history can lead to a correct diagnosis. Questions should include history of premature birth, prior apnea, level of consciousness at the time of the event, presence or absence of respiratory effort, limpness or stiffness, jerking movements (seizure), feeding history, intercurrent illnesses, any trauma, and the social situation of the family. The physical examination should focus on bruising and injury, the general and neurologic condition of the infant, nutritional status, respiratory pattern, and cardiac status. The laboratory evaluation may include serum electrolytes, serum glucose, blood urea nitrogen, creatinine, hemoglobin, hematocrit, white blood cell count, a chest radiograph, and blood gas analysis. Testing for respiratory viruses and pertussis in patients with evidence of respiratory infection should occur. If gastroesophageal reflux is suspected, a barium swallow or pH probe study may be useful. Cardiorespiratory monitoring for 12 to 24 hours in the hospital can provide information on respiratory and cardiac patterns and feeding difficulties (choking, gagging, emesis); provide time to get more history and assess the home situation; and alleviate parental anxiety. Useful tests to determine CNS causes include a head computed tomography (CT) scan, magnetic resonance imaging of the brain, and an electroencephalogram (EEG) (for seizures).

Treatment and Prevention
There are no standard recommendations for when home monitoring should be prescribed. Polysomnography is not useful in predicting which children with ALTEs are likely to progress to sudden infant death syndrome (SIDS). The key to prevention of future events is to identify the underlying cause and treat it. Teaching parents infant cardiopulmonary resuscitation (CPR) and attempting to alleviate anxiety surrounding the event are recommended.

Sudden Infant Death Syndrome
Etiology and Epidemiology
SIDS is defined as the unexpected death of an infant younger than 1 year of age in which the cause remains unexplained after an autopsy, death scene investigation, and review of clinical history. The risk of SIDS is higher in premature and low birth weight infants, infants of young impoverished mothers who smoke cigarettes, African American and Native American infants, and in infants whose mothers have abused drugs. The risk of SIDS is increased three- to fivefold in siblings of infants who have died of SIDS and is highest during the winter. SIDS is rare before 4 weeks or after 6 months of age and is most common between 2 and 4 months of age. The incidence of SIDS has decreased dramatically since the 1980s.

A variety of unproven mechanisms have been proposed to explain SIDS. SIDS is associated with prone position during sleep, especially on soft bedding. The widely advocated supine sleeping position explains, in part, the decreased incidence of SIDS during the past two decades. Current theories for a predisposition to SIDS include cellular brainstem abnormalities and maturational delay related to neural or cardiorespiratory control. A portion of SIDS deaths may be due to prolongation of the Q-T interval, abnormal CNS control of respiration, and CO2 rebreathing from sleeping face down (especially in soft bedding).

Differential Diagnosis
See Table 134-1 for the differential diagnosis of SIDS.

Prevention
There has been a significant decline in SIDS with the back-to-sleep program and avoiding soft bedding. Thus, all parents should be instructed to place their infants in the supine position unless there are medical contraindications. All soft

<table>
<thead>
<tr>
<th>Table 134-1</th>
<th>Differential Diagnosis of Sudden Infant Death Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFECTION</strong></td>
<td>Fulminant infection*</td>
</tr>
<tr>
<td><strong>DISEASE</strong></td>
<td>Infant botulism‡</td>
</tr>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td>Seizure disorder†</td>
</tr>
<tr>
<td></td>
<td>Brain tumor‡</td>
</tr>
<tr>
<td></td>
<td>Intracranial hemorrhage due to accidental or non-accidental trauma*‡</td>
</tr>
<tr>
<td></td>
<td>Drug intoxication‡</td>
</tr>
<tr>
<td><strong>METABOLIC</strong></td>
<td>Hypoglycemia†</td>
</tr>
<tr>
<td></td>
<td>Medium-chain acyl-coenzyme A dehydrogenase deficiency‡</td>
</tr>
<tr>
<td></td>
<td>Carnitine deficiency*‡</td>
</tr>
<tr>
<td></td>
<td>Urea cycle defect‡</td>
</tr>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td>Laryngospasm</td>
</tr>
<tr>
<td></td>
<td>Accidental suffocation‡</td>
</tr>
<tr>
<td></td>
<td>Hemosiderosis/pulmonary hemorrhage syndrome</td>
</tr>
<tr>
<td><strong>CARDIOVASCULAR</strong></td>
<td>Cardiac arrhythmia</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td>Gastroesophageal reflux‡</td>
</tr>
<tr>
<td></td>
<td>Midgut volvulus/shock‡</td>
</tr>
</tbody>
</table>

*Obvious or suspected at autopsy.
†Relatively common.
‡Diagnostic test required.
bedding should be avoided, and parents who share beds with their infants should be counseled on the risks. Decreasing maternal cigarette smoking, both during and after pregnancy, is recommended.

**Apnea**

**Etiology**

Apnea is defined as the cessation of airflow due to either lack of respiratory effort (central apnea) or upper airway obstruction (obstructive apnea). Central apnea lasting less than 10 seconds is common in healthy infants and can be present in normal children during sleep, especially after a sigh breath. Central pauses lasting longer than 15 to 20 seconds are considered abnormal. Central apnea is more common in infants, and obstructive apnea, especially during sleep, is more common in older children.

Premature infants can have apnea of prematurity, which consists of recurrent apneic episodes that are often of central origin, though they can be mixed central/obstructive. Apnea of prematurity should resolve by 44 weeks postconceptional age. Older infants and children with apnea warrant thorough investigation (Table 134-2).

Central apnea outside of infancy is a rare occurrence and may be primary or secondary. Secondary causes of central hypoventilation, which are more common, include medications impairing central respiratory drive (narcotics), increased intracranial pressure, CNS tumors, myelomeningocele and/or Arnold-Chiari malformation, and mitochondrial/metabolic disorders. Genetic syndromes associated with abnormal central respiratory control and developmental delays include Rett, Joubert, and Prader-Willi syndromes and tuberous sclerosis.

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder in which there is profound loss of respiratory effort during sleep leading to central apnea, hypercarbia, and hypoxemia. Most patients with CCHS have a defect in the PHOX2B gene, which is necessary for autonomic nervous system development. Most infants with CCHS have respiratory difficulties within the first several weeks of life, although it can also present later in childhood. CCHS is associated with an increased risk of Hirschsprung disease and neural crest tumors (neuroblastoma).

**Obstructive sleep apnea syndrome** (OSA), which affects 2% to 3% of young children with peak prevalence at 2 to 8 years, is caused by complete or partial upper airway obstruction during sleep. It presents as episodes of respiratory pauses, gasping, and restless sleep that can result in hypoxia and hypercarbia. Children may have difficulty awakening in the morning, daytime somnolence, behavioral changes, poor school performance, and poor somatic growth as a result of poor sleep quality. Nighttime hypoxia or hypercarbia can lead to morning headaches and, in severe cases, to pulmonary hypertension and cor pulmonale. Adenotonsillar hypertrophy is the most common cause of OSA in young children, but other risk factors for OSA include obesity, craniofacial malformations (Pierre Robin sequence, trisomy 21), glossoptosis, and neuromuscular diseases. Not all children who snore have OSA, and not all children who have OSA snore. Many young children with OSA do not have the classic findings of daytime somnolence and gasping respirations; restless sleep, behavioral problems, and inattention/hyperactivity are much more common. Thus, when the diagnosis is in question, it should be confirmed with a polysomnogram.

**Polysomnogram (PSG)** is the only definitive test for evaluation of obstructive and central sleep apnea. It involves continuous recording of EEG and electro-oculogram for sleep staging, oronasal airflow and pressure, audible snore, chest and abdominal wall excursion, leg and chin electromyogram, electrocardiogram, pulse oximetry, and capnography. The measured score from a PSG is the apnea-hypopnea index (AHI) or number of times in an hour of sleep that the child has cessation or reduction of airflow of a significant magnitude to negatively affect ventilation or sleep stage. An AHI less than 1 is the generally accepted norm for pediatric patients, although the decision to treat often hinges on the severity of daytime impairment. Measured AHI is typically worse in rapid eye movement (REM) sleep and when the child is supine, so an ideal study captures all sleep stages and positions.

Treatment of OSA starts with determining whether the child will benefit from an adenoidectomy, with or without a tonsillectomy. If surgical intervention is not indicated or fails

<table>
<thead>
<tr>
<th>Table 134-2</th>
<th>Categories of Apnea</th>
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</thead>
<tbody>
<tr>
<td><strong>DISEASE</strong></td>
<td><strong>EXAMPLE(S)</strong></td>
</tr>
<tr>
<td>Apnea of prematurity</td>
<td>Premature (&lt;36 wk)</td>
</tr>
<tr>
<td>Central apnea/ hypopnea</td>
<td>CCHS, Arnold-Chiari malformation</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>Obesity, adenotonsillar hypertrophy, Pierre Robin sequence, Down syndrome, cerebral palsy</td>
</tr>
<tr>
<td>Breath-holding spells</td>
<td>&lt;3 yr old who turns blue after crying, may have syncope</td>
</tr>
</tbody>
</table>

BiPAP, Bi-level positive airway pressure; CCHS, congenital central hypoventilation syndrome; CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula.
to alleviate the problem, then the use of continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) via nasal interfaces can be used to distend the upper airway during sleep. This requires a tight-fitting nasal mask, which may not be well tolerated in young children. Supplemental oxygen can blunt hypoxemia in milder cases of OSA but does not alter obstruction and sleep fragmentation. In extreme cases, especially those associated with craniofacial abnormalities or hypotonia, tracheostomy may be indicated.

### UPPER AIRWAY OBSTRUCTION

#### ETIOLOGY

Upper airway obstruction (UAO), which is defined as blockage of any part of the airway located above the thoracic inlet, ranges from nasal obstruction due to the common cold to life-threatening obstruction of the larynx or upper trachea (subglottic space). In children, nasal obstruction is usually more of a nuisance than a danger because the mouth can serve as an airway, but it may be a serious problem for neonates, who breathe predominantly through their noses. The differential diagnosis of airway obstruction varies with patient age and can also be subdivided into supraglottic, glottic, and subglottic causes (Tables 135-1, 135-2, and 135-3).

#### CLINICAL MANIFESTATIONS

UAO is more pronounced during inspiration because the negative pressure generated collapses the upper airway, increasing resistance to airflow and leading to inspiratory noise. The respiratory noise most commonly associated with UAO is **stridor**, a harsh sound caused by the vibration of the airway structures. Stridor often decreases during sleep, because of lower inspiratory flow rates, and increases during feeding, excitement, and agitation, because of higher flow rates. Occasionally stridor may also be present on exhalation. **Laryngomalacia** (floppy larynx) is the most common cause of inspiratory stridor in infants and may be aggravated by swallowing problems and gastroesophageal reflux. Hoarseness suggests **vocal cord** involvement. Children with UAO may have increased inspiratory work of breathing manifested by suprasternal retractions.

#### DIAGNOSTIC STUDIES

Although **radiographic evaluation** of a child with stridor may not be helpful, lateral views of the neck and nasopharynx may provide information about adenoidal hypertrophy and airway swelling. On anteroposterior (AP) views of the neck taken with the head in extension, the subglottic space should be symmetrical and the lateral walls of the airway should fall away steeply. Asymmetry suggests subglottic stenosis or a mass lesion, whereas tapering suggests subglottic edema. However, these findings may be subtle. Computed tomography (CT) scans of the upper airway can help delineate the site of the obstruction but may require sedation in younger children. Flexible nasopharyngoscopy/laryngoscopy, which can be done without sedation, is extremely useful in assessing airway patency, the presence of adenoid tissue, vocal cord and other airway lesions, and laryngomalacia. Bronchoscopy can be useful in assessing the subglottic space and intrathoracic large airways, but this procedure requires sedation.

### Table 135-1 Age-Related Differential Diagnosis of Upper Airway Obstruction

<table>
<thead>
<tr>
<th>NEWBORN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choanal atresia</td>
</tr>
<tr>
<td>Micrognathia (Pierre Robin syndrome, Treacher Collins syndrome, DiGeorge syndrome)</td>
</tr>
<tr>
<td>Macroglossia (Beckwith-Wiedemann syndrome, hypothyroidism, Pompe disease, trisomy 21, hemangioma)</td>
</tr>
<tr>
<td>Pharyngeal collapse</td>
</tr>
<tr>
<td>Laryngeal web, cleft, atresia</td>
</tr>
<tr>
<td>Vocal cord paralysis/paresis (weak cry, unilateral or bilateral, with or without increased intracranial pressure from Arnold-Chiari malformation or other central nervous system pathology)</td>
</tr>
<tr>
<td>Congenital subglottic stenosis</td>
</tr>
<tr>
<td>Nasal encephalocele</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INFANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngomalacia (most common non-infectious etiology)</td>
</tr>
<tr>
<td>Viral croup (most common infectious etiology)</td>
</tr>
<tr>
<td>Subglottic stenosis (congenital or acquired, e.g., after intubation)</td>
</tr>
<tr>
<td>Laryngeal web or cyst</td>
</tr>
<tr>
<td>Laryngeal papillomatosis</td>
</tr>
<tr>
<td>Vascular rings/slings</td>
</tr>
<tr>
<td>Airway hemangioma</td>
</tr>
<tr>
<td>Rhinitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TODDLERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral croup (most common etiology in children 6 mo to 4 yr of age)</td>
</tr>
<tr>
<td>Spasmodic/recurrent croup</td>
</tr>
<tr>
<td>Bacterial tracheitis (toxic, high fever)</td>
</tr>
<tr>
<td>Foreign body (airway or esophageal)</td>
</tr>
<tr>
<td>Laryngeal papillomatosis</td>
</tr>
<tr>
<td>Retropharyngeal abscess</td>
</tr>
<tr>
<td>Hypertrophied tonsils and adenoids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OLDER CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epiglottitis (infection, uncommon)</td>
</tr>
<tr>
<td>Inhalation injury (burns, toxic gas, hydrocarbons)</td>
</tr>
<tr>
<td>Foreign bodies</td>
</tr>
<tr>
<td>Angioedema (familial history, cutaneous angioedema)</td>
</tr>
<tr>
<td>Anaphylaxis (allergic history, wheezing, hypotension)</td>
</tr>
<tr>
<td>Trauma (tracheal or laryngeal fracture)</td>
</tr>
<tr>
<td>Peritonsillar abscess (adolescents)</td>
</tr>
<tr>
<td>Mononucleosis</td>
</tr>
<tr>
<td>Ludwig angina</td>
</tr>
</tbody>
</table>

---

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### Table 135-2  Differential Diagnosis of Acute Upper Airway Obstruction

<table>
<thead>
<tr>
<th>CLINICAL/HISTORICAL FEATURE</th>
<th>LARYNGOTRACHEOBRONCHITIS (CROUP)</th>
<th>LARYNGITIS</th>
<th>SPASMODIC CROUP</th>
<th>EPIGLOTTITIS</th>
<th>MEMBRANOUS CROUP (BACTERIAL TRACHEITIS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>6 mo–3 yr</td>
<td>5 yr–teens</td>
<td>3 mo–3 yr</td>
<td>2–6 yr</td>
<td>Any age (3–10 yr)</td>
</tr>
<tr>
<td>Location</td>
<td>Subglottic</td>
<td>Subglottic</td>
<td>Subglottic</td>
<td>Supraglottic</td>
<td>Trachea with secondary bacterial infection (Staphylococcus aureus, Moraxella catarrhalis)</td>
</tr>
<tr>
<td>Etiologic agent(s)</td>
<td>Parainfluenza virus, influenza virus, RSV; rarely Mycoplasma, measles, adenovirus</td>
<td>As per croup</td>
<td>Noninfectious Haemophilus influenzae type b inflammation</td>
<td>Respiratory virus</td>
<td></td>
</tr>
<tr>
<td>Prodrome/onset</td>
<td>Fever, URI</td>
<td>URI, sore throat at night</td>
<td>Sudden onset, short prodrome, prior episodes</td>
<td>Rapid onset</td>
<td>High fever with rapid deterioration</td>
</tr>
<tr>
<td>Stridor</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>Rarely</td>
<td>Yes</td>
</tr>
<tr>
<td>Retractions</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Voice</td>
<td>Hoarse</td>
<td>Hoarse</td>
<td>Hoarse</td>
<td>Muffled</td>
<td>Normal or hoarse</td>
</tr>
<tr>
<td>Body positioning</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Tripod sitting, leaning forward</td>
<td>Normal</td>
</tr>
<tr>
<td>Appearance</td>
<td>Normal to anxious</td>
<td>Anxious</td>
<td>Agitated; toxic</td>
<td>Anxious; toxic</td>
<td></td>
</tr>
<tr>
<td>Swallowing</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Drioling</td>
<td>Normal</td>
</tr>
<tr>
<td>Barking cough</td>
<td>Yes</td>
<td>Rare</td>
<td>Yes</td>
<td>No</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Rare</td>
<td>No</td>
<td>No</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Fever</td>
<td>Body temperature usually &lt;38.5°C</td>
<td>Body temperature usually &lt;38.5°C</td>
<td>None</td>
<td>Body temperature usually &gt;39°C</td>
<td>Body temperature usually &gt;39°C</td>
</tr>
<tr>
<td>Radiographic appearance</td>
<td>Subglottic narrowing; steeple sign</td>
<td>Normal</td>
<td>Subglottic narrowing of the epiglottis</td>
<td>Thumb sign of thickened epiglottis</td>
<td>Ragged irregular tracheal border; steeple sign</td>
</tr>
<tr>
<td>WBC count</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Leukocytosis with elevated % bands</td>
<td>Leukocytosis with elevated % bands</td>
</tr>
<tr>
<td>Therapy</td>
<td>Racemic epinephrine aerosol, systemic steroids, aerosolized steroids, cold mist</td>
<td>None</td>
<td>Same as for viral croup</td>
<td>Endotracheal intubation; antibiotics</td>
<td>Antibiotics; intubation if needed</td>
</tr>
<tr>
<td>Prevention</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>H. influenzae type b conjugated vaccine</td>
<td>None</td>
</tr>
</tbody>
</table>

### Table 135-2 Continued

<table>
<thead>
<tr>
<th>CLINICAL/HISTORICAL FEATURE</th>
<th>RETROPHARYNGEAL ABSCESS</th>
<th>FOREIGN BODY</th>
<th>ANGIOEDEMA</th>
<th>PERITONSILLAR ABSCESS</th>
<th>LARYNGEAL PAPILLOMATOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;6 yr</td>
<td>6 mo–5 yr</td>
<td>All ages</td>
<td>&gt;10 yr</td>
<td>3 mo–3 yr</td>
</tr>
<tr>
<td>Location</td>
<td>Posterior pharynx</td>
<td>Supra- or subglottic, variable</td>
<td>Variable</td>
<td>Oropharynx</td>
<td>Larynx, vocal cords, trachea</td>
</tr>
<tr>
<td>Etiology</td>
<td>Staphylococcus aureus</td>
<td>Small objects, vegetables, toys, coins</td>
<td>C1-esterase deficiency, anaphylaxis</td>
<td>Group A streptococci anaerobes</td>
<td>HPV</td>
</tr>
<tr>
<td>Prodom/onset</td>
<td>Insidious or sudden</td>
<td>Sudden</td>
<td>Sudden</td>
<td>Biphasic with sudden worsening</td>
<td>Chronic</td>
</tr>
<tr>
<td>Stridor</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td>Retractions</td>
<td>Yes</td>
<td>Yes—variable</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Voice</td>
<td>Muffled</td>
<td>Complete obstruction—aphonic</td>
<td>Hoarse, may be normal</td>
<td>Hot potato, muffled</td>
<td>Hoarse</td>
</tr>
<tr>
<td>Body positioning</td>
<td>Arching of neck or normal</td>
<td>Normal</td>
<td>Normal; may have facial edema, anxiety</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Continued
### Table 135-2  Differential Diagnosis of Acute Upper Airway Obstruction—cont’d

<table>
<thead>
<tr>
<th>CLINICAL/HISTORICAL FEATURE</th>
<th>RETROPHARYNGEAL ABSCESS</th>
<th>FOREIGN BODY</th>
<th>ANGIOEDEMA</th>
<th>PERITONSILLAR ABSCESS</th>
<th>LARYNGEAL PAPILLOMATOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Drooling</td>
<td>Variable, usually normal</td>
<td>Normal</td>
<td>Drooling, trismus</td>
<td>Normal</td>
</tr>
<tr>
<td>Cough</td>
<td>None</td>
<td>Variable; brassy if tracheal</td>
<td>Possible</td>
<td>None</td>
<td>Variable</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Moderate to severe</td>
<td>None, but dyspeic</td>
<td>None, unless anaphylactic shock or severe anoxia is present</td>
<td>Dyspnea</td>
<td>None</td>
</tr>
<tr>
<td>Fever</td>
<td>Body temperature usually &gt;38.5°C</td>
<td>None</td>
<td>None</td>
<td>Body temperature usually &gt;38.5°C</td>
<td>None</td>
</tr>
<tr>
<td>Radiographic appearance</td>
<td>Thickened retropharyngeal space</td>
<td>Radiopaque object may be seen</td>
<td>Same as for viral croup</td>
<td>None needed</td>
<td>May be normal</td>
</tr>
<tr>
<td>WBC count</td>
<td>Leukocytosis with increased band count</td>
<td>Normal</td>
<td>Normal</td>
<td>Leukocytosis with increased % bands</td>
<td>Normal</td>
</tr>
<tr>
<td>Therapy</td>
<td>Antibiotics; surgical drainage of abscess</td>
<td>Endoscopic removal</td>
<td>Anaphylaxis: epinephrine, IV fluids, steroids; C1-esterase deficiency: danazol, C1-esterase infusion</td>
<td>Antibiotics; aspiration</td>
<td>Laser therapy, repeated excision, interferon</td>
</tr>
<tr>
<td>Prevention</td>
<td>None</td>
<td>Avoid small objects; supervision</td>
<td>Avoid allergens; FFP for congenital angioedema</td>
<td>Treat group A streptococcal infections promptly</td>
<td>Treat maternal genitourinary lesions; possible cesarean section?</td>
</tr>
</tbody>
</table>


FFP, Fresh frozen plasma; HPV, human papillomavirus; RSV, respiratory syncytial virus; URI, upper respiratory tract infection (with coryza, sneezing); WBC, white blood cell.

### Table 135-3  Differentiating Supraglottic from Subglottic Causes of Airway Obstruction

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>SUPRAGLOTTIC OBSTRUCTION</th>
<th>SUBGLOTTIC OBSTRUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common clinical syndromes</td>
<td>Epiglottitis, peritonsillar and retropharyngeal abscess</td>
<td>Croup, angioedema, foreign body, tracheitis</td>
</tr>
<tr>
<td>Stridor</td>
<td>Quiet</td>
<td>Loud</td>
</tr>
<tr>
<td>Voice</td>
<td>Muffled</td>
<td>Hoarse</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sitting-up or arching posture</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Barking cough</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fever</td>
<td>High (temperature &gt;39°C)</td>
<td>Low grade (temperature 38°C–39°C)</td>
</tr>
<tr>
<td>Toxic</td>
<td>Yes</td>
<td>No, unless tracheitis is present</td>
</tr>
<tr>
<td>Trismus</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Drooling</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Facial edema</td>
<td>No</td>
<td>No, unless angioedema is present</td>
</tr>
</tbody>
</table>

Differential Diagnosis

Adenoidal and Tonsillar Hypertrophy

Etiology
The most common cause of chronic UAO in children is hypertrophy of the adenoids and tonsils. Adenoidal and tonsillar hyperplasia may be aggravated by recurrent infection, allergy, and inhaled irritants.

Clinical Manifestations
The signs of adenoidal and tonsillar hypertrophy are mouth breathing, snoring, and, in some patients, obstructive sleep apnea (see Chapter 134). The eustachian tubes enter the nasopharynx at the choanae and can be obstructed by enlarged adenoids, predisposing to recurrent or persistent otitis media.

Diagnostic Studies
Adenoidal hypertrophy is assessed by a lateral radiograph of the nasopharynx or by flexible nasopharyngoscopy.

Treatment
If the adenoids or tonsils are large and thought to be significantly contributing to UAO, then the most effective treatment is removal. Because the adenoids are not a discrete organ but rather consist of lymphoid tissue, regrowth is possible, especially in preschool children. If the tonsils are large and the obstruction is severe, then removing the tonsils in addition to the adenoids may be necessary.

Choanal Stenosis (Atresia)
Choanal stenosis/atresia is a congenital problem presenting in the neonatal period. It may be bilateral or unilateral and is relatively rare. Neonates are generally obligate nose breathers, so obstruction of nasal passages can cause significant respiratory distress, especially when feeding. Crying bypasses the obstruction because crying infants breathe through their mouths. Inability to easily pass a small catheter through the nostrils should raise the suspicion of choanal atresia. The diagnosis is confirmed by CT scan and by inspecting the area directly with a flexible nasopharyngoscope. An oral airway may be useful in the short term, but the definitive treatment is surgery.

Croup (Laryngotracheobronchitis)

Bacterial Tracheitis
SEE CHAPTER 107.

Laryngomalacia (Floppy Larynx)

Etiology
Laryngomalacia is due to exaggerated collapse of the glottic structures, especially the epiglottis and arytenoid cartilages, during inspiration. It may be due to decreased muscular tone of the larynx and surrounding structures or to immature cartilaginous structures. Inspiratory stridor beginning at or shortly after birth should raise the suspicion of laryngomalacia (see Table 135-1). This is the most common cause of stridor in infants. It usually does not result in significant respiratory distress, but occasionally it is severe enough to cause hypoventilation, with hypercarbia, hypoxemia, and difficulty with feeding.

Clinical Manifestations
The primary sign of laryngomalacia is inspiratory stridor with little or no expiratory component. The stridor is typically loudest when the infant is feeding or active and decreases when the infant is relaxed or placed prone, or when the neck is flexed. Any condition that increases upper airway inflammation will exacerbate laryngomalacia, including viral respiratory infections, dysphagia (swallowing dysfunction), and gastroesophageal reflux. Laryngomalacia normally peaks by 3 to 5 months of age and resolves between 6 and 12 months of age. However, occasionally it can persist in otherwise normal children up until 24 months of age and even longer in children with underlying conditions, especially those with neurologic diseases affecting control of upper airway muscles (such as cerebral palsy).

Diagnostic Studies
In many infants with presumed laryngomalacia, the diagnosis can be tentatively established by history and physical examination. If the patient follows the typical course for laryngomalacia, then no further workup is necessary. However, to firmly establish the diagnosis, which is important in more severe or atypical cases, the patient should undergo flexible nasopharyngoscopy to assess the patency and dynamic movement (collapse) of the larynx and surrounding structures. This procedure can also identify vocal cord abnormalities and airway lesions above the vocal cords.

Treatment
In most cases, no therapy is required for laryngomalacia. The infant should be observed closely during times of respiratory infection for evidence of respiratory compromise. If the patient follows the typical course for laryngomalacia, then no further workup is necessary. However, to firmly establish the diagnosis, which is important in more severe or atypical cases, the patient should undergo flexible nasopharyngoscopy to assess the patency and dynamic movement (collapse) of the larynx and surrounding structures. This procedure can also identify vocal cord abnormalities and airway lesions above the vocal cords.

Epiglottitis

SEE CHAPTER 107.
Subglottic Stenosis

**Etiology**
Subglottic stenosis is the narrowing of the portion of the trachea immediately below the vocal cords. It may be congenital but more often is acquired. Endotracheal intubation, especially prolonged or repeated intubation required in some premature infants, can lead to inflammation and scarring of the subglottic space.

**Clinical Manifestations**
Subglottic stenosis can present as stridor that is frequently biphasic (on both inspiration and expiration). However, the stridor is usually more prominent on inspiration. With increasing respiratory effort, the stridor becomes louder. Very small infants may not be able to breathe with enough force to generate a sound. Subglottic stenosis may also be associated with a barking cough similar to that noted with croup. Respiratory infections can cause subglottic edema, exacerbating the clinical manifestations of subglottic stenosis.

**Diagnostic Studies**
Definitive diagnosis requires endoscopic evaluation, either by flexible or rigid bronchoscopy.

**Treatment**
Mild subglottic stenosis can be managed conservatively and may improve sufficiently with airway growth alone. More severe cases require surgical intervention. Depending on the nature of the lesion, endoscopic laser treatment may be effective. Other surgical options include tracheoplasty and cricoid split procedures. A tracheostomy tube may be required to bypass the subglottic space until the airway is patent enough to allow adequate airflow.

Mass Lesions
Upper airway mass lesions are relatively uncommon. The most common laryngeal tumor in childhood is the hemangioma, which usually presents before 6 months of age. (See Chapter 194.) Subglottic lesions produce asymmetrical narrowing of the subglottic space on AP radiographs of the larynx, but definitive diagnosis requires endoscopy. If the obstruction is severe, then a tracheostomy tube may be needed until the lesion spontaneously involutes or improves with therapy. Laryngeal webs are the result of failed recanalization of the glottic airway in utero, whereas laryngeal cysts typically occur as a consequence of airway trauma (intubation). Both can produce biphasic stridor and are best identified by bronchoscopy. Foreign body should be considered in any infant or child capable of ingesting small objects who develops acute onset of stridor.

Juvenile laryngeal papillomatosis is a rare condition of benign tumors caused by human papillomavirus (HPV-6 and HPV-11) acquired at birth from maternal genital warts. Clinical manifestations usually start in infancy and include biphasic stridor and hoarse voice/cry. The lesions are most commonly located in the larynx, but they can spread distally into the trachea, large bronchi, and even to the lung parenchyma. Treatment options, which are limited and rarely curative, include laser therapy and interferon. Tracheostomy may be required to ensure an adequate airway, but should be avoided if possible as reports suggest a related seeding of the distal airways with tumor.

Vocal Cord Paralysis

**Etiology**
Vocal cord paralysis is an important cause of laryngeal dysfunction. Paralysis may be unilateral or bilateral and is more often caused by damage to the recurrent laryngeal nerve than by a central lesion. The left recurrent laryngeal nerve passes around the aortic arch and is more susceptible to damage than the right laryngeal nerve. Peripheral nerve injury may be caused by trauma (neck traction during delivery of infants or thoracic surgical procedures) and mediastinal lesions. Central causes include Arnold-Chiari malformation (meningomyelocele), hydrocephalus, and intracranial hemorrhage.

**Clinical Manifestations**
Vocal cord paralysis presents as biphasic stridor and alterations in voice and cry, including a weak cry (in infants), hoarseness, and aphonia. Children with vocal cord paralysis are at risk for aspiration, often manifested as coughing/choking with drinking and coarse airway sounds audibly and by auscultation.

**Treatment and Prognosis**
Patients with traumatic injury to the recurrent laryngeal nerve often have spontaneous improvement over time, usually within 3 to 6 months. If the paralyzed vocal cord has not recovered within 1 year of the injury, then it is likely to be permanently damaged. In some cases, Gelfoam injection of a paralyzed vocal cord can reposition the cord to improve phonation and airway protection. Patients with vocal cord paralysis resulting in severe airway obstruction and aspiration may require tracheostomy tube placement.
Chapter 136

LOWER AIRWAY, PARENCHYMAL, AND PULMONARY VASCULAR DISEASES

ETIOLOGY

There are many causes of lower airway diseases (Table 136-1). Lower airway diseases often result in airway obstruction. The most common lower airway disease in children is asthma, which results in diffuse bronchial obstruction from airway inflammation, constriction of bronchial smooth muscle, and excessive secretions. Virus-induced wheezing episodes are common, especially in children under 3 years of age. Wheezing that begins in the first weeks or months of life or that persists despite aggressive asthma therapy is likely not due to asthma, and further diagnostic evaluation may be warranted. Wheezing that is localized to one area of the chest suggests focal airway narrowing (foreign body aspiration or extrinsic compression by masses or lymph nodes).

CLINICAL MANIFESTATIONS

In contrast to upper airway obstruction, obstruction below the thoracic inlet causes more wheezing on expiration than on inspiration. A wheeze is a continuous sound that is produced by vibration of airway walls and generally has a more musical quality than does stridor. Intrathoracic pressure is increased relative to atmospheric pressure during exhalation, which tends to collapse the intrathoracic airways and accentuates airway narrowing on expiration. This manifests as expiratory wheeze, prolonged expiratory phase, and increased expiratory work of breathing. In patients with chronic airway infection (e.g., cystic fibrosis), the bronchi become permanently damaged and dilated (bronchiectasis). Patients with bronchiectasis have episodes of cough, often productive of purulent sputum, and may have inspiratory crackles.

DIAGNOSTIC STUDIES

When asthma is suspected, empiric trials of therapy (bronchodilators, short courses of oral corticosteroids, long-term use of inhaled corticosteroids) are useful in arriving at a diagnosis. In children older than 6 years, pulmonary function tests (spirometry) can assess airflow obstruction and response to bronchodilators. Radiographic evaluation is not needed with each episode of wheezing, but those with significant respiratory distress, fever, history consistent with foreign body

<table>
<thead>
<tr>
<th>Table 136-1 Causes of Wheezing in Childhood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACUTE</strong></td>
</tr>
<tr>
<td>Reactive airway disease</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Exercise-induced asthma</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Bronchial edema</td>
</tr>
<tr>
<td>Infection (e.g., bronchiolitis)</td>
</tr>
<tr>
<td>Inhalation of irritant gases or particulates</td>
</tr>
<tr>
<td>Increased pulmonary venous pressure</td>
</tr>
<tr>
<td>Bronchial hypersecretion</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Inhalation of irritant gases or particulates</td>
</tr>
<tr>
<td>Cholinergic drugs</td>
</tr>
<tr>
<td>Aspiration</td>
</tr>
<tr>
<td>Foreign body</td>
</tr>
<tr>
<td>Aspiration of gastric contents</td>
</tr>
<tr>
<td><strong>CHRONIC OR RECURRENT</strong></td>
</tr>
<tr>
<td>Reactive airway disease (see under Acute)</td>
</tr>
<tr>
<td>Hypersensitivity reactions, allergic bronchopulmonary aspergillosis (seen only in children with either asthma or cystic fibrosis)</td>
</tr>
<tr>
<td>Dynamic airway collapse</td>
</tr>
<tr>
<td>Bronchomalacia/tracheomalacia</td>
</tr>
<tr>
<td>Vocal cord adduction (paradoxical vocal cord motion)</td>
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<tr>
<td>Airway compression by mass or blood vessel</td>
</tr>
<tr>
<td>Vascular ring/sling</td>
</tr>
<tr>
<td>Anomalous innominate artery</td>
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<tr>
<td>Pulmonary artery dilatation (absent pulmonary valve)</td>
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<tr>
<td>Bronchial or pulmonary cysts</td>
</tr>
<tr>
<td>Lymph nodes (tuberculosis, lymphoma)</td>
</tr>
<tr>
<td>Aspiration</td>
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<tr>
<td>Foreign body</td>
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<tr>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Swallowing dysfunction (dysphagia)</td>
</tr>
<tr>
<td>Tracheoesophageal fistula</td>
</tr>
<tr>
<td>Bronchial hypersecretion or failure to clear secretions</td>
</tr>
<tr>
<td>Bronchitis, bronchiectasis</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Primary ciliary dyskinesia</td>
</tr>
<tr>
<td>Intrinsic airway lesions</td>
</tr>
<tr>
<td>Endobronchial tumors (carcinoid)</td>
</tr>
<tr>
<td>Endobronchial granulation tissue</td>
</tr>
<tr>
<td>Endobronchial tuberculosis</td>
</tr>
<tr>
<td>Bronchial or tracheal stenosis</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
</tbody>
</table>
aspiration, or focal auscultatory findings should have posteroanterior (PA) and lateral chest radiographs obtained. Generalized hyperinflation, indicated by flattening of the diaphragms and an increased anteroposterior (AP) chest diameter, suggests diffuse obstruction of the small airways. Hyperinflation in association with patchy densities due to atelectasis is often seen in asthma and mistaken for pneumonia. Localized hyperinflation, especially on expiratory views, suggests localized bronchial obstruction (foreign body or an anatomic anomaly). Dysphagia leading to aspiration and airway inflammation can present with persistent wheezing. This is best assessed with a **videofluoroscopic swallowing study.** Gastroesophageal reflux may aggravate asthma and may lead to wheezing in very young children, especially if it is associated with aspiration.

**DIFFERENTIAL DIAGNOSIS**

**Asthma**

Decision-Making Algorithm

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Wheezing

SEE CHAPTER 78.

**Tracheomalacia**

**Etiology**

Tracheomalacia is a floppy trachea due to lack of structural integrity of the tracheal wall. The tracheal cartilaginous rings normally extend through an arc of approximately 320°, maintaining rigidity of the trachea during changes in intrathoracic pressure. With tracheomalacia, the cartilaginous rings may not extend as far around the circumference (leaving the membranous posterior trachea wider than usual), may be completely absent, or may be present but damaged. These abnormalities can result in excessive collapse of the trachea, most pronounced during expiration. Tracheomalacia may be congenital (tracheoesophageal fistula or bony dysplasia syndromes) or acquired (long-term mechanical ventilation). Tracheomalacia must be differentiated from extrinsic tracheal compression by masses or vascular structures. Localized tracheomalacia may persist after the trachea has been relieved of extrinsic compression. Viral infections may exacerbate tracheomalacia, leading to coarse expiratory wheezing and barking cough. The expiratory noises of tracheomalacia are often mistakenly ascribed to asthma or bronchiolitis, and the barking cough is often misdiagnosed as croup.

**Clinical Manifestations**

With tracheomalacia, the tracheal collapse may only be apparent during forced exhalation or with cough. It is commonly aggravated by respiratory infections. The airway collapse may cause recurrent coarse expiratory wheeze and a prolonged expiratory phase. Secretions may be retained behind the segment of malacia, predisposing to infection. Infants with severe tracheomalacia may completely collapse their tracheas during agitation, resulting in cyanotic episodes that resemble breath-holding spells. The voice is normal, as is inspiratory effort. In older children, the hallmark sign is a brassy, barking cough due to the vibration of the tracheal walls. This cough can be loud and persistent and is often misdiagnosed as croup.

**Treatment**

Infants with mild to moderate tracheomalacia usually require no intervention. Tracheomalacia improves with airway growth as the lumen increases in diameter and the tracheal wall becomes more firm. The treatment of older symptomatic children is geared toward treating any precipitating cause for cough and providing supportive care. Antibiotics may be necessary to treat concurrent infection. Children, especially infants, with severe tracheomalacia may require tracheostomy tubes to administer continuous positive airway pressure (CPAP), which serves to stent open the airway. Custom-length tracheostomy tubes have been used to stent open the airway when CPAP fails. Surgically placed airway stents are problematic in children because the stents cannot grow and thus serve as a source of fixed stenosis and obstruction.

**Tracheoesophageal Fistula**

SEE CHAPTER 128.

**Extrinsic Tracheal Compression**

Compression of the trachea by vascular structures or masses can cause significant respiratory compromise. Tracheal compression by aberrant great vessels (aorta, innominate artery) may cause wheezing, stridor, cough, and dyspnea. The most common cause of tracheal compression is anterior compression from an **anomalous innominate artery** that arises more distally than normal from the aortic arch. This usually results in mild respiratory symptoms, and surgical correction is rarely necessary. Complete vascular rings, which compress the esophagus posteriorly and the trachea anteriorly, include the double aortic arch and a right aortic arch with a persistent ligamentum arteriosum (most common). Both lesions have right-sided aortic arches, which may be visible on chest radiograph. In addition to respiratory symptoms, complete vascular rings may cause dysphagia as a result of esophageal compression. The diagnosis of vascular anomalies can often be made by a barium swallow, which identifies the esophageal compression. Bronchoscopy will identify a pulsatile compression of the airway, but the diagnostic procedure of choice is a computed tomography (CT) angiogram of the chest and great vessels. Complete vascular rings almost always require surgical repair. Other causes of extrinsic tracheal compression include enlarged mediastinal lymph nodes (tuberculosis), mediastinal masses (teratoma, lymphoma, thymoma, germ cell tumors), and, rarely, cystic hygromas.

**Foreign Body Aspiration**

**Epidemiology**

Aspiration of foreign bodies into the trachea and bronchi is relatively common. The majority of children who aspirate foreign bodies are under 4 years of age. Most deaths secondary to foreign body aspiration occur in this age group. Because the right mainstem bronchus takes off at a less acute angle than the left mainstem bronchus, foreign bodies tend to lodge in right-sided airways. Some foreign bodies, especially nuts, can
also lodge more proximally in the larynx or subglottic space, totally occluding the airway. Many foreign bodies are not radiopaque, which makes them difficult to detect radiographically. The most common foreign bodies aspirated by young children are food (especially nuts) and small toys. Coins more often lodge in the esophagus than in the airways. Older children have been known to aspirate rubber balloons, which can be life-threatening.

Clinical Manifestations

Many children who aspirate foreign bodies have clear histories of choking, witnessed aspiration, or physical or radiographic evidence of foreign body aspiration. However, a small percentage of patients have a negative history because the aspiration went unrecognized. Physical findings observed with acute foreign body aspiration may include cough, localized wheezing, unilateral absence of breath sounds, stridor, and, rarely, bloody sputum.

Most foreign bodies are small and quickly expelled, but some may remain in the lung for long periods of time and may come to medical attention because of persistent cough, sputum production, or recurrent unilateral pneumonia. Foreign body aspiration should be in the differential diagnosis of patients with persistent wheezing unresponsive to bronchodilator therapy, persistent atelectasis, recurrent or persistent pneumonia, or chronic cough without another explanation. Foreign bodies may also lodge in the esophagus and compress the trachea, thus producing respiratory symptoms. Therefore, esophageal foreign bodies should be included in the differential diagnosis of infants or young children with persistent stridor or wheezing, particularly if dysphagia is present.

Diagnostic Studies

Radiographic studies will reveal the presence of radiopaque objects and can also identify focal air trapping, especially on expiratory views. Thus, when foreign body aspiration is suspected, expiratory or lateral decubitus chest radiographs should be ordered. In addition, fluoroscopy may be helpful, especially in children who cannot perform expiratory views. If there is strong evidence (or history) of foreign body aspiration, the patient should undergo rigid bronchoscopy. Flexible bronchoscopy can be used to locate an aspirated foreign body and may be useful when the presentation is not straightforward, but foreign body removal is best performed via rigid bronchoscopy.

Prevention

The best approach to preventing foreign body aspiration is to educate parents and caregivers. Before molar teeth have erupted, infants and children should not be given nuts, uncooked carrots, or other foods that may be easily broken into small pieces and aspirated. Sound parental judgment is required to determine at what age and stage of development small objects should be accessible to children.

Bronchiolitis

SEE CHAPTER 109.

Bronchopulmonary Dysplasia

SEE CHAPTER 61.

Endobronchial Mass Lesions

Endobronchial mass lesions are relatively uncommon in children. The most common lesion is granulation tissue, which usually results from local inflammation. Tuberculosis can cause endobronchial granulomas. Primary tumors of the lung are extremely rare in children. The most common airway malignancy is the nonsecreting carcinoid tumor. Endobronchial lesions that partially obstruct an airway present with wheezing or obstructive emphysema and occasionally with hemoptysis. If the lesion completely occludes the airway, then atelectasis may result. Radiographs and CT scans of the chest aid in making the diagnosis. Bronchoscopy is often used to confirm the diagnosis.

Congenital Lung Anomalies

Congenital lobar overdistention (formerly referred to as congenital lobar emphysema) consists of overinflation of one lobe of a lung. This overdistention may cause severe respiratory distress in the neonatal period due to compression of surrounding normal lung tissue, but it can also be asymptomatic and remain undiagnosed for years. Radiographically, it may be mistaken for a pneumothorax. Lobectomy may be required if respiratory distress is severe or progressive, but if the patient is asymptomatic, then surgical resection may not be indicated.

Pulmonary hypoplasia, or a relative decrease in amount of alveoli, may be the result of a number of congenital insults, such as congenital diaphragmatic hernia (see Chapter 61) or unilateral congenital absence of a pulmonary artery. Alveolar growth occurs after birth predominantly up to 3 years, but has been documented up to 8 years.

Emphysema

Emphysema is a condition due to disruption or destruction of alveolar septa. In pediatrics, the term emphysema often refers to hyperinflation or to leakage of air into the pulmonary interstitial spaces (interstitial emphysema, which may be seen in mechanically ventilated premature infants) or the subcutaneous tissue (subcutaneous emphysema). Although emphysema is common in adults, it is rare in children. However, generalized or localized hyperinflation, which can be
caused by airway obstruction from a variety of causes, is common. Emphysema is commonly observed in the disease α1-antitrypsin deficiency, but it rarely appears before the second decade of life.

**Primary Ciliary Dyskinesia**

**Etiology**

Primary ciliary dyskinesia (PCD, immotile cilia syndrome) is an inherited disorder in which ultrastructural abnormalities in the cilia result in absent or disordered movement of the cilia. This disorder affects approximately 1 in 19,000 persons. There are many reported abnormalities in ciliary structure, but the most common are due to defects in the dynein arms, ultrastructural features that provide energy via adenosine triphosphatase (ATPase), which is necessary for ciliary motility.

**Clinical Manifestations**

The classic presentation is recurrent otitis media, chronic sinusitis, and bronchiectasis. Kartagener syndrome, the triad of situs inversus, pansinusitis, and bronchiectasis, accounts for approximately 50% of cases. Males are infertile as a result of immotile sperm. Because the cilia fail to beat normally, secretions accumulate in the airways, and endobronchial infection results. Chronic infection, if untreated, leads to bronchiectasis by early adulthood. Primary ciliary dyskinesia should be suspected in patients with early-onset chronic bronchitis or bronchiectasis associated with recurrent/persistent sinusitis and/or frequent otitis media.

**Diagnostic Studies**

PCD is confirmed by electron microscopy of respiratory cilia, obtained from scrapings/biopsy of nasal or airway epithelium. Results may be difficult to interpret as chronic infection and inflammation may lead to ultrastructural abnormalities in nasal cilia. The measurement of nasal nitric oxide has been used as a screening tool for PCD. Low nasal nitric oxide values (<200 parts per billion) are consistent with PCD, whereas values greater than 400 parts per billion make the diagnosis less likely. However, the validity of nasal nitric oxide assays as a diagnostic test for PCD has not been fully substantiated.

**Treatment**

Treatment is geared toward treating infections and improving clearance of respiratory secretions. High resolution chest CT scans are useful to confirm and monitor bronchiectasis. Surveillance cultures help identify organisms involved and guide antibiotic therapy. Sinus surgical procedures are often done to manage chronic sinusitis, but their benefit is questionable. Most children require placement of pressure equalization (PE) tubes for management of recurrent otitis media. Chest physiotherapy and prompt treatment of bacterial infections are helpful, but the course of the disease tends to be slowly progressive. Preventive antibiotics, such as thrice-weekly macrolides, may reduce the number of exacerbations per year.

**Pneumonia**

SEE CHAPTER 110.

**Pulmonary Edema**

**Etiology**

Pulmonary edema is the seepage of fluid into the alveolar and interstitial spaces. Capillary hydrostatic forces and interstitial osmotic pressures tend to push fluid into the airspaces, whereas plasma osmotic pressures and tissue mechanical forces tend to move fluid away from the airspaces. Under normal circumstances, the sum of these forces favors absorption, so the alveolar and interstitial spaces remain dry. Fluid entering the alveoli is normally removed by pulmonary lymphatics. Pulmonary edema forms when transcapillary fluid flux exceeds lymphatic drainage. Reduced left ventricular function leads to pulmonary venous hypertension and increased capillary hydrostatic pressure, and fluid moves into the interstitial space and alveoli. Fluid initially enters the interstitial space around the terminal bronchioles, alveoli, and arterioles (interstitial edema), causing increased lung stiffness and premature closure of bronchioles on expiration. If the process continues, fluid then enters the alveoli, further reducing compliance and resulting in intrapulmonary shunting (alveolar units that are perfused but not ventilated). Decreased ventilation (hypercarbia) is a late finding.

Pulmonary edema is most commonly due to heart failure from left ventricular or biventricular dysfunction. Pulmonary hypertension and associated cor pulmonale (right ventricular dysfunction) do not usually cause pulmonary edema as the increased vascular resistance is proximal to the capillary bed. Increased capillary permeability, seen in disease states such as sepsis and acute respiratory distress syndrome, can lead to pulmonary edema. Pulmonary edema may also occur with excessive swings in intrathoracic pressure, as seen after tracheal foreign body aspiration or severe obstruction from hypertrophied tonsils and adenoids (postobstructive pulmonary edema). Pulmonary edema may also be present in conditions with decreased serum oncotic pressure (hypoalbuminemia); after administration of large volumes of intravenous (IV) fluids, especially if there is capillary injury; with ascent to high altitude (high altitude pulmonary edema); and after central nervous system injury (neurogenic pulmonary edema).

**Clinical Manifestations**

**Cough**
The clinical manifestations of pulmonary edema are dyspnea, tachypnea, and cough (often with frothy, pink-tinged sputum). As the edema worsens, there is increased work of breathing and hypoxemia; diffuse inspiratory crackles can be heard on auscultation.

**Diagnostic Studies**
Chest radiographs may reveal diffuse hazy infiltrates, classically in a perihilar pattern, but these findings may be obscured by underlying lung disease. Interstitial edema (Kerley B lines) may be seen, especially at the lung bases.

**Treatment and Prognosis**
Treatment and prognosis depend on the cause of the pulmonary edema and response to therapy. Patients should be positioned in an upright posture and given supplemental O2. Diuretic therapy and rapidly acting IV inotropic agents may be helpful in cardiogenic pulmonary edema. Continuous positive airway pressure (CPAP) or intubation with positive pressure ventilation using high positive end-expiratory pressures (PEEP) may be required.

**Acute Respiratory Distress Syndrome**
SEE CHAPTER 39.

**Pulmonary Arterial Hypertension and Cor Pulmonale**

**Etiology**
Pulmonary hypertension (PH) is classified in five groups based on mechanism. Group 1 is pulmonary arterial hypertension (PAH) due to diseases within veins and small pulmonary muscular arteries such as persistent pulmonary hypertension of the newborn, congenital heart disease (including those with excessive pulmonary blood flow due to left-to-right cardiac shunting), exposure to various drugs (e.g., cocaine, amphetamines), and idiopathic pulmonary arterial hypertension (previously called primary pulmonary hypertension). Hereditary IPAH is also in this group and has been linked with the bone morphogenetic receptor-2 (BMPR2) gene. Group 2 is caused by dysfunction of the left heart such as valvular disease. Group 3 is secondary to lung disease or chronic hypoxia, including upper airway obstruction resulting in obstructive sleep apnea and hypoxemia. In Group 4, PH is secondary to chronic pulmonary thromboembolism. Group 5 includes PH of unclear but multifactorial diseases, including some autoimmune diseases and metabolic diseases. With prolonged PAH, irreversible changes may occur in the intima and media of the pulmonary arterioles.

Pulmonary arterial hypertension strains the right side of the heart, which leads to hypertrophy and dilation of the right ventricle. This may result in cor pulmonale, a condition in which right-sided heart failure leads to hepatic congestion, fluid retention, and tricuspid insufficiency. In severe cor pulmonale, the ventricular septum may be displaced toward the left ventricle, hindering left ventricular function. The most common causes of cor pulmonale in children are chronic lung diseases, especially severe bronchopulmonary dysplasia and scleroderma, and severe untreated obstructive sleep apnea (with chronic hypoxia).

**Clinical Manifestations and Diagnostic Studies**
Pulmonary arterial hypertension should be suspected whenever there is prolonged hypoxemia or hemodynamically significant left-to-right cardiac shunting. In addition to other physical findings associated with pulmonary and cardiac diseases, an accentuated pulmonary component of the second heart sound may be heard. Definitive diagnosis is made by echocardiography, but echocardiography may confirm the presence of right ventricular hypertrophy, ventricular dysfunction, interventricular septal flattening, and tricuspid insufficiency, which can be used to estimate the pulmonary artery pressures.

**Treatment and Prognosis**
For those with pulmonary hypertension in groups 2 through 5, treatment should focus on the underlying condition. In all conditions of PH and PAH, the relief of hypoxemia with supplemental O2 therapy is essential. Heart failure may require treatment with diuretics and restrictions of salt and fluid intake. Vasodilator therapy (sildenafil) is helpful in some patients, and inhaled nitric oxide can be used short term. Continuous infusions of prostacyclin may be helpful both acutely and chronically and is available in inhaled, subcutaneous, and intravenous forms. Endothelium antagonists may be beneficial. Unfortunately, many patients with the idiopathic form of PAH have progressive courses, and lung or heart-lung transplantation may be the only treatment option.

**Pulmonary Hemorrhage**

**Etiology**
Pulmonary hemorrhage is a rare but potentially life-threatening condition in children. It can be due to bleeding from the airways (hemangiomas, bronchial vessel bleeds) or from diffuse capillary bleeding (alveolar hemorrhage). Alveolar hemorrhage is usually due to diffuse capillary disruption/inflammation caused by autoimmune disorders and after bone marrow transplantation. Airway bleeding can be due to airway hemangiomas, pulmonary arteriovenous malformations (as with hereditary hemorrhagic telangiectasia), and bronchial artery collaterals, which develop in some patients with chronic lung infections, especially cystic fibrosis. Idiopathic pulmonary hemosiderosis is a rare disorder characterized by recurrent alveolar bleeding, iron deficiency anemia, and hemosiderin-laden macrophages in the lung, which can be identified microscopically with the use of special iron-staining techniques in bronchoalveolar lavage or lung biopsy specimens. Although the term hemosiderosis is sometimes used interchangeably with pulmonary hemorrhage, it is a pathologic finding that results from bleeding anywhere in the lung, airway, pharynx, nasopharynx, or mouth leading to hemosiderin accumulation in the lung. Pulmonary hemorrhage is a preferable term for bleeding from an intrathoracic source.

**Clinical Manifestations**

**Decision-Making Algorithm**

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Most children with pulmonary hemorrhage present with hemoptysis. It is important to rule out extrapulmonary sources of bleeding, including hematemesis and bleeding from the nasopharynx or mouth, as these are more common than true pulmonary hemorrhage. In addition to hemoptysis, the presenting signs and symptoms of pulmonary hemorrhage include cough, wheeze, shortness of breath, pallor, fatigue, cyanosis, and fever. Episodic pulmonary hemorrhage frequently manifests as recurrent respiratory symptoms associated with pulmonary infiltrates on chest radiographs. Symptomatic airway hemorrhage may result in significant hemoptysis with few radiographic changes, whereas alveolar bleeding often causes profound respiratory symptoms, hypoxemia, diffuse infiltrates on radiographs, and minimal hemoptysis. Some patients experience a localized bubbling sensation in the chest, which may be helpful in differentiating local from diffuse sources of pulmonary bleeding. Physical examination findings may include locally or diffusely decreased breath sounds, cyanosis, and crackles on auscultation.

The differential diagnosis of pulmonary hemorrhage includes alveolar and airway bleeding. The causes of alveolar (capillary) bleeding include: idiopathic pulmonary hemosiderosis; diffuse alveolitis (capillaritis) secondary to autoimmune disease; clotting disorders; venoocclusive disease; diffuse alveolar injury; and cardiac conditions associated with elevated pulmonary venous and capillary pressures (Table 136-2). Rarely, a previously well infant will present with life-threatening acute alveolar hemorrhage. Often no cause is found, and, once the acute episode resolves, the infant returns to normal. Most of these infants never have a second bleeding episode. Hemoptysis can have cardiovascular, pulmonary, or immunologic causes (see Table 136-2).

Diagnostic Studies
It is important to perform a thorough upper airway examination to rule out epistaxis. Sometimes this requires nasopharyngoscopy. If extrapulmonary sources of bleeding have been excluded, then a chest radiograph, CT angiogram of the chest, bronchoscopy, echocardiogram, and evaluation for rheumatologic/autoimmune diseases, especially Goodpasture disease, granulomatosis with polyangiitis, Henoch-Schönlein purpura, and systemic lupus erythematosus, should be considered.

Treatment
The management of acute episodes of pulmonary bleeding includes the administration of supplemental O2, blood transfusions, and, often with acute alveolar hemorrhages, mechanical ventilation with PEEP to tamponade the bleeding. Attempts should be made to identify the cause of the bleeding. Treatment is directed toward the underlying disorders and providing supportive care. In bronchial arterial bleeding, arteriography with vessel embolization has been shown to be successful.

Pulmonary Embolism
Etiology
Pulmonary embolism is rare in children. When it occurs, it is often associated with indwelling central venous catheters, oral contraceptives, or hypercoagulable states. In adolescents, trauma, obesity, abortion, and malignancy may lead to deep vein thromboses (DVTs) and pulmonary embolism.

Clinical Manifestations
Because the pulmonary vascular bed is distensible, small emboli, even if multiple, may be asymptomatic unless they are infected (septic emboli) and cause pulmonary infection. Large emboli may cause acute dyspnea, pleuritic chest pain, cough, and hemoptysis. Hypoxia is common, as are nonspecific ST-segment and T-wave changes on the electrocardiogram (ECG). The P2 heart sound may be increased, and an S4 sound may be present.
Diagnostic Studies
Although the chest x-ray is usually normal, atelectasis or cardiomegaly may be seen. The measurement of D-dimers can be used as a screening test, but it must be interpreted in light of the probability of a pulmonary embolism. If the D-dimer is normal and the probability for embolism is low, then no further workup may be necessary. However, if the D-dimer is elevated, or if it is normal but the probability of embolism is moderate or high, then the diagnostic test of choice is a CT angiogram of the chest. Ventilation-perfusion scans may revealing defects in perfusion without matching ventilation defects, but they are difficult to perform in young children. Doppler or compression ultrasonography can be useful in assessing patients for lower extremity DVTs. For definitive diagnosis of pulmonary embolism, the gold standard is still pulmonary angiography, though with the improvement in CT angiography, angiograms are now rarely necessary. Children with pulmonary embolism without an obvious cause should be evaluated for hypercoagulable states, the most common of which is factor V Leiden.

Treatment
Once a pulmonary embolism is suspected, the patient should be anticoagulated, usually with low-molecular-weight heparin. All patients should receive supplemental O2, and it is important to treat the predisposing factors. Thrombolytic therapy and surgical resection of emboli are rarely indicated. Occasionally an inferior vena caval filter needs to be placed to prevent recurrent emboli.

CF is a chronic progressive disease that can present with protein and fat malabsorption (failure to thrive, hypoalbuminemia, steatorrhea), liver disease (cholestasis jaundice), or chronic respiratory infection (Table 137-1). Many infants currently are diagnosed based on newborn screening, which has been available in all 50 states and the District of Columbia since 2010. Older children commonly present with pulmonary manifestations such as poorly controlled asthma and chronic respiratory infections. The respiratory epithelium of patients with CF exhibits marked impermeability to chloride and an excessive reabsorption of sodium. This leads to a relative dehydration of airway secretions, which results in airway obstruction and impaired mucociliary transport. This, in turn, leads to endobronchial colonization with bacteria, especially *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Chronic bronchial infection results in persistent or recurrent cough that is often productive of sputum, especially in older children. Chronic airway infection leads to airway obstruction and bronchiectasis and, eventually, to pulmonary insufficiency and premature death. The median age of survival (years) is currently in the mid-30s. **Digital clubbing** is common in patients with CF, even in those without significant lung disease. Chronic sinusitis and **nasal polyposis** are common.

Pulmonary infections with virulent strains of *Burkholderia cepacia* are difficult to treat and may be associated with accelerated clinical deterioration. **Allergic bronchopulmonary aspergillosis (ABPA)** is a hypersensitivity reaction to *Aspergillus* in the CF Airways. It causes airway inflammation/obstruction and aggravates CF lung disease. The treatment for ABPA is systemic corticosteroids (prednisone) and antifungal agents (itraconazole). Minor hemoptysis is usually due to airway infection, but major hemoptysis is often caused by bleeding from bronchial artery collateral vessels in damaged/chronically infected portions of the lung. Pneumothoraces can occur in patients with advanced lung disease.

ETIOLOGY AND EPIDEMIOLOGY
Cystic fibrosis (CF) is an autosomal recessive disorder that is the most common life-limiting genetic disease in whites. In the United States, the incidence of CF is approximately 1 in 3200 whites, 1 in 15,000 African Americans, and 1 in 31,000 persons of Asian heritage. The gene for CF, located on the long arm of chromosome 7, encodes for a polypeptide, the **cystic fibrosis transmembrane regulator (CFTR)**, a chloride channel located on the apical surface of epithelial cells. CFTR is important for the proper movement of salt and water across cell membranes and maintaining the appropriate composition of various secretions, especially in the airways, liver, and pancreas. The most common mutation is a deletion of three base pairs resulting in the absence of phenylalanine at the 508 position (ΔF508). More than 1500 mutations of the CFTR gene have been identified.

The secretory and absorptive characteristics of epithelial cells are affected by abnormal CFTR, resulting in the clinical manifestations of CF. The altered chloride ion conductance in the sweat gland results in excessively high sweat sodium and chloride levels. This is the basis of the sweat chloride test, which is still the standard diagnostic test for this disorder. It is positive (elevated sweat chloride > 60 mEq/L) in 99% of patients with CF. Abnormal airway secretions make the airway more prone to colonization with bacteria. Defects in CFTR may also reduce the function of airway defenses and promote bacterial adherence to the airway epithelium. This all leads to chronic airway infections and eventually to bronchial damage (bronchiectasis).

**CLINICAL MANIFESTATIONS**

<table>
<thead>
<tr>
<th>Decision-Making Algorithms</th>
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</table>

- Neck Masses
- Hoarseness
- Hemoptysis
- Chest Pain
- Diarrhea
- Constipation
- Hepatomegaly
- Eosinophilia
- Polyuria
- Failure to Thrive
- Alkalemia
- Hyponatremia

**Chapter 137**

**CYSTIC FIBROSIS**

**Table 137-1**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
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<tbody>
<tr>
<td>Failure to Thrive</td>
<td>Weight and growth failure</td>
</tr>
<tr>
<td>Polyuria</td>
<td>Frequent urination</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>Increase in eosinophils in blood and tissues</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Enlarged liver</td>
</tr>
<tr>
<td>Constipation</td>
<td>Difficulty in passing stool</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Frequent bowel movements</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>Pain or discomfort in chest area</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Unusual voice嘶哑</td>
</tr>
<tr>
<td>Neck Masses</td>
<td>Lumps or swollen areas in neck</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Low sodium levels in blood</td>
</tr>
</tbody>
</table>

**ETIOLOGY AND EPIDEMIOLOGY**

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The secretory and absorptive characteristics of epithelial cells are affected by abnormal CFTR, resulting in the clinical manifestations of CF. The altered chloride ion conductance in the sweat gland results in excessively high sweat sodium and chloride levels. This is the basis of the sweat chloride test, which is still the standard diagnostic test for this disorder. It is positive (elevated sweat chloride > 60 mEq/L) in 99% of patients with CF. Abnormal airway secretions make the airway more prone to colonization with bacteria. Defects in CFTR may also reduce the function of airway defenses and promote bacterial adherence to the airway epithelium. This all leads to chronic airway infections and eventually to bronchial damage (bronchiectasis).
Ninety percent of patients with CF are born with exocrine pancreatic insufficiency. The inspissation of mucus and subsequent destruction of the pancreatic ducts result in the inability to excrete pancreatic enzymes into the intestine. This leads to malabsorption of proteins, sugars (to a lesser extent), and especially fat. Fat malabsorption manifests clinically as steatorrhea (large foul-smelling stools), deficiencies of fat-soluble vitamins (A, D, E, and K), and failure to thrive. Protein malabsorption can present early in infancy as hypoproteinemia and peripheral edema. Approximately 10% of patients with CF are born with intestinal obstruction caused by inspissated meconium (meconium ileus). In older patients, intestinal obstruction may result from thick inspissated mucus in the intestinal lumen (distal intestinal obstruction syndrome). In adolescent or adult patients, progressive pancreatic damage can lead to enough islet cell destruction to cause insulin deficiency. This initially presents as glucose intolerance, but true diabetes that requires insulin therapy (CF-related diabetes) may develop. The failure of the sweat ducts to conserve sodium and chloride may lead to hypochloremia and hypochloremic metabolic alkalosis, especially in infants. Insipissation of mucus in the reproductive tract leads to reproductive dysfunction in both males and females. In males, congenital absence of the vas deferens and azoospermia are nearly universal. In females, secondary amenorrhea is often present as a result of chronic illness and reduced body weight. Fertility is also diminished by abnormal secretions in the fallopian tubes and cervix, but women with CF can conceive.

All infants with a positive newborn screen and/or with meconium ileus should be evaluated for CF. The diagnosis of CF should be seriously considered in any infant presenting with failure to thrive, cholestatic jaundice, chronic respiratory symptoms, or electrolyte abnormalities (hyponatremia, hypochloremia, metabolic alkalosis). CF should be in the differential diagnosis of children with chronic respiratory or gastrointestinal symptoms, especially if there is digital clubbing. Any child with nasal polyps, especially those younger than 12 years, should be evaluated for CF. All siblings of patients with CF should also be evaluated.

### Diagnostic Studies

Readily available commercial DNA tests detect many CF mutations, but because there are more than 1500 identified mutations (and others yet to be identified), DNA analysis will not detect all cases of CF. All U.S. states have newborn screening for CF, based either on elevated immunoreactive trypsinogen (IRT) levels or DNA tests, identifying the majority of infants with CF, but there are both false-positive and false-negative results. Therefore, the diagnostic test of choice is still the sweat test. Indications for performing a sweat test are listed in Table 137-2. The following criteria should be met to establish the diagnosis of CF:

- The presence of one or more typical clinical features of CF (chronic pulmonary disease, characteristic gastrointestinal and nutritional abnormalities, salt loss syndromes, or obstructive azoospermia) AND
- 1. Two elevated sweat chloride tests performed at an accredited CF Foundation certified laboratory (positive if the value is >60 mEq/L, borderline if 40 to 60 mEq/L, and negative if <40mEq/L, with adequate sweat collection)
- 2. Two mutations known to cause CF identified by DNA analysis or
- 3. A characteristic abnormality in ion transport across nasal epithelium demonstrated in vivo (nasal potential difference testing)

For those identified by positive newborn screening or because a sibling has CF, positive sweat chloride testing or the

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**Table 137-1 Complications of Cystic Fibrosis**

<table>
<thead>
<tr>
<th>RESPIRATORY COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiectasis, bronchitis, bronchiolitis, pneumonia</td>
</tr>
<tr>
<td>Atelectasis</td>
</tr>
<tr>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Nasal polyps</td>
</tr>
<tr>
<td>Sinusitis</td>
</tr>
<tr>
<td>Airway reactivity</td>
</tr>
<tr>
<td>Cor pulmonale (associated with chronic hypoxemia)</td>
</tr>
<tr>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Mucoid impaction of the bronchi</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GASTROINTESTINAL COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meconium ileus (infants)</td>
</tr>
<tr>
<td>Meconium peritonitis (infants)</td>
</tr>
<tr>
<td>Volvulus (infants)</td>
</tr>
<tr>
<td>Intestinal atresia (infants)</td>
</tr>
<tr>
<td>Distal intestinal obstruction syndrome (non-neonatal obstruction)</td>
</tr>
<tr>
<td>Rectal prolapse</td>
</tr>
<tr>
<td>Intussusception</td>
</tr>
<tr>
<td>Fibrosing colonopathy (strictures)</td>
</tr>
<tr>
<td>Appendicitis</td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Hepatic cirrhosis (portal hypertension: esophageal varices, hypersplenism)</td>
</tr>
<tr>
<td>Neonatal obstructive jaundice</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Cholelithiasis</td>
</tr>
<tr>
<td>Growth failure (malabsorption)</td>
</tr>
<tr>
<td>Fat soluble vitamin deficiency states (vitamins A, K, E, D)</td>
</tr>
<tr>
<td>Insulin deficiency, symptomatic hyperglycemia, diabetes</td>
</tr>
<tr>
<td>Malignancy (rare)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
</tr>
<tr>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Edema-hypoproteinemia (due to protein malabsorption)</td>
</tr>
<tr>
<td>Dehydration-heat exhaustion</td>
</tr>
<tr>
<td>Electrolyte disturbances (hyponatremia, hypokalemia, hypochloremia, and metabolic alkalosis)</td>
</tr>
<tr>
<td>Hypertrophic osteoarthropathy-arthritis</td>
</tr>
<tr>
<td>Digital clubbing</td>
</tr>
</tbody>
</table>

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For those identified by positive newborn screening or because a sibling has CF, positive sweat chloride testing or the
presence of known disease-causing DNA mutations are the only criteria required for diagnosis, as clinical symptoms may not be manifested early in life.

Although the sweat test is both specific and sensitive for CF, it is subject to technical problems, and there are false-positive and false-negative results (Table 137-3). Cutoff diagnostic measurements for infants less than 6 months may be lower. Other supportive tests include the measurement of bioelectrical potential differences across nasal epithelium (not widely available) and measurement of fecal elastase levels. Low fecal elastase levels indicate exocrine pancreatic insufficiency.

CF genotyping done by commercial laboratories identifies approximately 95% of patients with CF, but there are mutations that are not identified by standard testing. Not all mutations in CFTR are considered disease-causing and have uncertain prognostic consequences. Some infants identified by newborn screening with borderline sweat tests and mutations of uncertain consequence are considered to have CFTR-related metabolic syndrome (CRMS). Older children that present with atypical clinical features and borderline sweat tests may be considered non-classical CF or mild variant CF.

Identification of carriers (heterozygotes) and prenatal diagnosis of children with the ΔF508 and other common mutations is offered at most medical centers. Present testing techniques can identify more than 90% of carriers. Prenatal detection of a known CF genotype may be accomplished by amniocentesis or chorionic villus sampling.

**TREATMENT**

The treatment of CF is multifactorial, but it is primarily directed toward the gastrointestinal and pulmonary complications. Presently, there is no effective single cure for cystic fibrosis. Therapies targeted at correcting the underlying CFTR defect are under investigation. Recently, a landmark medication known as small-molecule potentiators targeted to improve function of defective CFTR has been approved for a small subset of CF patients who have an abnormal gating mechanism of their CFTR protein. Management of pulmonary complications is directed toward facilitating clearance of secretions from the airways and minimizing the effects of chronic bronchial infection. Airway secretion clearance techniques (chest physiotherapy) help remove mucus from the airways, and aerosolized DNase and 7% hypertonic saline, both delivered by nebulizer, decrease the viscosity of mucus. Antibiotic therapy is important in controlling chronic infection. Monitoring pulmonary bacterial flora via airway cultures and providing aggressive therapy with appropriate antibiotics (oral, aerosolized, and IV) help to slow the progression of lung

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**Table 137-2** Indications for Sweat Testing

<table>
<thead>
<tr>
<th>RESPIRATORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic or recurrent cough</td>
</tr>
<tr>
<td>Chronic or recurrent pneumonia</td>
</tr>
<tr>
<td>Recurrent bronchiolitis</td>
</tr>
<tr>
<td>Recurrent wheezing/difficult to control asthma</td>
</tr>
<tr>
<td>Recurrent or persistent atelectasis</td>
</tr>
<tr>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa in the respiratory tract (if not explained by other factors, e.g., tracheostomy or prolonged intubation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GASTROINTESTINAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meconium ileus</td>
</tr>
<tr>
<td>Neonatal intestinal obstruction (meconium plug, atresia)</td>
</tr>
<tr>
<td>Steatorrhea, malabsorption</td>
</tr>
<tr>
<td>Hepatic cirrhosis in childhood (including any manifestations such as esophageal varices or portal hypertension)</td>
</tr>
<tr>
<td>Cholestatic jaundice in infancy</td>
</tr>
<tr>
<td>Pancreatitus</td>
</tr>
<tr>
<td>Rectal prolapse</td>
</tr>
<tr>
<td>Fat-soluble vitamin deficiency states (A, D, E, K)</td>
</tr>
<tr>
<td>Hypoproteinemia, hypoalbuminemia, peripheral edema explained by other causes</td>
</tr>
<tr>
<td>Prolonged, direct-reacting neonatal jaundice</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MISCELLANEOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digital clubbing</td>
</tr>
<tr>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Family history of cystic fibrosis (e.g., in sibling or cousin)</td>
</tr>
<tr>
<td>Salty taste of skin (typically noted by parent on kissing affected child—from salt crystals formed after evaporation of sweat)</td>
</tr>
<tr>
<td>Hyponatremic hypochloremic alkalosis in infants</td>
</tr>
<tr>
<td>Nasal polyps</td>
</tr>
<tr>
<td>Recurrent sinusitis</td>
</tr>
<tr>
<td>Aspermia</td>
</tr>
<tr>
<td>Absent vas deferens</td>
</tr>
</tbody>
</table>

**Table 137-3** Causes of False Positive and False Negative Results on Sweat Testing

<table>
<thead>
<tr>
<th>FALSE POSITIVE</th>
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</thead>
<tbody>
<tr>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Eczema</td>
</tr>
<tr>
<td>Ectodermal dysplasia</td>
</tr>
<tr>
<td>Nephrogenic diabetes insipidus</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Fucosidosis</td>
</tr>
<tr>
<td>Mucopolysaccharidiosis</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Malnutrition</td>
</tr>
<tr>
<td>Poor technique/inadequate sweat collection</td>
</tr>
<tr>
<td>Type I glycogen storage disease</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
</tr>
<tr>
<td>Pseudohypoaldosteronism</td>
</tr>
<tr>
<td>Hyoparathyroidism</td>
</tr>
<tr>
<td>Prostaglandin Eα administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FALSE NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Poor technique/inadequate sweat collection</td>
</tr>
<tr>
<td>Atypical cystic fibrosis (unusual gene mutations—uncommon)</td>
</tr>
</tbody>
</table>

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disease. Patients often require 2- to 3-week courses of high-dose intravenous antibiotics and aggressive chest physiotherapy to treat pulmonary exacerbations. Antibiotics are selected based on organisms identified by sputum culture. If patients are unable to provide sputum, then a throat culture for CF pathogens can be used to direct therapy. Common infecting organisms are *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

**Exocrine pancreatic insufficiency** is treated with enteric-coated pancreatic enzyme capsules, which contain lipase and proteases. Patients with CF are encouraged to follow high-calorie diets, often with the addition of nutritional supplements. Even with optimal pancreatic enzyme replacement, stool losses of fat and protein may be high. Fat should not be withheld from the diet, even when significant steatorrhea exists. Rather, pancreatic enzyme doses should be titrated to optimize fat absorption, although there is a limit to the doses that should be used. Lipase dosages exceeding 2500 U/kg/meal are contraindicated because they have been associated with **fibrosing colonopathy**. Fat-soluble vitamins (A, D, E, and K) are recommended, preferably in a water-miscible form.

Newborns with **meconium ileus** may require surgical intervention, but some can be managed with contrast (Gastrografin) enemas. Intestinal obstruction in CF patients beyond the neonatal period is often due to distal intestinal obstruction syndrome (DIOS), which may need to be treated with courses of oral laxatives (polyethylene glycol) or, in more refractory cases, with balanced intestinal lavage solutions. Pancreatic enzyme dosage adjustment, adequate hydration, and dietary fiber may help prevent recurrent episodes. Patients with CF-related diabetes are treated with insulin, primarily to improve nutrition and prevent dehydration, as ketoacidosis is rare. Although transaminase elevation is common in patients with CF, only 1% to 3% of patients have progressive cirrhosis resulting in portal hypertension. Cholestasis is treated with the bile salt ursodeoxycholic acid. Portal hypertension and esophageal varices due to cirrhosis of the liver are managed, when necessary, with portal vein shunting procedures or liver transplantation. Patients with symptomatic sinus disease and nasal polyps may require sinus surgical procedures.

The management of CF is complex and is best coordinated by personnel at accredited CF centers. As with other severe chronic diseases, management of CF patients requires a multidisciplinary team working with patients and their families to maintain an optimistic, comprehensive, and aggressive approach to treatment.

**CHEST WALL AND PLEURA**

**SCOLIOSIS**

*Thoracic scoliosis*, when it is severe (curve >60°), can be associated with chest wall deformity and limitation of chest wall movement. This, in turn, can lead to decreased lung volumes (restrictive lung disease), ventilation/perfusion mismatching, hypoventilation, and even respiratory failure (see Chapter 202). Surgical correction of scoliosis may prevent further loss of lung function, but it rarely improves pulmonary function above presurgical levels.

**PECTUS EXCAVATUM AND CARINATUM**

**Pectus Excavatum**

Sternal concavity (**pectus excavatum**), a common chest wall deformity in children, is usually not associated with significant pulmonary compromise. However, occasionally, if severe, it may result in restrictive lung disease, obstructive defects, and/or decreased cardiac function. Often it comes to medical attention because of concerns over the appearance of the chest. Adolescents with pectus excavatum may complain of exercise intolerance. Routine spirometry is often normal but may show decreased vital capacity consistent with restrictive lung disease. The main reason for surgical correction is generally to improve appearance (cosmetic reasons), although in some cases surgical repair is justified to improve cardiac function and exercise tolerance.

**Pectus Carinatum**

Pectus carinatum is an abnormality of chest wall shape in which the sternum bows out. It is not associated with abnormal pulmonary function. Underlying pulmonary disease may contribute to the deformity. It can be observed after cardiac surgery performed via midsternal approach. Surgical correction of this condition is rarely indicated, but occasionally is done for cosmetic purposes.

**PNEUMOTHORAX**

**Etiology**

Pneumothorax, which is the accumulation of air in the pleural space, may result from external trauma or from leakage of air from the lungs or airways. **Spontaneous primary pneumothorax** (no underlying cause) occurs in teenagers and young adults, more commonly in tall, thin males and smokers. Factors predisposing to **secondary pneumothorax** (underlying cause identified) include barotrauma from mechanical ventilation, asthma, cystic fibrosis, trauma to the chest, and severe necrotizing pneumonia.

**Clinical Manifestations**

The most common signs and symptoms of pneumothorax are chest and shoulder pain and dyspnea. If the pneumothorax is large and compresses functional lung (**tension pneumothorax**), severe respiratory distress and cyanosis may be present. Subcutaneous emphysema may result when the air leak communicates with the mediastinum. Physical findings associated with pneumothorax include decreased breath sounds on the affected side, a tympanitic percussion note, and evidence of...
mediastinal shift (deviation of the point of maximal impact [PMI] and trachea away from the side of the pneumothorax). If the pneumothorax is small, there may be few or no clinical findings. However, the patient’s clinical condition can deteriorate rapidly if the pneumothorax expands, especially if the air in the pleural space is under pressure (tension pneumothorax). This is a life-threatening condition that can result in death if the pleural space is not decompressed by evacuation of the pleural air.

Diagnostic Studies
The presence of a pneumothorax can usually be confirmed by upright chest radiographs. Computed tomography (CT) scans of the chest are useful in quantifying the size of pneumothoraces and differentiating air within the lung parenchyma (cystic lung disease) from air in the pleural space and for identifying subpleural blebs that may be present in spontaneous recurrent pneumothoraces. In infants, transillumination of the chest wall may be of some use in making a rapid diagnosis of pneumothorax.

Treatment
The type of intervention depends on the size of the pneumothorax and the nature of the underlying disease. Small pneumothoraces (<20% of thorax occupied with pleural air) may not require intervention as they often resolve spontaneously. Inhalation of high concentrations of supplemental O₂ may enhance reabsorption of pleural air by washing out nitrogen from the blood. Larger pneumothoraces and any tension pneumothorax require immediate drainage of the air, preferably via chest tube. In an emergency situation, a simple needle aspiration may suffice, although placement of a chest tube is often required for resolution. In patients with recurrent or persistent pneumothoraces, sclerosing the pleural surfaces to obliterate the pleural space (pleurodesis) may be necessary. This can be done either chemically, by instilling talc or sclerosis agents (doxycycline) through the chest tube, or mechanically, by surgical abradement. Surgical approaches, open thoracotomy and video-assisted thoracoscopic surgery (VATS), enable visualization of the pleural space and resection of pleural blebs, when indicated.

PNEUMOMEDIASTINUM
Pneumomediastinum results from the dissection of air from the pulmonary parenchyma into the mediastinum. It is usually a mild, self-limited process that does not require aggressive intervention. The most common causes in children are severe forceful coughing and acute asthma exacerbations. Common symptoms are chest pain and dyspnea. There are often no physical findings, although a crunching noise over the sternum can sometimes be appreciated on auscultation, and subcutaneous emphysema may be detected about the neck. The diagnosis is confirmed by chest radiograph, and treatment is directed toward the underlying lung disease.

PLEURAL EFFUSION
Etiology
Fluid accumulates in the pleural space when the local hydrostatic forces that are pushing fluid out of the vascular space exceed the oncotic forces that are drawing fluid back into the vascular space. Pleural effusions can be transudates (intact membrane but abnormal hydrostatic or oncotic forces) or exudates (decreased integrity of the membrane due to inflammatory processes or impaired lymphatic drainage). There are relatively few causes of transudates, the primary ones being congestive heart failure and hypoproteinemia states, whereas the causes of exudates are legion. Almost any pulmonary inflammatory process can result in pleural fluid accumulation. Among the most common causes of exudates are infection (tuberculosis, bacterial pneumonia), collagen vascular diseases (systemic lupus erythematosus), and malignancy. Chylous pleural effusions (elevated triglyceride levels) are seen with thoracic duct injury and abnormalities of lymphatic drainage (lymphangiomyomatosis, lymphangiec-tasia). Bacterial pneumonia can lead to an accumulation of pleural fluid (parapneumonic effusion). When this fluid is purulent or infected, then it is called an empyema, although often the terms parapneumonic effusion and empyema are used interchangeably. Parapneumonic effusion/empyema is the most common effusion in children. Most parapneumonic effusions are due to pneumonia caused by Strep-tococcus pneumoniae, group A streptococci, or Staphylococcus aureus.

Clinical Manifestations
Small pleural effusions may be asymptomatic, but if they are large enough to compress lung tissue, then they can cause dyspnea, tachypnea, and occasionally chest pain. Effusions due to infection are usually associated with fever, malaise, poor appetite, pleuritic chest pain, and splinting. Physical findings include tachypnea, decreased breath sounds, dullness to percussion, and decreased tactile fremitus. Large effusions may occupy more than half the hemithorax and cause a mediastinal shift away from the affected side, compromising respiratory status, particularly in young children.

Diagnostic Studies
The presence of pleural fluid can often be confirmed by chest radiograph. In addition to anteroposterior and lateral projections, a decubitus view should be done to assess for layering of fluid. Chest ultrasonography is useful for confirming the presence of the effusion and quantifying its size. CT scans of the chest can help differentiate pleural fluid from parenchymal lesions and pleural masses. Both ultrasonography and CT scans can determine whether parapneumonic effusions contain loculations (fibrous strands that compartmentalize the effusion).

The analysis of pleural fluid is useful in differentiating a transudate from an exudate. Routine tests on pleural fluid such as cell count, pH, protein, lactate dehydrogenase, and glucose characterize the effusions. Triglyceride levels, cytology, hematocrit, gram and acid fast bacilli stain, culture, and adenosine deaminase levels can be useful in diagnosing
chylous, malignant, and tuberculous effusions (Table 138-1). However, the yield of pleural fluid cultures is low. Transudative pleural effusions have a low specific gravity (<1.015) and protein content (<2.5 g/dL), low lactate dehydrogenase activity (<200 IU/L), and a low white blood cell (WBC) count with few polymorphonuclear cells. In contrast, exudates are characterized by high specific gravity and high protein (>3 g/dL) and lactate dehydrogenase (>250 IU/L) levels. They may also have a low pH (<7.2); low glucose level (<40 mg/dL); and a high WBC count with many lymphocytes or polymorphonuclear leukocytes.

**Treatment**

Therapy is directed at the underlying condition causing the effusion and at relief of the mechanical consequences of the fluid collection. For small effusions, especially if they are transudates, no pleural drainage is required. Large effusions that are causing respiratory compromise should be drained. Transudates and most exudates other than parapneumonic effusions can be drained with a chest tube. With parapneumonic effusions/empyema, a chest tube alone is often not sufficient because the fluid may be thick and loculated. In such cases, pleural drainage is best achieved with either the administration of fibrinolytic agents via chest tubes or video-assisted thoracoscopic surgery (VATS). Both fibrinolytic therapy via chest tubes and VATS can reduce morbidity and length of hospital stay, but many patients with small to moderate-sized parapneumonic effusions can be managed conservatively with intravenous antibiotics alone.

**Suggested Reading**

CARDIOVASCULAR SYSTEM ASSESSMENT

HISTORY
A maternal history of medication, drug, or alcohol use or excessive smoking may contribute to cardiac and other systemic findings. The prenatal history may reveal a maternal infection early in pregnancy (possibly teratogenic) or later in pregnancy (causing myocarditis or myocardial dysfunction in infants). Infants with heart failure exhibit poor growth, with weight being more significantly affected than height and head circumference.

Heart failure may present with fatigue or diaphoresis with feeds or fussiness. Tachypnea without significant dyspnea may be present. Older children with heart failure may have easy fatigability, shortness of breath on exertion, and sometimes orthopnea. Not keeping up with other children during play or exercise is a sign of exercise intolerance. Heart failure may be misdiagnosed as recurrent pneumonia, bronchitis, wheezing, or asthma.

A history of a heart murmur is important, but many well children have an innocent murmur at some time in their lives. Other cardiac symptoms include cyanosis, palpitations, chest pain, syncope, and near-syncope. A review of systems assesses for possible systemic diseases or congenital malformation syndromes that may cause cardiac abnormalities (Tables 139-1 and 139-2). Current and past medication use as well as history of drug use, is important. Family history should be reviewed for hereditary diseases, early atherosclerotic heart disease, congenital heart disease, sudden unexplained deaths, thrombophilia, rheumatic fever, hypertension, and hypercholesterolemia.

PHYSICAL EXAMINATION
A complete cardiovascular examination starts in the supine position and includes evaluation in sitting and standing positions when possible. Inspection is supplemented by palpation and auscultation to provide a complete examination.

The examination starts with vital signs. The normal heart rate varies with age and activity. Newborn resting heart rates are approximately 120 beats/minute, slightly higher in infants 3 to 6 months of age and then gradually declining through adolescence to near 80 beats/minute. The range of normal for any given age is approximately 30 beats/minute above or below the average. Tachycardia may be a manifestation of anemia, dehydration, shock, heart failure, or dysrhythmia. Bradycardia can be a normal finding in patients with high vagal tone (athletes), but may be a manifestation of atrioventricular block. The respiratory rate of infants is best assessed while the infant is quiet. Respiratory rate may be increased when there is a left-to-right shunt or pulmonary venous congestion.

Normal blood pressure also varies with age. A properly sized cuff should have a bladder width that is at least 90% and a length that is 80% to 100% of the arm circumference. Initially, blood pressure in the right arm is measured. If elevated, measurements in the left arm and legs are indicated to evaluate for possible coarctation of the aorta. The pulse pressure is determined by subtracting the diastolic pressure from the systolic pressure. It is normally below 50 mm Hg or half the systolic pressure, whichever is less. A wide pulse pressure

<table>
<thead>
<tr>
<th>Table 139-1</th>
<th>Cardiac Manifestations of Systemic Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYSTEMIC DISEASE</td>
<td>CARDIOVASCULAR COMPLICATIONS</td>
</tr>
<tr>
<td>Hunter-Hurler syndrome</td>
<td>Valvular insufficiency, heart failure, hypertension</td>
</tr>
<tr>
<td>Duchenne dystrophy</td>
<td>Cardiomyopathy, heart failure</td>
</tr>
<tr>
<td>Pompe disease</td>
<td>Short PR interval, cardiomegaly, heart failure, arrhythmias</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>Coronary artery aneurysm, thrombosis, myocardial infarction, myocarditis</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>Aortic and mitral insufficiency, dissecting aortic aneurysm</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Pericarditis, Libman-Sacks endocarditis, congenital AV block</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>Arrhythmias, myocarditis, heart failure</td>
</tr>
<tr>
<td>Graves disease (hyperthyroidism)</td>
<td>Tachycardia, arrhythmias, heart failure</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Cardiac rhabdomyoma</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>Pulmonic stenosis, coarctation of aorta</td>
</tr>
</tbody>
</table>

AV, atrioventricular.
Often, specific congenital malformation syndromes are associated with cardiac defects. A few examples include VATER/L syndrome (vertebral, anal, tracheoesophageal, radial, and ear anomalies), VACTERL syndrome (vertebral, anal, cardiac, tracheoesophageal, radial, renal, limb anomalies), trisomy 18, and trisomy 21.

### Heart Sounds

**S₁** is associated with closure of the mitral and tricuspid valves, is usually single, and is best heard at the lower left sternal border (LLSB) or apex (Fig. 139-1). Although it can normally be split, if a split S₁ is heard, the possibility of an ejection click or, much less commonly, an S₂ should be considered. **S₂** is associated with closure of the aortic and pulmonary valves. It should normally split with inspiration and be single with exhalation.

Abnormalities of splitting and intensity of the pulmonary component are associated with significant anatomic and physiologic abnormalities (Table 139-3). **S₃** is heard in early diastole and is related to rapid ventricular filling. It is best heard at the LLSB or apex and may be a normal sound, but a loud S₃ is abnormal and heard in conditions with dilated ventricles. **S₄** occurs late in diastole just before S₁, is best heard at the LLSB/apex, and is associated with decreased ventricular compliance. It is rare and is always abnormal.

### Clicks

A click implies a valvular abnormality or dilated great artery. It may be ejection or midystolic in timing and may or may not be associated with a murmur. A midystolic click is associated with mitral valve prolapse. Ejection clicks occur early in systole. Pulmonary ejection clicks are best heard at the left upper sternal border and vary in intensity with respiration. Aortic clicks are often louder at the apex, left midsternal border, or right upper sternal border and do not vary with respiration.

### Murmurs

Murmur evaluation should determine timing, duration, location, intensity, radiation, and frequency or pitch of the murmur. The timing determines a murmur’s significance and can be used to develop a differential diagnosis (see Fig. 139-1).
Murmurs should be classified as systolic, diastolic, or continuous. Most murmurs are systolic and can be divided further into systolic ejection murmurs or holosystolic (also called pansystolic or regurgitant) murmurs. **Ejection murmurs** are crescendo-decrescendo with a short time between $S_1$ and the onset of the murmur (isovolumic contraction). Systolic ejection murmurs require the ejection of blood from the ventricle and may occur with aortic stenosis, pulmonary stenosis, atrial septal defects (ASDs), and coartation of the aorta. **Holosystolic murmurs** have their onset with $S_1$. The murmur has a plateau quality and may be heard with ventricular septal defects (VSDs) and mitral or tricuspid regurgitation. A **late regurgitant** murmur may be heard after a midsystolic click in mitral valve prolapse.

Murmurs are often heard along the path of blood flow. Ejection murmurs usually are best heard at the base of the heart, whereas holosystolic murmurs are louder at the LLSB and apex. Pulmonary ejection murmurs radiate to the back and axilla. Aortic ejection murmurs radiate to the neck. The **intensity** or loudness of a heart murmur is assessed as grade I through VI (Table 139-4). The **frequency** or pitch of a murmur provides information regarding the pressure gradient. The higher the pressure gradient across a narrowed area (valve, vessel, or defect), the faster the flow and higher the frequency of the murmur. Low-frequency murmurs imply low pressure gradients and mild obstruction or less restriction to flow.
Diastolic murmurs are much less common than systolic murmurs, and should be considered abnormal. Early diastolic murmurs occur when there is regurgitation through the aortic or pulmonary valve. Mid-diastolic murmurs are caused by increased flow (ASD, VSD) or anatomic stenosis across the mitral or tricuspid valves.

Continuous murmurs are heard when there is flow through the entire cardiac cycle and are abnormal with one common exception, the venous hum. A PDA is the most common abnormal continuous murmur. Continuous murmurs can also be heard with coarctation of the aorta when collateral vessels are present.

Normal physiologic or innocent murmurs are common, occurring in at least 80% of normal infants and children, heard most often during the first 6 months of life, from 3 to 6 years of age, and in early adolescence. They have also been called benign, functional, vibratory, and flow murmurs. Characteristic findings of innocent murmurs include the quality of the sound, lack of significant radiation, and significant alteration in the intensity of the murmur with positional changes (Table 139-5). Most important, the cardiovascular history and examination are otherwise normal. The presence of symptoms, including failure to thrive or dysmorphic features, should make one more cautious about diagnosing a normal murmur. Diastolic, holosystolic, late systolic, and continuous (except for the venous hum) murmurs and the presence of a thrill are not normal.

### Laboratory and Imaging Tests

#### Pulse Oximetry

Mild desaturation that is not clinically apparent may be the only early finding in complex congenital heart defects. Comparing pulse oximetry between the right arm and a lower extremity may allow diagnosis of a ductal dependent lesion in which desaturated blood flows right to left across a PDA to perfuse the lower body. This is now becoming a routine screening test in newborn infants to rule out congenital heart disease.

#### Electrocardiography

The 12-lead electrocardiogram (ECG) provides information about the rate, rhythm, depolarization, and repolarization of the cardiac cells and the size and wall thickness of the chambers. It should be assessed for rate, rhythm, axis (P wave, QRS, and T wave), intervals (PR, QRS, QTc) (Fig. 139-2), and voltages (left atrial, right atrial, left ventricular, right ventricular) adjusted for the child's age.

The P wave represents atrial depolarization. A criterion for right atrial enlargement is an increase of the amplitude of the P wave, reflected best in lead II. The diagnosis of left atrial enlargement is made by prolongation of the second portion of the P wave, exhibited best in the chest leads.

The PR interval, measured from the beginning of the P wave to the beginning of the QRS complex, increases with age. Conduction time is shortened when the conduction velocity is increased (glycogen storage disease) or when the atrioventricular node is bypassed (Wolff-Parkinson-White syndrome). A prolonged PR interval usually indicates slow conduction through the atrioventricular node. Diseases in the atrial myocardiun, bundle of His, or Purkinje system may also contribute to prolonged PR intervals.

The QRS complex represents ventricular depolarization. A greater ventricular volume or mass causes a greater magnitude of the complex. The proximity of the right ventricle to the chest surface accentuates that ventricle's contribution to the complex. Changes in the normal ECG occur with age. Normative data for each age group must be known to make a diagnosis from the ECG.

The QT interval is measured from the beginning of the QRS complex to the end of the T wave. The corrected QT interval (corrected for rate) should be less than 0.45 second (QTc = QT/√[preceding R to R interval]). The interval may be prolonged in children with hypocalcemia or severe hypokalemia. It is also prolonged in a group of children at risk for severe ventricular arrhythmias and sudden death (prolonged QT syndrome). Drugs such as quinidine and erythromycin may prolong the QT interval.

#### Chest Radiography

A systematic approach to reading a chest radiograph includes assessment of extracardiac structures, the shape and size of the heart, and the size and position of the pulmonary artery and aorta (Fig. 139-3). Assessment of the location and size of the heart and cardiac silhouette may suggest a cardiac defect. On a good inspiratory film, the cardiothoracic ratio should be

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**Table 139-5** Normal or Innocent Heart Murmurs

<table>
<thead>
<tr>
<th>MURMUR</th>
<th>TIMING/LOCATION/QUALITY</th>
<th>USUAL AGE AT DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still's murmur/ vibratory murmur</td>
<td>Systolic ejection murmur LLSB or between LLSB and apex Grades I-III/VI Vibratory, musical quality Intensity decreases in upright position</td>
<td>3–6 yr</td>
</tr>
<tr>
<td>Venous hum</td>
<td>Continuous murmur Infraclavicular region (right &gt; left) Grades I-III/VI Louder with patient in upright position Changes with compression of jugular vein or turning head</td>
<td>3–6 yr</td>
</tr>
<tr>
<td>Carotid bruit</td>
<td>Systolic ejection murmur Neck, over carotid artery Grade I-III/VI</td>
<td>Any age</td>
</tr>
<tr>
<td>Adolescent ejection murmur</td>
<td>Systolic ejection murmur LUSB Grade I-III/VI Usually softer in upright position Does not radiate to back</td>
<td>8–14 yr</td>
</tr>
<tr>
<td>Peripheral pulmonary stenosis</td>
<td>Systolic ejection murmur Axilla and back, LUSB/ RUSB Grade I-III/VI Harsh, short, high-frequency</td>
<td>Newborn to 6 mo</td>
</tr>
</tbody>
</table>

LLSB, Left lower scapular border; LUSB, left upper scapular border; RUSB, right upper scapular border.
less than 55% in infants under 1 year of age and less than 50% in older children and adolescents. An enlarged heart may be due to an increased volume load (left-right shunt) or due to myocardial dysfunction (dilated cardiomyopathy). The shape of the heart may suggest specific congenital heart defects. The most common examples are the boot-shaped heart seen with tetralogy of Fallot, the egg-on-a-string seen with dextroposed transposition of the great arteries, and the “snowman” seen with supracardiac total anomalous pulmonary venous return. The chest x-ray can aid in the assessment of pulmonary blood flow. Defects associated with left-to-right shunting have increased pulmonary blood flow (shunt vascularity) on x-ray. Right-to-left shunts have decreased pulmonary blood flow.

**Echocardiography**

Echocardiography has become the most important noninvasive tool in the diagnosis and management of cardiac disease, providing a full anatomic evaluation in most congenital heart defects (Fig. 139-4). Physiologic data on the direction of blood flow can be obtained with the use of pulsed, continuous wave, and color flow Doppler. Imaging from multiple views provides an assessment of spatial relationships. Three-dimensional (3D) and four-dimensional (4D) imaging now allows reconstruction of the heart and manipulation of the images to provide more detail, especially with regard to valve structure and function. Prenatal or fetal echocardiography can diagnose congenital heart disease by 18 weeks of gestation and allows for

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**Figure 139-2** Nomenclature of electrocardiogram (ECG) waves and intervals.

**Figure 139-3** A, Parts of the heart whose outlines can be identified on a routine chest x-ray. B, Routine posteroanterior x-ray of the normal cardiac silhouette. Ao, Aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava. (From Andreoli TE, Carpenter CCJ, Plum F, et al, editors: Cecil Essentials of Medicine, ed 2, Philadelphia, 1990, WB Saunders.)
delivery of the infant at a tertiary care hospital, improving the timeliness of therapy. Many congenital heart defects now are surgically repaired based on the echocardiogram without need for cardiac catheterization.

Transesophageal echocardiography (TEE) provides better imaging when transthoracic imaging is inadequate. It is used intraoperatively to assess results and cardiac function after surgery. TEE and intracardiac echocardiography are used to guide interventional catheterization and radiofrequency ablation of dysrhythmias.

**Cardiac Catheterization**

Cardiac catheterization is performed in patients who need additional anatomic information or precise hemodynamic information before operating or establishing a management plan. Pressures, oxygen saturations, and oxygen content are measured in each chamber and blood vessel entered (Fig. 139-5). This information is used to calculate systemic and pulmonary blood flow and resistance. Angiography is performed by injecting contrast material into selected sites to define anatomy and supplement noninvasive information. An increasing percentage of cardiac catheterizations are done to perform an intervention, including balloon dilation of stenotic valves and vessels, balloononing and stenting of stenotic lesions, closure of collateral vessels by coil embolization, and device closure of PDA, secundum ASDs, patent foramen ovales, and muscular VSDs. Catheterization with electrophysiologic studies allows for precise mapping of the electrical activity, can assess the risk of abnormal heart rhythms, and often is done in anticipation of radiofrequency ablation of the site of a dysrhythmia.

**SYNCOPE**

**ETIOLOGY**

Syncope is the transient loss of consciousness and muscle tone that, by history, does not suggest other altered states of consciousness. Presyncope or near-syncope has many or all of the prodromal symptoms without loss of consciousness. Syncope is relatively common (Table 140-1). The frequency of episodes, amount of stress, and functional impairment caused by syncope vary. Most syncopal events are relatively benign, but can represent a serious cardiac condition that may lead to death (Table 140-1). The differential diagnosis for typical syncope includes seizure, metabolic cause (hypoglycemia), hyperventilation, atypical migraine, and breath holding.

**CLINICAL MANIFESTATIONS**

Typical syncope events usually occur in the upright position or are related to changing position. Syncope may be associated with anxiety, pain, blood drawing or the sight of blood, fasting, a hot environment, or crowded places. The patient often appears pale. A prodrome, consisting of dizziness, lightheadedness, nausea, diaphoresis, visual changes (blacking out), or possibly palpitations, warns the patient and often prevents
### Chapter 141: Chest Pain

#### Table 140-1 Syncope and Dizziness: Etiology

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>History</th>
<th>Signs/Symptoms</th>
<th>Description</th>
<th>Heart Rate/Blood Pressure</th>
<th>Duration</th>
<th>Postsyncope</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocardiogenic (vasodepressor)</td>
<td>At rest</td>
<td>Pallor, nausea, visual changes</td>
<td>Brief ± convulsion</td>
<td>I/I</td>
<td>&lt;1 min</td>
<td>Residual pallor, sweaty, hot; recurs if child stands</td>
<td>Common</td>
</tr>
<tr>
<td>Other vagal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micturition</td>
<td>Postvoiding</td>
<td>Pallor, nausea</td>
<td>Brief; convulsions rare</td>
<td>I/I</td>
<td>&lt;1 min</td>
<td>Residual pallor, sweaty, hot, can recur if stands too soon</td>
<td>(+)</td>
</tr>
<tr>
<td>Hair grooming</td>
<td>Standing getting hair done or ears touched</td>
<td>Pallor, nausea, visual changes, lightheaded</td>
<td>Brief</td>
<td></td>
<td>&lt;1 min</td>
<td>Residual pallor, sweaty, hot, can recur if stands too soon</td>
<td>(+)</td>
</tr>
<tr>
<td>Cough (deglutition)</td>
<td>Paroxysmal cough</td>
<td>Cough</td>
<td>Abrupt onset</td>
<td></td>
<td>&lt;5 min</td>
<td>Fatigue or baseline</td>
<td>(+)</td>
</tr>
<tr>
<td>Cardiac syncope</td>
<td>Tight collar, turned head</td>
<td>Vague, visual changes</td>
<td>Sudden onset, pallor</td>
<td></td>
<td>&lt;5 min</td>
<td>Fatigue or baseline</td>
<td>(+)</td>
</tr>
<tr>
<td>LVOT obstruction</td>
<td>Exercise</td>
<td>± Chest pain, SOB</td>
<td>Abrupt during or after exertion, pallor</td>
<td>I/I</td>
<td>Any duration</td>
<td>Fatigue, residual pallor, and sweating</td>
<td>(+)</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>Any time, especially exercise</td>
<td>SOB</td>
<td>Cyanosis and pallor</td>
<td></td>
<td>Any duration</td>
<td>Fatigue, residual cyanosis</td>
<td>(+)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Post–viral infection exercise</td>
<td>SOB ± chest pain, palpitations</td>
<td>Pallor</td>
<td></td>
<td>Any duration</td>
<td>Fatigue</td>
<td>(+)</td>
</tr>
<tr>
<td>Tumor or mass</td>
<td>Recumbent, paroxysmal</td>
<td>SOB ± chest pain</td>
<td>Pallor</td>
<td></td>
<td>Any duration</td>
<td>Baseline</td>
<td>(+)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>Exercise</td>
<td>SOB ± chest pain</td>
<td>Pallor</td>
<td></td>
<td>Any duration</td>
<td>Fatigue, chest pain</td>
<td>(+)</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>Any time</td>
<td>Palpitations ± chest pain</td>
<td>Pallor</td>
<td>1 or I/I</td>
<td>Usually &lt;10 min</td>
<td>Fatigue or baseline</td>
<td>(+)</td>
</tr>
</tbody>
</table>


LVOT, Left ventricular outflow tract; SOB, shortness of breath; ±, with or without; (+), yes but not consistent or predictable.

Injury. Unconsciousness lasts for less than 1 minute. A return to normal consciousness occurs relatively quickly. Most of these syncopal episodes are vasovagal or neurocardiogenic in origin. The physical examination is normal.

**DIAGNOSTIC STUDIES**

Syncopal episodes may require no more than reassurance to the patient and family. If the episodes have a significant impact on daily activities, further evaluation may be indicated. An electrocardiogram (ECG) should be obtained with attention to the QTc and PR intervals (see Chapter 139). Although reassurance and increasing fluid and salt intake may be adequate to treat most cases of syncope, medical management is sometimes indicated.

**ETIOLOGY**

Chest pain in the pediatric patient often generates a significant amount of patient and parental concern. Although chest pain is rarely cardiac in origin in children, common knowledge about atherosclerotic heart disease raises concerns about a child experiencing chest pain. Most diagnosable chest pain in childhood is musculoskeletal in origin. A significant amount
remains idiopathic, however. Knowledge of the complete differential diagnosis is necessary to make an accurate assessment (Table 141-1).

**CLINICAL MANIFESTATIONS**
Assessment of a patient with chest pain includes a thorough history to determine activity at the onset; the location, radiation, quality, and duration of the pain; what makes the pain better and worse during the time that it is present; and any associated symptoms. A family history and assessment of how much anxiety the symptom is causing are important and often revealing. A careful general physical examination should focus on the chest wall, heart, lungs, and abdomen. A history of chest pain associated with exertion, syncope, or palpitations or acute onset associated with fever suggests a cardiac etiology. Cardiac causes of chest pain are generally ischemic, inflammatory, or arrhythmic in origin.

**DIAGNOSTIC STUDIES**
Tests rarely are indicated based on the history. A chest x-ray, electrocardiogram (ECG), 24-hour Holter monitoring, echocardiogram, and exercise stress testing may be obtained based on history and examination. Referral to a pediatric cardiologist is based on the history, physical examination findings, family history, and, frequently, the level of anxiety in the patient or family members regarding the pain.

<table>
<thead>
<tr>
<th>COMMON</th>
<th>Differential Diagnosis of Pediatric Chest Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td>Costochondritis</td>
</tr>
<tr>
<td></td>
<td>Trauma or muscle overuse/strain</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Asthma (often exercise-induced)</td>
</tr>
<tr>
<td></td>
<td>Severe cough</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Reflux esophagitis</td>
</tr>
<tr>
<td></td>
<td>Psychogenic</td>
</tr>
<tr>
<td></td>
<td>Anxiety, hyperventilation</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td>Precordial catch syndrome (Texidor's twinge)</td>
</tr>
<tr>
<td></td>
<td>Sickle cell vasoocclusive crisis</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UNCOMMON/RARE</th>
<th>Cardiac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemia (coronary artery abnormalities, severe AS or PS, HOCM, cocaine)</td>
<td></td>
</tr>
<tr>
<td>Infection/inflammation (myocarditis, pericarditis, Kawasaki disease)</td>
<td></td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td>Abnormalities of rib cage/thoracic spine</td>
</tr>
<tr>
<td></td>
<td>Tietze syndrome</td>
</tr>
<tr>
<td></td>
<td>Slipping rib</td>
</tr>
<tr>
<td></td>
<td>Tumor</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td>Pleurisy</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax, pneumomediastinum</td>
</tr>
<tr>
<td></td>
<td>Pleural effusion</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Esophageal foreign body</td>
</tr>
<tr>
<td></td>
<td>Esophageal spasm</td>
</tr>
<tr>
<td><strong>Psychogenic</strong></td>
<td>Conversion symptoms</td>
</tr>
<tr>
<td></td>
<td>Somatization disorders</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
</tbody>
</table>

AS, Aortic stenosis; HOCM, hypertrophic obstructive cardiomyopathy; PS, pulmonary stenosis.

**Chapter 142**

**DYSRHYTHMIAS**

**ETIOLOGY AND DIFFERENTIAL DIAGNOSIS**
Cardiac dysrhythmias or abnormal heart rhythms are uncommon in pediatrics but may be caused by infection and inflammation, structural lesions, metabolic abnormalities, and intrinsic conduction abnormalities (Table 142-1). Many pediatric dysrhythmias are normal variants that do not require treatment or even further evaluation.

**Sinus rhythm** originates in the sinus node and has a normal axis P wave (upright in leads I and AVF) preceding each QRS complex. Because normal rates vary with age, sinus bradycardia and sinus tachycardia are defined based on age. **Sinus arrhythmia** is a common finding in children and represents a normal variation in the heart rate associated with breathing. The heart rate increases with inspiration and decreases with expiration, producing a recurring pattern on the electrocardiogram (ECG) tracing. Sinus arrhythmia is normal and does not require further evaluation or treatment.
Supraventricular tachycardia (SVT) is the most common symptomatic dysrhythmia in pediatric patients. The rhythm has a rapid, regular rate with a narrow QRS complex. SVT in infants is often 280 to 300 beats/minute with slower rates for older children and adolescents. The tachycardia has an abrupt onset and termination. In a child with a structurally normal heart, most episodes are relatively asymptomatic other than a pounding heartbeat. If there is structural heart disease or the episode is prolonged (>12 hours), there may be alteration in the cardiac output and development of symptoms of heart failure. Although most patients with SVT have structurally normal hearts and normal baseline ECGs, some children have Wolff-Parkinson-White syndrome or preexcitation as the cause of the dysrhythmia.

Ventricular Dysrhythmias
Premature ventricular contractions (PVCs) are less common than premature atrial contractions in infancy but more common in older children and adolescents (Table 142-2). The premature beat is not preceded by a P wave and the QRS complex is wide and bizarre. If the heart is structurally normal, and the PVCs are singleton, uniform in focus, and disappear with increased heart rate. The PVCs are usually benign and require no treatment. Any deviation from the presentation (history of syncope or a family history of sudden death) requires further investigation and possibly treatment with antiarrhythmic medications.

Ventricular tachycardia, defined as three or more consecutive PVCs, is also relatively rare in pediatric patients. Although there are multiple causes of ventricular tachycardia, it usually is a sign of serious cardiac dysfunction or disease. Rapid-rate ventricular tachycardia results in decreased cardiac output and cardiovascular instability. Treatment in symptomatic patients is synchronized cardioversion. Medical management with lidocaine or amiodarone may be appropriate in a conscious asymptomatic patient. Complete evaluation of the etiologic picture is necessary, including electrophysiologic study.

Heart Block
First-degree heart block is the presence of a prolonged PR interval. It is asymptomatic and, when present in otherwise normal children, requires no evaluation or treatment. Second-degree heart block is when some, but not all, of the P waves are followed by a QRS complex. Mobitz type I (also known as Wenckebach) is characterized by a progressive prolongation of the PR interval until a QRS complex is dropped. This form may progress to complete heart block. Mobitz type II is present when the PR interval does not change, but a QRS is intermittently dropped. This form may progress to complete heart block and may require pacemaker placement. Third-degree heart block, whether congenital or acquired, is present when there is no relationship between atrial and ventricular activity. The ventricular rate is much slower than the atrial rate. Congenital complete heart block is associated with maternal collagen vascular disease (such as systemic lupus erythematosus or Sjögren syndrome) or congenital heart disease. The acquired form most often occurs after cardiac surgery but may be secondary to infection, inflammation, or drugs.
TREATMENT

Most atrial dysrhythmias require no intervention. Treatment of SVT depends on presentation and symptoms. Acute treatment of SVT in infants usually consists of vagal maneuvers, such as application of cold (ice bag) to the face. Intravenous (IV) adenosine usually converts the dysrhythmia because the atrioventricular node forms a part of the reentry circuit in most patients with SVT. In patients with cardiovascular compromise at the time of presentation, synchronized cardioversion is indicated using 1 to 2 J/kg. In patients with palpitations, it is important to document heart rate and rhythm during their symptoms before considering therapeutic options. The frequency, length, and associated symptoms during the episodes, as well as what is required to convert the rhythm, determine the need for treatment. Some patients require only education regarding the dysrhythmia and follow-up. Ongoing pharmacologic management with either digoxin or a β-blocker is usually the first choice. However, digoxin is contraindicated in patients with Wolff-Parkinson-White syndrome. Additional antiarrhythmic medications are rarely needed. In patients who are symptomatic or those not wanting to take daily medications, radiofrequency ablation may be performed.

A variety of antiarrhythmic agents are used to treat ventricular dysrhythmias that require intervention (Table 142-3). Management of third-degree heart block depends on the ventricular rate and presence of symptoms. Treatment, if needed, often requires placement of a pacemaker.
Chapter 143  Acyanotic Congenital Heart Disease

ACYANOTIC CONGENITAL HEART DISEASE

ETIOLOGY AND EPIDEMIOLOGY
Congenital heart disease occurs in 8 per 1000 births. The spectrum of lesions ranges from asymptomatic to fatal. Although most cases of congenital heart disease are multifactorial, some lesions are associated with chromosomal disorders, single gene defects, teratogens, or maternal metabolic disease (see Table 139-2).

Congenital heart defects can be divided into three pathophysiologic groups (Table 143-1).
1. Left-to-right shunts
2. Right-to-left shunts
3. Obstructive, stenotic lesions

Acyanotic congenital heart disease includes left-to-right shunts resulting in an increase in pulmonary blood flow (patent ductus arteriosus [PDA], ventricular septal defect [VSD], atrial septal defect [ASD]) and obstructive lesions (aortic stenosis, pulmonary stenosis, coarctation of the aorta), which usually have normal pulmonary blood flow.

VENTRICULAR SEPTAL DEFECT

Etiology and Epidemiology
The ventricular septum is a complex structure that can be divided into four components. The largest component is the muscular septum. The inlet or posterior septum comprises endocardial cushion tissue. The subarterial or supracristal septum comprises conotruncal tissue. The membranous septum is below the aortic valve and is relatively small. VSDs occur when any of these components fails to develop normally (Fig. 143-1). VSD, the most common congenital heart defect, accounts for 25% of all congenital heart disease. Perimembranous VSDs are the most common of all VSDs (67%).

Although the location of the VSD is important prognostically and in approach to repair, the amount of flow crossing a VSD depends on the size of the defect and the pulmonary vascular resistance. Large VSDs are not symptomatic at birth because the pulmonary vascular resistance is normally elevated at this time. As the pulmonary vascular resistance decreases over the first 6 to 8 weeks of life, the amount of shunt increases, and symptoms may develop.

Clinical Manifestations
Small VSDs with little shunt are often asymptomatic but have a loud murmur. Moderate to large VSDs result in pulmonary overcirculation and heart failure. The typical physical finding with a VSD is a pansystolic murmur, usually heard best at the lower left sternal border. There may be a thrill. Large shunts increase flow across the mitral valve causing a mid-diastolic murmur at the apex. The splitting of S2 and intensity of P2 depend on the pulmonary artery pressure.

Imaging Studies
Electrocardiogram (ECG) and chest x-ray findings depend on the size of the VSD. Small VSDs usually have normal studies. Larger VSDs cause volume overload to the left side of the heart, resulting in ECG findings of left atrial and ventricular enlargement and hypertrophy. A chest x-ray may reveal cardiomegaly, enlargement of the left ventricle, an increase in the pulmonary artery silhouette, and increased pulmonary blood flow. Pulmonary hypertension due to either increased flow or increased pulmonary vascular resistance may lead to right ventricular enlargement and hypertrophy.

Treatment
Approximately one third of all VSDs close spontaneously. Small VSDs usually close spontaneously and, if they do not

Table 143-1  Classification of Congenital Cardiac Defects

<table>
<thead>
<tr>
<th>SHUNTING</th>
<th>STENOTIC</th>
<th>RIGHT → LEFT</th>
<th>LEFT → RIGHT</th>
<th>MIXING</th>
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<tr>
<td>Aortic stenosis</td>
<td>Tetralogy</td>
<td>Patent ductus arteriosus</td>
<td>Truncus</td>
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</tr>
<tr>
<td>Pulmonary stenosis</td>
<td>Transposition</td>
<td>Ventricular septal defect</td>
<td>TAPVR</td>
<td></td>
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<tr>
<td>Coarctation of the aorta</td>
<td>Tricuspid atresia</td>
<td>Atrial septal defect</td>
<td>HLH</td>
<td></td>
</tr>
</tbody>
</table>

HLH, Hypoplastic left heart syndrome; TAPVR, total anomalous pulmonary venous return.

Figure 143-1  Ventricular septal defect. AO, Aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.
close, surgical closure may not be required. Initial treatment for moderate to large VSDs includes diuretics (± digoxin) and afterload reduction. Continued poor growth or pulmonary hypertension despite therapy requires closure of the defect. Most VSDs are closed surgically, but some VSDs, especially muscular defects, can be closed with devices placed at cardiac catheterization.

**ATRIAL SEPTAL DEFECT**

**Etiology and Epidemiology**

During the embryologic development of the heart, a septum grows toward the endocardial cushions to divide the atria. Failure of septal growth or excessive reabsorption of tissue leads to ASDs (Fig. 143-2). ASDs represent approximately 10% of all congenital heart defects. A secundum defect, with the hole in the region of the foramen ovale, is the most common ASD. A primum ASD, located near the endocardial cushions, may be part of a complete atrioventricular canal defect or may be present with an intact ventricular septum. The least common ASD is the sinus venosus defect, which may be associated with anomalous pulmonary venous return.

**Clinical Manifestations**

The pathophysiology and amount of shunting depend on the size of the defect and the relative compliance of the both ventricles. Even with large ASDs and significant shunts, infants and children are rarely symptomatic. A prominent right ventricular impulse at the left lower sternal border (LLSB) often can be palpated. A soft (grade I or II) systolic ejection murmur in the region of the right ventricular outflow tract and a fixed split S₂ (due to overload of the right ventricle with prolonged ejection into the pulmonary circuit) are often audible. A larger shunt may result in a mid-diastolic murmur at the LLSB as a result of the increased volume passing across the tricuspid valve.

**Imaging Studies**

ECG and chest x-ray findings reflect the increased blood flow through the right atrium, right ventricle, pulmonary arteries, and lungs. The ECG may show right axis deviation and right ventricular enlargement. A chest radiograph may show cardiomegaly, right atrial enlargement, and a prominent pulmonary artery.

**Treatment**

Medical management is rarely indicated. If a significant shunt is still present at around 3 years of age, closure is usually recommended. Many secundum ASDs can be closed with an ASD closure device in the catheterization laboratory. Primum and sinus venosus defects require surgical closure.

**PATENT DUCTUS ARTERIOSUS**

**Etiology and Epidemiology**

The ductus arteriosus allows blood to flow from the pulmonary artery to the aorta during fetal life. Failure of the normal closure of this vessel results in a PDA (Fig. 143-3). With a falling pulmonary vascular resistance after birth, left-to-right shunting of blood and increased pulmonary blood flow occur. Excluding premature infants, PDAs represent approximately 5% to 10% of congenital heart disease.

**Clinical Manifestations**

Symptoms depend on the amount of pulmonary blood flow. The magnitude of the shunt depends on the size of the PDA (diameter, length, and tortuosity) and the pulmonary vascular resistance. Small PDAs are asymptomatic; moderate to large shunts can produce the symptoms of heart failure as the pulmonary vascular resistance decreases.

The physical examination findings depend on the size of the shunt. A widened pulse pressure is often present as a result of the runoff of blood into the pulmonary circulation during diastole. A continuous, machine-like murmur can be heard at the left infraclavicular area, radiating along the pulmonary arteries and often well heard over the left side of the back. Larger shunts with increased flow across the mitral valve may
atrial ventricular canal defects. AO, Aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

result in a mid-diastolic murmur at the apex and a hyperdynamic precordium. Splitting of S2 and intensity of P2 depend on the pulmonary artery pressure. A thrill may be palpable.

Imaging Studies
ECG and chest x-ray findings are normal with small PDAs. Moderate to large shunts may result in a full pulmonary artery silhouette and increased pulmonary vascularity. ECG findings vary from normal to evidence of left ventricular hypertrophy. If pulmonary hypertension is present, there is also right ventricular hypertrophy.

Treatment
Spontaneous closure of a PDA after a few weeks of age is uncommon in full-term infants. Moderate and large PDAs may be managed initially with diuretics, but eventually require closure. Elective closure of small, hemodynamically insignificant PDAs is controversial. Most PDAs can be closed in the catheterization laboratory by either coil embolization or a PDA closure device.

ENDOCARDIAL CUSHION DEFECT
Etiology and Epidemiology
Endocardial cushion defects, also referred to as atrioventricular canal defects, may be complete or partial (Fig. 143-4). Failure of the septum to fuse with the endocardial cushion results in abnormal atrioventricular valves as well. The complete defect results in a primum ASD, a posterior or inlet VSD, and clefts in the anterior leaflet of the mitral and septal leaflet of the tricuspid valves. In addition to left-to-right shunting at both levels, there may be atrioventricular valve insufficiency.

Clinical Manifestations
The symptoms of heart failure usually develop as the pulmonary vascular resistance decreases over the first 6 to 8 weeks of life. Symptoms may be earlier and more severe with significant atrioventricular valve insufficiency. Pulmonary hypertension resulting from increased pulmonary circulation often develops early. The presence of murmurs varies depending on the amount of shunting at both atrial and ventricular levels. If there is a large VSD component, S2 will be single. Growth is usually poor. Complete endocardial cushion defects are most commonly seen in children with Down syndrome.

Imaging Tests
The diagnosis usually is made with echocardiography. A chest radiograph reveals cardiomegaly with enlargement of all chambers and the presence of increased vascularity. An ECG reveals left axis deviation and combined ventricular hypertrophy and may show combined atrial enlargement.

Treatment
Initial management includes diuretics (± digoxin) and after-load reduction for treatment of heart failure. Surgical repair of the defect ultimately is required.

PULMONARY STENOSIS
Etiology
Pulmonary stenosis accounts for approximately 10% of all congenital heart disease and can be valvular, subvalvular, or supravalvular in nature. Pulmonary stenosis results from the failure of the development, in early gestation, of the three leaflets of the valve, insufficient resorption of infundibular tissue, or insufficient canalization of the peripheral pulmonary arteries.

Clinical Manifestations
Symptoms depend on the degree of obstruction present. Mild pulmonary stenosis is asymptomatic. Moderate to severe stenosis results in exertional dyspnea and easy fatigability. Newborns with severe stenosis may be more symptomatic and even cyanotic because of right-to-left shunting at the atrial level.

Pulmonary stenosis causes a systolic ejection murmur at the second left intercostal space which radiates to the back. A thrill may be present. S2 may be widely split with a quiet pulmonary component. With more severe pulmonary stenosis, an impulse at the lower left sternal border results from right ventricular hypertrophy. Valvular stenosis may result in a click that varies with respiration. Worsening stenosis causes an increase in the duration of the murmur and a higher frequency of the sound. The systolic ejection murmurs of peripheral pulmonary stenosis are heard distal to the site of obstruction in the pulmonary circulation, including radiation to the back.

Imaging Tests
ECG and chest x-ray findings are normal in mild stenosis. Moderate to severe stenosis results in right axis deviation and right ventricular hypertrophy. The heart size is usually normal on chest x-ray, although dilation of the main pulmonary artery may be seen. Echocardiography provides assessment of the site of stenosis, degree of hypertrophy, and valve morphology, as well as an estimate of the pressure gradient.
Treatment
Valvular pulmonary stenosis usually does not progress, especially if it is mild. Balloon valvuloplasty is usually successful in reducing the gradient to acceptable levels for more significant or symptomatic stenosis. Surgical repair is required if balloon valvuloplasty is unsuccessful or when subvalvular (muscular) stenosis is present.

Aortic Stenosis
Etiology and Epidemiology
Valvular, subvalvular, or supravalvular aortic stenosis represents approximately 5% of all congenital heart disease. Lesions result from failure of development of the three leaflets or failure of resorption of tissue around the valve.

Clinical Manifestations
Mild to moderate obstructions cause no symptoms. More severe stenosis results in easy fatigability, exertional chest pain, and syncope. Infants with critical aortic stenosis may present with symptoms of heart failure.

A systolic ejection murmur is heard at the right second intercostal space along the sternum and radiating into the neck. The murmur increases in length and becomes higher in frequency as the degree of stenosis increases. With valvular stenosis, a systolic ejection click often is heard, and a thrill may be present at the right upper sternal border or in the suprasternal notch. The aortic component of S2 may be decreased in intensity.

Imaging Studies
ECG and chest x-ray findings are normal with mild degrees of stenosis. Left ventricular hypertrophy develops with moderate to severe stenosis and is detected on the ECG and chest x-ray. Dilation of the ascending aorta or aortic knob due to an intrinsic aortopathy may be seen on chest radiographs. Echocardiography shows the site of stenosis, valve morphology, and the presence of left ventricular hypertrophy, and it allows an estimate of the pressure gradient.

Treatment
The degree of aortic stenosis frequently progresses with growth and age. Aortic insufficiency often develops or progresses. Serial follow-up with echocardiography is indicated. Balloon valvuloplasty is usually the first interventional procedure for significant stenosis. It is not as successful as pulmonary balloon valvuloplasty and has a higher risk of significant valvular insufficiency. Surgical management is necessary when balloon valvuloplasty is unsuccessful or significant valve insufficiency develops.

Coarctation of the Aorta
Etiology and Epidemiology
Coarctation of the aorta occurs in approximately 10% of all congenital heart defects. It is almost always juxaductal in position. During development of the aortic arch, the area near the insertion of the ductus arteriosus fails to develop correctly, resulting in a narrowing of the aortic lumen.

Clinical Manifestations
Timing of presentation depends on the severity of obstruction and associated cardiac defects. Infants presenting with coarctation of the aorta frequently have hypoplastic aortic arches, abnormal aortic valves, and VSDs. They may be dependent on a patent ductus arteriosus to provide descending aortic flow. Symptoms develop when the aortic ampulla of the ductus closes. Less severe obstruction causes no symptoms.

Symptoms, including poor feeding, respiratory distress, and shock, may develop before 2 weeks of age. Classically the femoral pulses are weaker and delayed compared with the right radial pulse. The blood pressure in the lower extremities is lower than that in the upper extremities. If cardiac function is poor, however, these differences may not be as apparent until appropriate resuscitation is accomplished. In this situation, there may be no murmur, but an S3 is often present.

Older children presenting with coarctation of the aorta are usually asymptomatic. There may be a history of leg discomfort with exercise, headache, or epistaxis. Decreased or absent lower extremity pulses, hypertension (upper extremity), or a murmur may be present. The murmur is typically best heard in the left interscapular area of the back. If significant collaterals have developed, continuous murmurs may be heard throughout the chest. An abnormal aortic valve is present approximately 50% of the time, causing a systolic ejection click and systolic ejection murmur of aortic stenosis.

Imaging Studies
The ECG and chest x-ray show evidence of right ventricular enlargement and hypertrophy in infantile coarctation with marked cardiomegaly and pulmonary edema. Echocardiography shows the site of coarctation and associated lesions. In older children, the ECG and chest x-ray usually show left ventricular hypertrophy and a mildly enlarged heart. Rib notching may also be seen in older children (>8 years of age) with large collaterals. Echocardiography shows the site and degree of coarctation, presence of left ventricular hypertrophy, and aortic valve morphology and function.

Treatment
Management of an infant presenting with cardiac decompression includes intravenous infusion of prostaglandin E1 (chemically opens the ductus arteriosus), inotropic agents, diuretics, and other supportive care. Balloon angioplasty has been done, especially in critically ill infants, but surgical repair of the coarctation is most commonly performed. Ballooning and stenting of older patients with coarctation has become more accepted as primary therapy, but surgical repair remains a common form of management.
Cyanotic congenital heart disease occurs when some of the systemic venous return crosses from the right side of the heart to the left and returns to the body without going through the lungs (right-to-left shunt). Cyanosis, the visible sign of this shunt, occurs when approximately 5 g/100 mL of reduced hemoglobin is present in systemic blood. Thus, a polycythemic patient appears cyanotic with a lower percentage of reduced hemoglobin. A patient with anemia requires a higher percentage of reduced hemoglobin for the recognition of cyanosis.

The most common cyanotic congenital heart defects are the five Ts:
- Tetralogy of Fallot
- Transposition of the great arteries
- Tricuspid atresia
- Truncus arteriosus
- Total anomalous pulmonary venous return

Other congenital heart defects that allow complete mixing of systemic and pulmonary venous return can present with cyanosis depending on the amount of pulmonary blood flow that is present. Many cyanotic heart lesions present in the neonatal period (Table 144-1).

**TETRALOGY OF FALLOT**

**Etiology and Epidemiology**
Tetralogy of Fallot is the most common cyanotic congenital heart defect, representing about 10% of all congenital heart defects (Fig. 144-1). There are four structural defects: ventricular septal defect (VSD), pulmonary stenosis, overriding aorta, and right ventricular hypertrophy. Tetralogy of Fallot is due to abnormal septation of the truncus arteriosus into the aorta and pulmonary artery that occurs early in gestation (3 to 4 weeks). The VSD is large and the pulmonary stenosis is most commonly subvalvular or infundibular. It may also be valvular, supravalvular, or, frequently, a combination of levels of obstruction.

**Clinical Manifestations**
Infants initially may be acyanotic. A pulmonary stenosis murmur is the usual initial abnormal finding. The amount of right-to-left shunting at the VSD (and the degree of cyanosis) increases as the degree of pulmonary stenosis increases. With increasing severity of pulmonary stenosis, the murmur becomes shorter and softer. In addition to varying degrees of cyanosis and a murmur, a single S₂ and right ventricular impulse at the left sternal border are typical findings.

When hypoxic (Tet) spells occur, they are usually progressive. During a spell, the child typically becomes restless and agitated and may cry inconsolably. An ambulatory toddler may

<table>
<thead>
<tr>
<th>Table 144-1</th>
<th>Categories of Presenting Symptoms and Signs in the Neonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPTOM/SIGN</td>
<td>PHYSIOLOGIC CATEGORY</td>
</tr>
<tr>
<td>Cyanosis with respiratory distress</td>
<td>Increased pulmonary blood flow</td>
</tr>
<tr>
<td>Cyanosis without respiratory distress</td>
<td>Decreased pulmonary blood flow</td>
</tr>
<tr>
<td>Hypoperfusion</td>
<td>Poor cardiac output</td>
</tr>
<tr>
<td>Respiratory distress with desaturation (not visible cyanosis)</td>
<td>Bidirectional shunting</td>
</tr>
<tr>
<td>Respiratory distress with normal saturation</td>
<td>Left-to-right shunting</td>
</tr>
</tbody>
</table>

ASD, Atrial septal defect; AV, atrioventricular; AVM, arteriovenous malformation; PDA, patent ductus arteriosus; VSD, ventricular septal defect.
Hyperpnea occurs with gradually increasing cyanosis and loss of the murmur. In severe spells, prolonged unconsciousness and convulsions, hemiparesis, or death may occur. Independent of hypoxic spells, patients with unrepaired tetralogy of Fallot are at increased risk for cerebral thromboembolism and cerebral abscesses resulting, in part, from their right-to-left intracardiac shunt.

**Imaging Studies**

The electrocardiogram (ECG) usually has **right axis deviation** and **right ventricular hypertrophy**. The classic chest x-ray finding is a **boot-shaped heart** created by the small main pulmonary artery and upturned apex secondary to right ventricular hypertrophy. Echocardiography shows the anatomic features, including the anatomic level and quantification of pulmonary stenosis. Coronary anomalies, most commonly a left anterior descending coronary artery arising from the right coronary artery and crossing the anterior surface of the right ventricular outflow tract, are present in 5% of patients with tetralogy of Fallot.

**Treatment**

The natural history of tetralogy of Fallot is progression of pulmonary stenosis and cyanosis. Treatment of hypoxic spells consists of oxygen administration and placing the child in the knee-chest position (to increase venous return). Traditionally, morphine sulfate is given (to relax the pulmonary infundibulum and for sedation). If necessary, the systemic vascular resistance can be increased acutely through the administration of an α-adrenergic agonist (phenylephrine). The occurrence of a cyanotic spell is an indication to proceed with surgical repair.

Complete surgical repair with VSD closure and removal or patching of the pulmonary stenosis can be performed in infancy. Occasionally, **palliative shunt surgery** between the subclavian artery and pulmonary artery is performed for complex forms of tetralogy of Fallot and more complete repair is done at a later time. **Subacute bacterial endocarditis prophylaxis** is indicated until 6 months after complete repair unless there is a residual VSD. Prophylaxis is then continued as long as there is a residual VSD.

**Clinical Manifestations**

A history of cyanosis is always present, although it depends on the amount of mixing. **Quiet tachypnea** and a **single S₂** are typically present. If the ventricular septum is intact, there may be no murmur.

Children with transposition and a large VSD have improved intracardiac mixing and less cyanosis. They may present with signs of heart failure. The heart is hyperdynamic, with palpable left and right ventricular impulses. A loud VSD murmur is heard. S₂ is single.

**Imaging Studies**

ECG findings typically include **right axis deviation** and **right ventricular hypertrophy**. The chest x-ray reveals **increased pulmonary vascularity**, and the cardiac shadow is classically an **egg on a string** created by the narrow superior mediastinum. Echocardiography shows the transposition of the great arteries, the sites and amount of mixing, and any associated lesions.
Treatment
Initial medical management includes prostaglandin E1 to maintain ductal patency. If significant hypoxia persists on prostaglandin therapy, a balloon atrial septostomy improves mixing between the two circulations. Complete surgical repair is most often an arterial switch. The arterial switch usually is performed within the first 2 weeks of life, when the left ventricle can still maintain systemic pressure.

TRICUSPID ATRESIA
Etiology and Epidemiology
Tricuspid atresia accounts for approximately 2% of all congenital heart defects (Fig. 144-3). The absence of the tricuspid valve results in a hypoplastic right ventricle. All systemic venous return must cross the atrial septum into the left atrium. A PDA or VSD is necessary for pulmonary blood flow and survival. 

Clinical Manifestations
Infants with tricuspid atresia are usually severely cyanotic and have a single S2. If a VSD is present, there may be a murmur. A diastolic murmur across the mitral valve may be audible. Frequently there is no significant murmur.

Imaging Studies
The ECG shows left ventricular hypertrophy and a superior QRS axis (between 0° and –90°). The chest x-ray reveals a normal or mildly enlarged cardiac silhouette with decreased pulmonary blood flow. Echocardiography shows the anatomy, associated lesions, and source of pulmonary blood flow.

TRUNCUS ARTERIOSUS
Etiology and Epidemiology
Truncus arteriosus occurs in less than 1% of all cases of congenital heart disease (Fig. 144-4). It results from the failure of septation of the truncus during the first 3 to 4 weeks of gestation. A single arterial trunk arises from the heart with a large VSD immediately below the truncal valve. The pulmonary arteries arise from the single arterial trunk either as a single vessel that divides or individually from the arterial trunk to the lungs.

Clinical Manifestations
Varying degrees of cyanosis depend on the amount of pulmonary blood flow. If not diagnosed at birth, the infant may develop signs of heart failure as pulmonary vascular resistance decreases. The signs then include tachypnea and cough. Peripheral pulses are usually bounding as a result of the diastolic runoff into the pulmonary arteries. A single S2 is due to the single valve. There may be a systolic ejection click, and there is often a systolic murmur at the left sternal border.

Imaging Studies
ECG findings include combined ventricular hypertrophy and cardiomegaly. A chest x-ray usually reveals increased pulmonary blood and may show displaced pulmonary arteries. Echocardiography defines the anatomy, including the VSD, truncal valve function, and origin of the pulmonary arteries.
Treatment
Medical management is usually needed and includes anticon­
gestive medications. Surgical repair includes VSD closure and placement of a conduit between the right ventricle and pulmonary arteries.

TOTAL ANOMALOUS PULMONARY VENOUS RETURN
Etiology and Epidemiology
Total anomalous pulmonary venous return accounts for about 1% of congenital heart disease (Fig. 144-5). Disruption of the development of normal pulmonary venous drainage during the third week of gestation results in one of four abnormalities. All of the pulmonary veins fail to connect to the left atrium and return abnormally via the right side of the heart. They may have supracardiac, infracardiac, cardiac, or mixed drainage. An atrial-level communication is required for systemic cardiac output and survival.

Clinical Manifestations
The most important determinant of presentation is the presence or absence of obstruction to the pulmonary venous drainage. Infants without obstruction have minimal cyanosis and may be asymptomatic. There is a hyperactive right ventricular impulse with a widely split S2 (owing to increased right ventricular volume) and a systolic ejection murmur at the left upper sternal border. There is usually a mid-diastolic murmur at the lower left sternal border from the increased flow across the tricuspid valve. Growth is relatively poor. Infants with obstruction present with cyanosis, marked tachypnea and dyspnea, and signs of right-sided heart failure including hepatomegaly. The obstruction results in little, if any, increase in right ventricular volume, so there may be no murmur or changes in S2.

Imaging Studies
For infants without obstruction, the ECG is consistent with right ventricular volume overload. Cardiomegaly with increased pulmonary blood flow is seen on chest x-ray. Infants with obstructed veins have right axis deviation and right ventricular hypertrophy on ECG. On chest x-ray, the heart is normal or mildly enlarged with varying degrees of pulmonary edema that can appear similar to hyaline membrane disease or pneumonia. Echocardiography shows the volume-overloaded right side of the heart, right-to-left atrial level shunting, and common pulmonary vein site of drainage and degree of obstruction.

HYPOPLASTIC LEFT HEART SYNDROME
Etiology and Epidemiology
Hypoplastic left heart syndrome accounts for 1% of all congenital heart defects (Fig. 144-6) but is the most common cause of death from cardiac defects in the first month of life. Hypoplastic left heart syndrome occurs when there is failure of development of the mitral or aortic valve or the aortic arch. A small left ventricle that is unable to support normal systemic circulation is a central finding, regardless of etiology. Associated degrees of hypoplasia of the ascending aorta and aortic arch are present. Left-to-right shunting occurs at the atrial level.

Clinical Manifestations
The newborn is dependent on right-to-left shunting at the ductus arteriosus for systemic blood flow. As the ductus arteriosus constricts, the infant becomes critically ill with signs and symptoms of heart failure from excessive pulmonary blood flow and obstruction of systemic blood flow. Pulses are diffusely weak or absent. S2 is single and loud. There is usually no heart murmur. Cyanosis may be minimal, but low cardiac output gives a grayish color to the cool, mottled skin.
Imaging Studies
ECG findings include right ventricular hypertrophy with decreased left ventricular forces. The chest x-ray reveals cardiomegaly (with right-sided enlargement) and pulmonary venous congestion or pulmonary edema. Echocardiography shows the small left side of the heart, the degree of stenosis of the aortic and mitral valves, the hypoplastic ascending aorta, and the adequacy of left-to-right atrial flow and right-to-left ductal flow.

Treatment
Medical management includes prostaglandin E₁ to open the ductus arteriosus, correction of acidosis, and ventilatory and blood pressure support as needed. Surgical repair is staged with the first surgery (Norwood procedure) done in the newborn period. Subsequent procedures create a systemic source for the pulmonary circulation (bidirectional Glenn and Fontan procedures), leaving the right ventricle to supply systemic circulation. There have been many modifications to all three stages of the repair. Prognosis for survival has improved significantly over the past two decades.

COMPLICATIONS OF CONGENITAL HEART DISEASE
Extracardiac complications are summarized in Table 144-2.
because the cardiac output equals stroke volume times the heart rate. Additional factors also affect cardiac performance (Table 145-1).

Heart failure occurs when the heart is unable to pump blood at a rate commensurate with metabolic needs (oxygen delivery). It may be due to a change in myocardial contractility that results in low cardiac output or to abnormal loading conditions being placed on the myocardium. The abnormal loading conditions may be afterload (pressure overload, such as with aortic stenosis, pulmonary stenosis, or coarctation of the aorta) or preload (volume overload, such as in ventricular septal defect (VSD), patent ductus arteriosus (PDA), or valvular insufficiency. Volume overload is the most common cause of heart failure in children.

The age of presentation is helpful in creating the differential diagnosis (Table 145-2). In the first weeks of life, excessive afterload being placed on the myocardium is most common. Heart failure presenting around 2 months of age is usually due to increasing left-to-right shunts that become apparent as the pulmonary vascular resistance decreases. Acquired heart disease, such as myocarditis and cardiomyopathy, can present at any age.

### Table 145-1: Factors Affecting Cardiac Performance

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRELOAD</strong> (LEFT VENTRICULAR DIASTOLIC VOLUME)</td>
<td>Total blood volume, Venous tone (sympathetic tone), Body position, Intrathoracic and intrapericardial pressure, Atrial contraction, Pumping action of skeletal muscle</td>
</tr>
<tr>
<td><strong>AFTERLOAD</strong> (IMPEDEANCE AGAINST WHICH THE LEFT VENTRICLE MUST EJECT BLOOD)</td>
<td>Peripheral vascular resistance, Left ventricular volume (preload, wall tension), Physical characteristics of the arterial tree (elasticity of vessels or presence of outflow obstruction)</td>
</tr>
<tr>
<td><strong>CONTRACTILITY</strong> (CARDIAC PERFORMANCE INDEPENDENT OF PRELOAD OR AFTERLOAD)</td>
<td>Sympathetic nerve impulses*, Circulating catecholamines*, Digitalis, calcium, other inotropic agents*, Increased heart rate or postextrasystolic augmentation*, Anoxia, acidosis†, Pharmacologic depression†, Loss of myocardium†, Intrinsic depression†</td>
</tr>
<tr>
<td><strong>HEART RATE</strong></td>
<td>Autonomic nervous system, Temperature, metabolic rate</td>
</tr>
</tbody>
</table>

### Table 145-2: Etiology of Heart Failure by Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FETUS</strong></td>
<td>Severe anemia (hemolysis, fetal-maternal transfusion, hypoplastic anemia)</td>
</tr>
<tr>
<td><strong>PREMATURE NEONATE</strong></td>
<td>Fluid overload, PDA, VSD, Cor pulmonale (BPD)</td>
</tr>
<tr>
<td><strong>FULL-TERM NEONATE</strong></td>
<td>Asphyxial cardiomyopathy, Arteriovenous malformation (vein of Galen, hepatic)</td>
</tr>
<tr>
<td><strong>INFANT/TODDLER</strong></td>
<td>Left-to-right cardiac shunts (VSD), Hemangioma (arteriovenous malformation), Anomalous left coronary artery, Metabolic cardiomyopathy, Acute hypertension (hemolytic uremic syndrome), Supraventricular tachycardia, Kawasaki disease, Postoperative repair of congenital heart disease</td>
</tr>
<tr>
<td><strong>CHILD/ADOLESCENT</strong></td>
<td>Rheumatic fever, Acute hypertension (glomerulonephritis), Viral myocarditis, Thyrotoxicosis, Hemochromatosis/hemosiderosis, Cancer therapy (radiation, doxorubicin), Sickle cell anemia, Endocarditis, Cor pulmonale (cystic fibrosis), Arrhythmias, Chronic upper airway obstruction (cor pulmonale), Unrepaired or palliated congenital heart disease, Cardiomyopathy</td>
</tr>
</tbody>
</table>

*B: Increases contractility.  
†: Decreases contractility.
Heart failure presents in infants as poor feeding, failure to thrive, tachypnea, and diaphoresis with feeding. Older children may present with shortness of breath, easy fatigability, and edema. The physical examination findings depend on whether pulmonary venous congestion, systemic venous congestion, or both are present. Tachycardia, a gallop rhythm, and thready pulses may be present with either cause. If left-sided failure is predominant, tachypnea, orthopnea, wheezing, and pulmonary edema are seen. Hepatomegaly, edema, and distended neck veins are signs of right-sided failure.

**IMAGING STUDIES**
The absence of cardiomegaly on a chest x-ray usually rules out the diagnosis of heart failure. An echocardiogram assesses the heart chamber sizes, measures myocardial function, and diagnoses congenital heart defects when present.

**TREATMENT**
Initial treatment is directed at improving myocardial function and optimizing preload and afterload. Diuretics, inotropic support, and, often, afterload reduction are employed (Table 145-3). Long-term therapy usually consists of diuretics and afterload reduction is added. Long-term therapy with β-blockers also may be beneficial, although this remains somewhat controversial in pediatric patients. Spironolactone is usually added to the medical regimen because of its effect on cardiac remodeling.

**RHEUMATIC FEVER**

**ETIOLOGY AND EPIDEMIOLOGY**
Although uncommon in the United States, acute rheumatic fever remains an important preventable cause of cardiac disease. It is most common in children 6 to 15 years of age. It is due to an immunologic reaction that is a delayed sequela of group A beta-hemolytic streptococcal infections of the pharynx. A family history of rheumatic fever and lower socioeconomic status are additional factors.

**CLINICAL MANIFESTATIONS**
Acute rheumatic fever is diagnosed using the clinical and laboratory findings of the revised Jones criteria (Table 146-1). The presence of either two major criteria or one major and two minor criteria, along with evidence of an antecedent streptococcal infection, confirm a diagnosis of acute rheumatic fever. The infection often precedes the presentation of rheumatic fever by 2 to 6 weeks. Streptococcal antibody tests, such as the antistreptolysin O titer, are the most reliable laboratory evidence of prior infection.
etiology

A cardiomyopathy is an intrinsic disease of the heart muscle and is not associated with other forms of heart disease (Table 147-1). There are three types of cardiomyopathy based on anatomic and functional features:

1. Dilated
2. Hypertrophic
3. Restrictive

Dilated cardiomyopathies are the most common. They are often idiopathic, but may be due to infection (echovirus or Coxsackie B virus) or be postinfectious, familial, or secondary to systemic disease or to cardiotoxic drugs. Hypertrophic cardiomyopathies are usually familial with autosomal dominant inheritance, but may occur sporadically. Restrictive cardiomyopathies are rare; they may be idiopathic or associated with systemic disease (Table 147-2).

clinical manifestations

Dilated cardiomyopathies result in enlargement of the left ventricle only or of both ventricles. Myocardial contractility is variably decreased. Children with dilated cardiomyopathy present with signs and symptoms of inadequate cardiac output and heart failure. Tachypnea and tachycardia are present on examination. Peripheral pulses are often weak because of a narrow pulse pressure. Rales may be audible on auscultation. The heart sounds may be muffled, and an S3 is often present. Concurrent infectious illness may result in circulatory collapse and shock in children with dilated cardiomyopathies.

Hypertrophic cardiomyopathy is initially difficult to diagnose. Infants, but not older children, frequently present with signs of heart failure. Sudden death may be the initial presentation in older children. Dyspnea, fatigue, chest pain, syncope or near-syncope, and palpitations may be present. A murmur is heard in more than 50% of children referred after identification of an affected family member. Restrictive cardiomyopathies are relatively rare in pediatrics. Presenting symptoms usually include dyspnea exacerbated by a respiratory illness, syncope, hepatomegaly, and an S4 heart sound on examination.
Table 147-2 | Anatomic and Functional Features of Cardiomyopathies

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DILATED</th>
<th>HYPTERTOPHIC</th>
<th>RESTRICTIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Infectious</td>
<td>Sporadic</td>
<td>Infiltrative (amyloidosis, sarcoidosis)</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td>Inherited (autosomal dominant)</td>
<td>Noninfiltrative (idiopathic, familial)</td>
</tr>
<tr>
<td>Toxic</td>
<td></td>
<td></td>
<td>Storage disease (hemochromatosis, Fabry disease)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td></td>
<td></td>
<td>Endomyocardial disease</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>Decreased systolic function</td>
<td>Diastolic dysfunction (impaired ventricular filling)</td>
<td>Diastolic dysfunction (impaired ventricular filling)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Positive inotropes</td>
<td>β-Blockers</td>
<td>Diuretics</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td></td>
<td>Antiarrhythmics</td>
</tr>
<tr>
<td></td>
<td>Afterload reduction</td>
<td>Calcium channel blockers</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td></td>
<td>β-Blockers</td>
<td></td>
<td>Cardiac transplantation</td>
</tr>
<tr>
<td></td>
<td>Antiarrhythmics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticoagulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac transplantation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Chapter 147 • Cardiomyopathies

**IMAGING STUDIES**

Cardiomegaly usually is seen on chest radiographs for all three types of cardiomyopathies. The electrocardiogram (ECG) in dilated cardiomyopathy may have nonspecific ST-T wave changes and left ventricular hypertrophy. ECG evidence of right ventricular hypertrophy is present in 25% of children with cardiomyopathy. The ECG with hypertrophic cardiomyopathy is universally abnormal, but changes are nonspecific. Primary hypertrophic cardiomyopathy is associated with a prolonged QT interval. Children with restrictive cardiomyopathies may show atrial enlargement on the ECG. Echocardiography features vary by type of cardiomyopathy.
Dilated cardiomyopathies result in left atrial and ventricular dilation, a decreased shortening fraction, and globally depressed contractility. Asymmetrical septal hypertrophy and left ventricular outflow tract obstruction are seen in hypertrophic cardiomyopathies. Massive atrial dilation is seen in restrictive cardiomyopathies. Endomyocardial biopsy specimens, obtained while the patient is hemodynamically stable, identify histologic type and allow tests for mitochondrial or infiltrative diseases.

**TREATMENT**

Supportive therapy, including diuretics, inotropic medications, and afterload reduction, is provided for all three types of cardiomyopathy. If a specific etiology can be identified, treatment is directed at the etiology. Symptomatic therapy with close monitoring and follow-up is crucial. Because of the high mortality rate associated with all forms of cardiomyopathy, cardiac transplantation must be considered.

### Table 148-1 Etiology of Pericarditis and Pericardial Effusion

<table>
<thead>
<tr>
<th>IDIOPATHIC (PRESUMED VIRAL) INFECTIOUS AGENTS</th>
<th>Sarcoïdosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Group A streptococci</td>
<td>TRAUMATIC</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Cardiac contusion (blunt trauma)</td>
</tr>
<tr>
<td>Pneumococcus, meningococcus*</td>
<td>Penetrating trauma</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>Postpericardiotomy syndrome</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Radiation</td>
</tr>
<tr>
<td><strong>Viral</strong>†</td>
<td>CONTIGUOUS SPREAD</td>
</tr>
<tr>
<td>Coxsackievirus (group A, B)</td>
<td>Pleural disease</td>
</tr>
<tr>
<td>Echovirus</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Mumps</td>
<td>Aortic aneurysm (dissecting)</td>
</tr>
<tr>
<td>Influenza</td>
<td>METABOLIC</td>
</tr>
<tr>
<td>Epstein-Barr</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Uremia</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
<td>Chylopericardium</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>NEOPLASTIC</td>
</tr>
<tr>
<td>Coccioidides immitis</td>
<td>Primary</td>
</tr>
<tr>
<td><em>Blastomyces dermatitidis</em></td>
<td>Contiguous (lymphoma)</td>
</tr>
<tr>
<td>Candida</td>
<td>Metastatic</td>
</tr>
<tr>
<td><strong>COLLAGEN VASCULAR-INFLAMMATORY AND GRANULOMATOUS DISEASES</strong></td>
<td>Infiltrative (leukemia)</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>OTHER ETIOLOGIC DISORDERS/FACTORS</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (idiopathic and drug-induced)</td>
<td>Drug reaction</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>After myocardial infarction</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Thalassemia</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>Central venous catheter perforation</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Heart failure</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage (coagulopathy)</td>
</tr>
</tbody>
</table>

*Infectious or immune complex.
†Common (viral pericarditis or myopericarditis is probably the most common cause of acute pericarditis in a previously normal host).
Table 148-2 | Manifestations of Pericarditis

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain (worsened if lying down or with inspiration)</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Malaise</td>
</tr>
<tr>
<td>Patient assumes sitting position</td>
</tr>
<tr>
<td><strong>SIGNS</strong></td>
</tr>
<tr>
<td><strong>Nonconstrictive</strong></td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Friction rub (accentuated by inspiration, body position)</td>
</tr>
<tr>
<td>Enlarged heart by percussion and x-ray examination</td>
</tr>
<tr>
<td>Distant heart sounds</td>
</tr>
<tr>
<td><strong>Tamponade</strong></td>
</tr>
<tr>
<td>As above, plus:</td>
</tr>
<tr>
<td>Distended neck veins</td>
</tr>
<tr>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Pulsus paradoxus (&gt;10 mm Hg with inspiration)</td>
</tr>
<tr>
<td>Narrow pulse pressure</td>
</tr>
<tr>
<td>Weak pulse, poor peripheral perfusion</td>
</tr>
<tr>
<td><strong>Constrictive</strong></td>
</tr>
<tr>
<td>Distended neck veins</td>
</tr>
<tr>
<td>Kussmaul sign (inspiratory increase in jugular venous pressure)</td>
</tr>
<tr>
<td>Distant heart sounds</td>
</tr>
<tr>
<td>Pericardial knock</td>
</tr>
<tr>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
</tbody>
</table>

**THE CLINICAL MANIFESTATIONS**

The symptoms of pericarditis (Table 148-2) depend on the amount of fluid in the pericardial space and how fast it accumulates. A small effusion usually is well tolerated. A large effusion may be well tolerated if it accumulates slowly. The faster the fluid accumulates, the sooner the patient is hemodynamically compromised and develops symptoms.

**IMAGING AND LABORATORY STUDIES**

Echocardiography is the most specific and useful diagnostic test for detection of pericardial effusions. A chest x-ray may reveal cardiomegaly. A large effusion creates a rounded, globular cardiac silhouette. The electrocardiogram (ECG) may show tachycardia, elevated ST segments, reduced QRS voltage or electrical alternans (variable QRS amplitude). The causative organism may be identified through viral titers, antistreptolysin O (ASO) titers, or diagnostic testing of the pericardial fluid.

**TREATMENT**

Pericardiocentesis is indicated for treatment of hemodynamically significant effusions and to determine the etiology of the pericarditis. Additional treatment is directed at the specific etiology. There is no specific treatment for viral pericarditis other than anti-inflammatory medications.

**Suggested Reading**

Moller JH, Hoffman JI, Benson DW, Van Hare GF, Wren C: Pediatric Cardiovascular Medicine, ed 2, West Sussex, UK, 2012, Wiley-Blackwell.
HEMATOLOGY ASSESSMENT

HISTORY
A detailed history of the onset, severity, progression, associated symptoms, presence of systemic complaints, and exacerbating factors is crucial to the diagnosis of a blood disorder. In many blood disorders, a detailed pedigree identifying a pattern of inheritance can point to the diagnosis.

PHYSICAL EXAMINATION AND COMMON MANIFESTATIONS

The physical examination of patients with blood disorders first focuses on hemodynamic stability. Acute episodes of anemia may be life-threatening, presenting with impairment of perfusion and cognitive status. The two most common findings of anemia include pallor and jaundice. The presence of petechiae, purpura, or deeper sites of bleeding, including generalized hemorrhage, indicates abnormalities of platelets, coagulation factors, or both. Growth parameters point to whether anemia is an acute or chronic process. Severe types of anemia, thrombocytopenia, and pancytopenia often are associated with congenital anomalies and a pattern of growth delay. Organ system involvement (especially hepatosplenomegaly and lymphadenopathy) or systemic illness point to a generalized illness as the cause for hematologic abnormalities (Table 149-1).

INITIAL DIAGNOSTIC EVALUATION
Diagnosis of pediatric blood disorders requires a detailed knowledge of normal hematologic values and varies according to age and, after puberty, according to sex (Table 149-2). Directed by the history, physical examination, and screening laboratory studies, specific diagnostic testing can confirm the diagnosis.

DEVELOPMENTAL HEMATOLOGY
Hematopoiesis begins by 3 weeks of gestation with erythropoiesis in the yolk sac. By 2 months’ gestation, the primary site of hematopoiesis migrates to the liver. By 5 to 6 months’ gestation, the process shifts from the liver to the bone marrow. An extremely premature infant may have significant extramedullary hematopoiesis due to limited bone marrow hematopoiesis. During infancy, virtually all marrow cavities are actively hematopoietic and the proportion of hematopoietic to stromal elements is quite high. As the child grows, hematopoiesis moves to the central bones of the body (vertebrae, sternum, ribs, and pelvis), and the marrow is gradually replaced with fat. Hemolysis or marrow damage may lead to marrow repopulation of cavities where hematopoiesis previously had ceased or may delay the shift of hematopoiesis. Hepatosplenomegaly in patients with chronic hemolysis may signify extramedullary hematopoiesis. When a patient with cytopenia is being evaluated, a bone marrow examination provides valuable information about processes that lead to underproduction of circulating cells. In addition, bone marrow infiltration by neoplastic elements or storage cells often occurs in concert with infiltration in the spleen, liver, and lymph nodes.

The hematopoietic cells consist of the following:
1. Small compartment of pluripotential progenitor stem cells that resemble small lymphocytes and are capable of forming all myeloid elements
2. Large compartment of committed, proliferating cells of myeloid, erythroid, and megakaryocytic lineage
3. Large compartment of postmitotic maturing cells (Fig. 149-1)

The bone marrow is the major storage organ for mature neutrophils and contains about seven times the intravascular pool of neutrophils. It contains 2.5 to 5 times as many cells of myeloid lineage as cells of erythroid lineage. Smaller numbers of megakaryocytes, plasma cells, histiocytes, lymphocytes, and stromal cells are also stored in the marrow.

Erythropoiesis (red blood cell [RBC] production) is controlled by erythropoietin, a glycoprotein that stimulates primitive pluripotential stem cells to differentiate along the
Figure 149-1  Major cytokine sources and actions to promote hematopoiesis. Cells of the bone marrow microenvironment, such as macrophages, endothelial cells, and reticular fibroblasts, produce macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF) after stimulation. For all lineages, optimal development requires a combination of early and late acting factors. BFU, Burst-forming unit; CFU, colony-forming unit; EPO, erythropoietin; IL, interleukin; MSC, myeloid stem cell; PSC, pluripotent stem cell; TNF, tumor necrosis factor; TPO, thrombopoietin. (From Sieff CA, Nathan DG,Clark SC: The anatomy and physiology of hematopoiesis. In Orkin SH, Nathan DG, editors: Hematology of Infancy and Childhood, ed 5, Philadelphia, 1998, WB Saunders, p 168.)

Table 149-1  Presentation of Hematologic Disorders

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>SYMPTOMS AND SIGNS</th>
<th>COMMON EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Pallor, fatigue, heart failure, jaundice</td>
<td>Iron deficiency, hemolytic anemia</td>
</tr>
<tr>
<td>Polycythemia</td>
<td>Irritability, cyanosis, seizures, jaundice, stroke, headache</td>
<td>Cyanotic heart disease, infant of diabetic mother, cystic fibrosis</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Fever, pharyngitis, oral ulceration, cellulitis, lymphadenopathy, bacteremia, gingivitis</td>
<td>Congenital or drug-induced agranulocytosis, leukemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Petechiae, ecchymosis, gastrointestinal hemorrhage, epistaxis</td>
<td>ITP, leukemia</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Bruising, hemarthrosis, mucosal bleeding</td>
<td>von Willebrand disease, hemophilia, DIC</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Pulmonary embolism, deep vein thrombosis</td>
<td>Lupus anticoagulant; protein C, protein S, or antithrombin III deficiency; factor V Leiden, prothrombin 20210</td>
</tr>
</tbody>
</table>

DIC, Disseminated intravascular coagulation; ITP, idiopathic thrombocytopenic purpura.
### Table 149-2 Hematologic Values During Infancy and Childhood

<table>
<thead>
<tr>
<th>AGE</th>
<th>HEMOGLOBIN (g/dL)</th>
<th>HEMATOCRIT (%)</th>
<th>RETICULOCYTES (%)</th>
<th>LEUKOCYTES (per mm³)</th>
<th>NEUTROPHILS (%)</th>
<th>LYMPHOCYTES (%)</th>
<th>EOSINOPHILS (%)</th>
<th>MONOCYTES (%)</th>
<th>NUCLEATED RED CELLS/100 WBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord blood</td>
<td>16.8</td>
<td>55</td>
<td>5</td>
<td>18,000</td>
<td>61</td>
<td>31</td>
<td>2</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>2 wk</td>
<td>16.5</td>
<td>50</td>
<td>1</td>
<td>12,000</td>
<td>40</td>
<td>48</td>
<td>3</td>
<td>9</td>
<td>3–10</td>
</tr>
<tr>
<td>3 mo</td>
<td>12.0</td>
<td>36</td>
<td>1</td>
<td>12,000</td>
<td>30</td>
<td>63</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6 mo–6 yr</td>
<td>12.0</td>
<td>37</td>
<td>1</td>
<td>10,000</td>
<td>45</td>
<td>48</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>7–12 yr</td>
<td>13.0</td>
<td>38</td>
<td>1</td>
<td>8000</td>
<td>55</td>
<td>38</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>14.0</td>
<td>42</td>
<td>1.6</td>
<td>7500</td>
<td>55</td>
<td>35–70</td>
<td>3</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>16.0</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


WBCs, White blood cells.
erythropoiesis, then replaced by (hemo-
about 120 days. The RBC continues to function for its normal life span of
heme. Iron is taken up via transferrin receptors and incor-
globin chains, glycolytic enzymes, and heme. Iron is taken up via transferrin receptors and incorporated into the heme ring, which combines with globin chains synthesized within the immature RBC. When the messenger RNA and mitochondria are gone from the RBC, heme or protein synthesis is no longer possible; however, the RBC continues to function for its normal life span of about 120 days.

Embryonic hemoglobins are produced during yolk sac erythropoiesis, then replaced by fetal hemoglobin (hemoglobin F, α2γ2) during the hepatic phase. During the third trimester, gamma chain production gradually diminishes, replaced by beta chains, resulting in hemoglobin A (α2β2). Some fetal factors (e.g., infant of a diabetic mother) delay onset of beta chain production, but premature birth does not. Just after birth, with rapid increases in oxygen saturation, erythropoietin production stops and, thus, erythropoiesis ceases. Fetal RBCs have a shorter survival time (60 days).

During the first few months of postnatal life, rapid growth, shortened RBC survival, and cessation of erythropoiesis cause a gradual decline in hemoglobin levels, with a nadir at 8 to 10 weeks of life. This so-called physiologic nadir is accentuated in premature infants. Erythropoietin is produced in response to the decline in hemoglobin and decreased oxygen delivery. Erythropoiesis subsequently resumes with an increase in the reticulocyte count. The hemoglobin level gradually increases, accompanied by synthesis of increasing amounts of hemoglobin A. By 6 months of age in healthy infants, only trace gamma chain synthesis occurs.

Production of neutrophil precursors is controlled predominately by two different colony-stimulating factors (see Fig. 149-1). The most immature neutrophil precursors are controlled by granulocyte-macrophage colony-stimulating factor (GM-CSF), produced by monocytes and lymphocytes. GM-CSF increases the entry of primitive precursor cells into the myeloid line of differentiation. Granulocyte colony-stimulating factor (G-CSF) augments the production of more mature granulocyte precursors. GM-CSF and G-CSF, working in concert, can augment production of neutrophils, shorten the usual 10- to 14-day production time from stem cell to mature neutrophil, and stimulate functional activity. The rapid increase in neutrophil count that occurs with infection is caused by release of stored neutrophils from the bone marrow, under the control of GM-CSF. During maturation, a mitotic pool of neutrophil precursors exists—myeloblasts, promyelocytes, and myelocytes possessing primary granules. The postmitotic pool consists of metamyelocytes, bands, and mature polymorphonuclear leukocytes containing secondary or specific granules that define the cell type. Only bands and mature neutrophils are fully functional with regard to phagocytosis, chemotaxis, and bacterial killing. Neutrophils migrate from the bone marrow, circulate for 6 to 7 hours, and enter the tissues, where they become end-stage cells that do not recirculate. Eosinophil production is under the control of a related glycoprotein hormone, interleukin 3. Eosinophils, which play a role in host defense against parasites, also are capable of living in tissues for prolonged periods. Megakaryocytes are giant, multinucleated cells derived from the primitive stem cell and are polyploid (16 to 32 times the normal DNA content) because of nuclear but not cytoplasmic cell division. Platelets form by invagination of the megakaryocytic cell membrane and bud off from the periphery. Thrombopoietin is the primary regulator of platelet production. Platelets adhere to damaged endothelium and subendothelial surfaces via specific receptors for the adhesive proteins, von Willebrand factor (vWF), and fibrinogen. Platelets also have specific granules that readily release their contents after stimulation and trigger the process of platelet aggregation. Platelets circulate for 7 to 10 days and have no nucleus.

Lymphocytes are particularly abundant in the bone marrow of young children. These are primarily B lymphocytes arising in the spleen and lymph nodes, but T lymphocytes also are present.
adequate marrow synthesis of red blood cells (RBCs). Vitamin B\textsubscript{12} and folic acid deficiencies lead to macrocytic anemia. Hemolytic diseases are mediated either by disorders intrinsic or extrinsic to the RBC that increase cell destruction. The most common RBC membrane disorders are hereditary spherocytosis and hereditary elliptocytosis. In both of these disorders, abnormalities of proteins within the cytoskeleton lead to abnormal RBC shape and function. Numerous RBC enzyme deficiencies may lead to hemolysis, but only two are common: glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency. Immune-mediated hemolysis may be extravascular when RBCs coated with antibodies or complement are phagocytosed by the reticuloendothelial system. The hemolysis may be intravascular when antibody binding leads to complement fixation and lysis of RBCs.

Acute onset of anemia can result in a poorly compensated state, manifested as an elevated heart rate, a flow murmur, poor exercise tolerance, headache, excessive sleeping (especially in infants) or fatigue, irritability, poor feeding, and syncope. In contrast, chronic anemia often is exceptionally well

**FIGURE 150-1** Use of the complete blood count, reticulocyte count, and blood smear in the diagnosis of anemia. DIC, Disseminated intravascular coagulation; G6PD, glucose-6-phosphate dehydrogenase; HUS, hemolytic uremic syndrome; R/O, rule out; RPI, reticulocyte production index; TTP, thrombotic thrombocytopenic purpura.

**CLINICAL MANIFESTATIONS**

<table>
<thead>
<tr>
<th>Decision-Making Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available @ StudentConsult.com</strong></td>
</tr>
</tbody>
</table>

- **Heart Murmurs**
- **Jaundice**
- **Splenomegaly**
- **Edema**
- **Anemia**

<table>
<thead>
<tr>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Azidothymidine (zidovudine)</td>
</tr>
</tbody>
</table>
A history of jaundice, pallor, previously affected siblings, drug ingestion by the mother, or excessive blood loss at the time of birth provides important clues to the diagnosis in newborns. A careful dietary history is crucial. The key findings in patients with hemolytic anemias are jaundice, pallor, and splenomegaly. Because of increased bilirubin production, gallstones (bilirubinate), a result of chronic hemolysis, are a common complication. Systemic complaints suggest acute or chronic illnesses as probable causes of anemia. In later childhood and adolescence, the presence of constitutional symptoms, unusual diets, drug ingestion, or blood loss, especially from menstrual bleeding, often points to a diagnosis. Congenital hemolytic disorders (enzyme deficiencies and membrane problems) often present in the first 6 months of life and frequently are associated with neonatal jaundice, although these disorders often go undiagnosed. A careful drug history is essential for detecting problems that may be drug induced. Pure dietary iron deficiency is rare except in infancy, when cow’s milk protein intolerance causes gastrointestinal blood loss and further complicates an already inadequate iron intake.

The physical examination may point to the potential causes (see Table 150-2). The physiologic stability of the patient may be abnormal with acute blood loss and acute hemolysis, manifesting as tachycardia, blood pressure changes, and, most ominously, an altered state of consciousness. The presence of jaundice suggests hemolysis. Petechiae and purpura indicate a coagulopathy. Hepatosplenomegaly and adenopathy suggest infiltrative disorders. Growth failure or poor weight gain suggests an anemia of chronic disease. An essential element of the physical examination is the investigation of the stool for the presence of occult blood.

### Laboratory Studies

A hemoglobin or hematocrit test indicates the severity of the anemia. Once anemia has been substantiated, the workup should include a complete blood count with differential, platelet count, indices, and reticulocyte count. Examination of the peripheral blood smear assesses the morphology of RBCs (Fig. 150-2), white blood cells (WBCs), and platelets. All cell lines should be scrutinized to determine whether anemia is the result of a process limited to the erythroid line or a process that affects other marrow elements. Using data obtained from the indices and reticulocyte count, the workup can be organized on the basis of whether RBC production is adequate or inadequate and whether the cells are microcytic, normocytic, or macrocytic (see Fig. 150-1).

An appropriate bone marrow response to anemia would be an elevated absolute reticulocyte number, suggesting increased production and implying either hemolysis or blood loss. Anemia with a normal reticulocyte number suggests decreased or ineffective production for the degree of anemia. Reticulocytopenia signifies an acute onset so that the marrow has not had adequate time to respond, that reticulocytes are being destroyed in the marrow (antibody-mediated), or that intrinsic bone marrow disease is present. The best indicators of the severity of hemolysis are the hemoglobin level and the elevation of the reticulocyte count. Biochemical evidence of hemolysis includes an increase in levels of bilirubin and lactate dehydrogenase and a decrease in haptoglobin.

### Table 150-1: Historical Clues in Evaluation of Anemia

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Iron deficiency rare in the absence of blood loss before 6 mo or in term infants or before doubling of birth weight in preterm infants Neonatal anemia with reticulocytosis suggests hemolysis or blood loss; with reticulocytopenia, suggests bone marrow failure Sickle cell anemia and β-thalassemia appear as fetal hemoglobin disappears (4–8 mo of age)</td>
</tr>
<tr>
<td>Family history and genetic considerations</td>
<td>X-linked: G6PD deficiency Autosomal dominant: spherocytosis Autosomal recessive: sickle cell anemia, Fanconi anemia Family member with history of cholecystectomy (for bilirubin stones) or splenectomy at an early age Ethnicity (thalassemia in persons of Mediterranean origin; G6PD deficiency in blacks, Greeks, and people of Middle Eastern origin) Race (β-thalassemia in persons of Mediterranean, African, or Asian descent; α-thalassemia in those of African and Asian descent; SC and SS in African descent)</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Cow’s milk diet: iron deficiency Strict vegetarian: vitamin B12 deficiency Goat’s milk diet: folate deficiency Pica: plumbism, iron deficiency Cholestasis, malabsorption: vitamin E deficiency</td>
</tr>
<tr>
<td>Drugs</td>
<td>G6PD: oxidants (e.g., nitrofurantoin, antimalarials) Immune-mediated hemolysis (e.g., penicillin) Bone marrow suppression (e.g., chemotherapy) Phenytoin, increasing folate requirements</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Malabsorption of vitamin B12 or E or iron Inflammatory bowel disease and anemia of inflammation (chronic disease) with or without blood loss Milk protein intolerance–induced blood loss Intestinal resection: vitamin B12 deficiency</td>
</tr>
<tr>
<td>Infection</td>
<td>Giardia lamblia infection: iron malabsorption Intestinal bacterial overgrowth (blind loop): vitamin B12 deficiency Fish tapeworm: vitamin B12 deficiency Epstein-Barr virus, cytomegalovirus infection: bone marrow suppression, hemophagocytic syndromes Mycoplasma infection: hemolysis Parvovirus infection: bone marrow suppression HIV infection Chronic infection Endocarditis Malaria: hemolysis Hepatitis: aplastic anemia</td>
</tr>
</tbody>
</table>

G6PD, Glucose-6-phosphate dehydrogenase.
### Table 150-2: Physical Findings in the Evaluation of Anemia

<table>
<thead>
<tr>
<th>SYSTEM/STRUCTURE</th>
<th>OBSERVATION</th>
<th>SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Hyperpigmentation</td>
<td>Fanconi anemia, dyskeratosis congenita</td>
</tr>
<tr>
<td>Cafe au lait spots</td>
<td>Fanconi anemia</td>
<td>Vitamin B₁₂ deficiency</td>
</tr>
<tr>
<td>Vitiligo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial oculocutaneous albinism</td>
<td></td>
<td>Chediak-Higashi syndrome</td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
<td>Hemolysis</td>
</tr>
<tr>
<td>Petechiae, purpura</td>
<td></td>
<td>Bone marrow infiltration, autoimmune hemolysis with autoimmune thrombocytopenia, hemolytic uremic syndrome, hemophagocytic syndromes</td>
</tr>
<tr>
<td>Erythematous rash</td>
<td></td>
<td>Parvovirus or Epstein-Barr virus infection</td>
</tr>
<tr>
<td>Bruising</td>
<td></td>
<td>Bleeding disorder, nonaccidental trauma, scurvy</td>
</tr>
<tr>
<td>Head</td>
<td>Frontal bossing</td>
<td>Thalassemia major, severe iron deficiency, chronic subdural hematoma</td>
</tr>
<tr>
<td>Microcephaly</td>
<td></td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Eyes</td>
<td>Microphthalmia</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td></td>
<td>Retinopathy</td>
<td>Hemoglobin SS, SC disease (see Table 150-7)</td>
</tr>
<tr>
<td></td>
<td>Optic atrophy</td>
<td>Osteopetrosis</td>
</tr>
<tr>
<td></td>
<td>Blocked lacrimal gland</td>
<td>Dykeratosis congenita</td>
</tr>
<tr>
<td></td>
<td>Kayser-Fleischer ring</td>
<td>Wilson disease</td>
</tr>
<tr>
<td></td>
<td>Blue sclera</td>
<td>Iron deficiency, osteopetrosis</td>
</tr>
<tr>
<td>Mouth</td>
<td>Glossitis</td>
<td>Vitamin B₁₂ deficiency, iron deficiency</td>
</tr>
<tr>
<td></td>
<td>Angular stomatitis</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td></td>
<td>Cleft lip</td>
<td>Diamond-Blackfan syndrome</td>
</tr>
<tr>
<td></td>
<td>Pigmentation</td>
<td>Peutz-Jeghers syndrome (intestinal blood loss)</td>
</tr>
<tr>
<td></td>
<td>Telangiectasia</td>
<td>Osler-Weber-Rendu syndrome (blood loss)</td>
</tr>
<tr>
<td></td>
<td>Leukoplakia</td>
<td>Dykeratosis congenita</td>
</tr>
<tr>
<td>Chest</td>
<td>Shield chest or widespread nipples</td>
<td>Diamond-Blackfan syndrome</td>
</tr>
<tr>
<td></td>
<td>Murmur</td>
<td>Endocarditis: prosthetic valve hemolysis; severe anemia</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Hepatomegaly</td>
<td>Hemolysis, infiltrative tumor, chronic disease, hemangioma, cholecystitis, extramedullary hematopoiesis</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly</td>
<td>Hemolysis, sickle cell disease, (early) thalassemia, malaria, leukemia/lymphoma, Epstein-Barr virus, portal hypertension</td>
</tr>
<tr>
<td></td>
<td>Nephromegaly</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td></td>
<td>Absent kidney</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Extremities</td>
<td>Absent thumbs</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td></td>
<td>Triphalangeal thumb</td>
<td>Diamond-Blackfan syndrome</td>
</tr>
<tr>
<td></td>
<td>Spoon nails</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td></td>
<td>Beau line (nails)</td>
<td>Heavy metal intoxication, severe illness</td>
</tr>
<tr>
<td></td>
<td>Mees line (nails)</td>
<td>Heavy metals, severe illness, sickle cell anemia</td>
</tr>
<tr>
<td></td>
<td>Dystrophic nails</td>
<td>Dykeratosis congenita</td>
</tr>
<tr>
<td>Rectal</td>
<td>Hemorrhoids</td>
<td>Portal hypertension</td>
</tr>
<tr>
<td></td>
<td>Heme-positive stool</td>
<td>Gastrointestinal bleeding</td>
</tr>
<tr>
<td>Nerves</td>
<td>Irritable, apathy</td>
<td>Iron deficiency</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Deficiency of vitamins B₁, B₁₂, and E; lead poisoning</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
<td>Deficiency of vitamins B₁₂ and E</td>
</tr>
<tr>
<td></td>
<td>Ataxia, posterior column signs</td>
<td>Vitamin B₁₂ deficiency</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>Sickle cell anemia, paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td>General</td>
<td>Small stature</td>
<td>Fanconi anemia, HIV infection, malnutrition</td>
</tr>
</tbody>
</table>

HIV, Human immunodeficiency virus; SLE, systemic lupus erythematosus.
DIFFERENTIAL DIAGNOSIS

Hypochromic, Microcytic Anemia
Iron Deficiency Anemia

**Etiology.** Infants fed cow’s milk when younger than 1 year of age, toddlers fed large volumes of cow’s milk, and menstruating teenage girls who are not receiving supplemental iron are at high risk for iron deficiency. **Dietary** iron deficiency anemia is most common in bottle-fed toddlers who are receiving large volumes of cow’s milk and eat minimal amounts of food high in iron content. (See Chapters 28 and 31.) Iron deficiency anemia also may be found in children with chronic inflammatory diseases, even without **chronic blood loss.**

**Epidemiology.** The prevalence of iron deficiency, the most common cause of anemia in the world, is about 9% in toddlers, 9% to 11% in adolescent girls, and less than 1% in teenage boys. Iron deficiency anemia occurs in about one third of children who are iron deficient (Table 150-3). Some underprivileged minority populations in the United States may be at increased risk for iron deficiency because of poor dietary intake (see Chapter 31). Breastfed infants are less likely to have iron deficiency than bottle-fed infants because, although there is less iron in breast milk, this iron is more efficiently absorbed.

**Clinical Manifestations.** In addition to cardiovascular manifestations of anemia, central nervous system (CNS) abnormalities (apathy, irritability, poor concentration) have been linked to iron deficiency, presumably resulting from alterations of iron-containing enzymes (monoamine oxidase) and cytochromes. Poor muscle endurance, gastrointestinal dysfunction, and impaired WBC and T-cell function have been associated with iron deficiency. Iron deficiency in infancy may be associated with later **cognitive deficits** and poor school performance.

**Treatment.** In an otherwise healthy child, a **therapeutic trial of iron** is the best diagnostic study for iron deficiency as long as the child is re-examined and a response is documented. The response to oral iron includes rapid subjective improvement, especially in neurologic function (within 24 to 48 hours) and reticulocytosis (48 to 72 hours); increase in hemoglobin levels (4 to 30 days); and repletion of iron stores (in 1 to 3 months). The usual therapeutic dose of 4 to 6 mg/day...
of elemental iron induces an increase in hemoglobin of 0.25 to 0.4 g/dL/day (a 1%/day increase in hematocrit). If the hemoglobin level fails to increase within 2 weeks after institution of iron treatment, careful re-evaluation for ongoing blood loss, development of infection, poor compliance, or other causes of microcytic anemia is required (Table 150-4; see Fig. 150-1).

**Prevention.** Bottle-fed infants should receive an iron-containing formula until 12 months of age, and breastfed infants older than 6 months of age should receive an iron supplement. The introduction of iron-enriched solid foods at 6 months of age, followed by a transition to a limited amount of cow’s milk and increased solid foods at 1 year, can help prevent iron deficiency anemia. Teenage girls who are menstruating should have a diet enriched with iron-containing foods. A vitamin with iron may also be used.

**Thalassemia Minor**

**Etiology and Epidemiology.** α-Thalassemia and β-thalassemia minor are common causes of microcytosis, either with or without a mild hypochromic, microcytic anemia. They are prevalent in certain ethnic groups (Mediterranean, Southeast Asian, African Americans). Individuals of Asian descent are at risk of having three or four α genes deleted, resulting in hemoglobin H disease (γ4) or hydrops fetalis with only Bart (α4) hemoglobin (Table 150-5 and Fig. 150-3).

**Laboratory Testing.** The thalassemia minor syndromes are characterized by a mild hypochromic, microcytic anemia with a low absolute reticulocyte count (see Table 150-5). The RBC count is usually elevated. As a result, if the mean corpuscular volume (MCV) divided by the RBC count is less than 12.5 (Mentzer index), the diagnosis is suggestive of thalassemia trait. The blood smear reveals only microcytosis with α-thalassemia trait. Outside the neonatal period, when Bart hemoglobin is detectable, hemoglobin electrophoresis usually is normal in α-thalassemia minor (see Fig. 150-3). Blood smears of patients with β-thalassemia minor show microcytic RBCs. Target cells and basophilic stippled RBCs, caused by precipitation of alpha chain tetramers, also may be present. The diagnosis is based on an elevation of hemoglobin A2 and F levels in β-thalassemia. Molecular testing is indicated for identification of more severe or unusual variants.

**Treatment.** No treatment is required for children with thalassemia minor. However, children with hemoglobin H disease (γ4), especially the Constant Spring variant or hydrops fetalis with only Bart (α4) hemoglobin, are likely to require chronic transfusion therapy.

**Lead Poisoning**

Lead poisoning may be associated with a hypochromic, microcytic anemia. Most patients have concomitant iron deficiency. The history of living in an older home (built before 1980) with chipped paint or lead dust should raise suspicion of lead poisoning, especially in a child with pica. Basophilic stippling on the blood smear is common. Lead intoxication

---

**Table 150-3** Stages in Development of Iron Deficiency Anemia

<table>
<thead>
<tr>
<th>HEMOGLOBIN (g/dL)</th>
<th>PERIPHERAL SMEAR</th>
<th>SERUM IRON (μg/dL)</th>
<th>BONE MARROW IRON</th>
<th>SERUM FERRITIN (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13+ (normal)</td>
<td>nc/nc</td>
<td>50–150</td>
<td>Fe²⁺</td>
<td>Male: 40–340</td>
</tr>
<tr>
<td>10–12</td>
<td>nc/nc</td>
<td>↓</td>
<td>Fe²⁺ absent, erythroid hyperplasia</td>
<td>&lt;12</td>
</tr>
<tr>
<td>8–10</td>
<td>hypo/nc</td>
<td>↓</td>
<td>Fe²⁺ absent, erythroid hyperplasia</td>
<td>&lt;12</td>
</tr>
<tr>
<td>&lt;8</td>
<td>hypo/micro*</td>
<td>↓</td>
<td>Fe²⁺ absent, erythroid hyperplasia</td>
<td>&lt;12</td>
</tr>
</tbody>
</table>


*Microcytosis, determined by a mean corpuscular volume (in fL) <2 SD below the mean, must be adjusted for age (e.g., –2 SD at 3–6 mo = 74; at 0.5–2 yr = 70; at 2–6 yr = 75; at 6–12 yr = 77; and at 12–18 yr = 78).†

**Table 150-4** Differentiating Features of Microcytic Anemias

<table>
<thead>
<tr>
<th>TEST</th>
<th>IRON DEFICIENCY ANEMIA</th>
<th>THALASSEMIA MINOR</th>
<th>ANEMIA OF INFLAMMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Serum iron-binding capacity</td>
<td>High</td>
<td>Normal</td>
<td>Low or normal</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>Low</td>
<td>Normal or high</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Marrow iron stores</td>
<td>Low or absent</td>
<td>Normal or high</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Marrow sideroblasts</td>
<td>Decreased or absent</td>
<td>Normal or high</td>
<td>Normal or high</td>
</tr>
<tr>
<td>Free erythrocyte protoporphyrin</td>
<td>High</td>
<td>Normal or slightly increased</td>
<td>High</td>
</tr>
<tr>
<td>Hemoglobin A₂ or F</td>
<td>Normal</td>
<td>High β-thalassemia; normal α-thalassemia</td>
<td>Normal</td>
</tr>
<tr>
<td>Red blood cell distribution width</td>
<td>High</td>
<td>Normal</td>
<td>Normal/1</td>
</tr>
</tbody>
</table>

*See Table 150-3 for definition of microcytosis.

†α-Thalassemia minor can be diagnosed by the presence of Bart hemoglobin on newborn screening.

‡Usually normochromic; 25% of cases are microcytic.

§Red blood cell distribution width quantitates the degree of anisocytosis (different sizes) of red blood cells.
rarely causes hemolytic anemia. Detection by routine screening, removal from exposure, chelation therapy, and correction of iron deficiency are crucial to the potential development of affected children.

**Normocytic Anemia**

**Etiology and Treatment.** Anemia is a common component of chronic inflammatory disease. Hepcidin, a protein made in the liver, plays a key role in iron homeostasis. Inflammation causes an increase in the production of hepcidin, interrupting the process of iron release by macrophages and the absorption of iron from the intestines leading to anemia. The **anemia of inflammation** may be normocytic or, less often, microcytic. This may pose a clinical challenge, when children with inflammatory disorders associated with blood loss (inflammatory bowel disease) exhibit a microcytic anemia. In these circumstances, only a bone marrow aspiration with staining of the sample for iron can differentiate the two entities clearly (see Table 150-4). Low ferritin levels indicate concurrent iron deficiency. A trial of iron therapy is not indicated without a specific diagnosis in children who appear to be systemically ill.

Bone marrow **infiltration by malignant cells** commonly leads to a normochromic, normocytic anemia. The mechanism
Congenital pure RBC aplasia (Diamond-Blackfan syndrome), a lifelong disorder, usually presents in the first few months of life or at birth with severe anemia and mild macrocytosis or a normocytic anemia. It is due to a deficiency of bone marrow red blood cell precursors (Table 150-6). More than a third of patients have short stature. Many patients (50% to 66%) respond to corticosteroid treatment, but must receive therapy indefinitely. Patients who do not respond to corticosteroid treatment are transfusion dependent and are at risk of the multiple complications of long-term transfusion therapy, especially iron overload. These patients have a higher rate of developing leukemia or other hematologic malignancies than the general population.

In contrast to the congenital hypoplastic anemias, transient erythroblastopenia of childhood, a normocytic anemia caused by suppression of RBC synthesis, usually appears after 6 months of age in an otherwise normal infant. Viral infections are thought to be the trigger, although the mechanism leading to RBC aplasia is poorly understood. The onset is gradual, but anemia may become severe. Recovery usually is spontaneous. Differentiation from Diamond-Blackfan syndrome, in which erythroid precursors also are absent or diminished in the bone marrow, may be challenging. Transfusion of packed RBCs may be necessary if the anemia becomes symptomatic before recovery.

Aplastic crises may complicate any chronic hemolytic anemia. These periods of severe reticulocytopenia, leading to an
acute exacerbation of the anemia, may precipitate cardiovascular decompensation. Human parvovirus B19 (the cause of fifth disease) infects erythroid precursors and shuts down erythropoiesis. Transient erythroid aplasia is without consequence in individuals with normal RBC survival. Recovery from parvovirus infection in hemolytic disease is spontaneous, but patients may need transfusion if the anemia is severe.

**Macrocytic Anemia**
SEE FIGURE 150-1.

**Marrow Failure/Pancytopenia**

**Decision-Making Algorithm**
Available @ StudentConsult.com

**Anemia**

**Etiology.** Pancytopenia is a quantitative decrease in formed elements of the blood—erythrocytes, leukocytes, and platelets. Patients more often exhibit symptoms of infection or bleeding than anemia because of the relatively short life span of WBCs and platelets compared with the life span of RBCs. Causes of pancytopenia include failure of production (implying intrinsic bone marrow disease), sequestration (hypersplenism), and increased peripheral destruction.

**Differential Diagnosis.** Features that suggest bone marrow failure and mandate an examination of bone marrow include a low reticulocyte count, teardrop forms of RBCs (implying marrow replacement, not just failure), presence of abnormal forms of leukocytes or myeloid elements less mature than band forms, small platelets, and an elevated mean corpuscular volume in the face of a low reticulocyte count. Pancytopenia resulting from bone marrow failure is usually a gradual process, starting with one or two cell lines, but later involving all three cell lines. Features suggesting increased destruction include reticulocytosis, jaundice, immature erythroid or myeloid elements on the blood smear, large platelets, and increased serum bilirubin and lactic dehydrogenase.

**Aplastic Anemia**

**Decision-Making Algorithms**
Available @ StudentConsult.com

**Anemia**

**Etiology and Epidemiology.** In a child with aplastic anemia, pancytopenia evolves as the hematopoietic elements of the bone marrow disappear and the marrow is replaced by fat. In developed countries, aplastic anemia is most often idiopathic. The disorder may be induced by drugs such as chloramphenicol and felbamate or by toxins such as benzene. Aplastic anemia also may follow infections, particularly hepatitis and infectious mononucleosis (see Table 150-6). Immunosuppression of hematopoiesis is postulated to be an important mechanism in patients with postinfectious and idiopathic aplastic anemia.

**Laboratory Studies.** A bone marrow biopsy is crucial to determine cellularity or the extent of depletion of the hematopoietic elements.

**Treatment.** Survival rate is about 20% in severe aplastic anemia with supportive care alone, although the duration of survival may be years when vigorous blood product and antibiotic support is provided. For children with severe aplastic anemia—defined by an absolute reticulocyte count less than 50,000/μL, absolute neutrophil count less than 500/mm³, platelet count less than 20,000/mm³, and bone marrow cellularity on biopsy specimen less than 25% of normal—the treatment of choice is hematopoietic stem cell transplantation (HSCT) from a sibling with identical HLA and compatible mixed lymphocytes. When HSCT occurs before the recipient is sensitized to blood products, survival rate is greater than 80%. The treatment of aplastic anemia without an HLA-matched donor for HSCT is evolving, with two major options: potent immunosuppressive therapy or unrelated or partially matched HSCT. Results of trials using immunosuppressive therapy with antithymocyte globulin, cyclosporine, and corticosteroids in combination with hematopoietic growth factors have been encouraging. Such therapy is often toxic, and relapses often occur when therapy is stopped.

**Fanconi Anemia**

**Etiology and Epidemiology.** Fanconi anemia is a constitutional form of aplastic anemia that usually presents in the latter half of the first decade of life and may evolve over years. A group of genetic defects in proteins involved in DNA repair have been identified in Fanconi anemia, which is inherited in an autosomal recessive manner. The diagnosis is based on demonstration of increased chromosomal breakage after exposure to agents that damage DNA. The repair mechanism for DNA damage is abnormal in all cells in Fanconi anemia, which may contribute to the increased risk of malignancies. Terminal acute leukemia develops in 10% of cases. Other malignancies include solid tumors of the head and neck, gastrointestinal tumors, and gynecologic tumors.

**Clinical Manifestations.** Patients with Fanconi anemia have numerous characteristic clinical findings (see Table 150-6).

**Treatment.** Hematopoietic stem cell transplantation can cure the pancytopenia caused by bone marrow aplasia. Many patients with Fanconi anemia and about 20% of children with aplastic anemia seem to respond for a time to androgenic therapy, which induces masculinization and may cause liver injury and liver tumors. Androgenic therapy increases RBC synthesis and may diminish transfusion requirements. The effect on granulocytes, and especially the platelet count, is less impressive.

**Marrow Replacement.** Marrow replacement may occur as a result of leukemia, solid tumors (especially neuroblastoma), storage diseases, osteopetrosis in infants, and myelofibrosis, which is rare in childhood. The mechanisms by which...
malignant cells impair marrow synthesis of normal hematopoietic elements are complex and incompletely understood. Bone marrow aspirate and biopsy are needed for precise diagnosis of the etiology of marrow synthetic failure.

**Pancytopenia Resulting from Destruction of Cells.** Pancytopenia resulting from destruction of cells may be caused by **intramedullary destruction** of hematopoietic elements (myeloproliferative disorders, deficiencies of folic acid and vitamin B₁₂) or by the **peripheral destruction** of mature cells. The usual site of peripheral destruction of blood cells is the spleen, although the liver and other parts of the reticuloendothelial system may participate. **Hypersplenism** may be the result of anatomic causes (portal hypertension or splenic hypertrophy from thalassemia); infections (including malaria); or storage diseases (Gaucher disease, lymphomas, or histiocytosis). Splenectomy is indicated only when the pancytopenia is of clinical significance.

**Hemolytic Anemias**

**Major Hemoglobinopathies**

**Etiology.** Because alpha chains are needed for fetal erythropoiesis and production of hemoglobin F (α₂γ₂), **alpha chain hemoglobinopathies** are present in utero. Four alpha genes are present on the two number 16 chromosomes (see Fig. 150-3 and Table 150-5). Single gene deletions produce no disorder (silent carrier state), but can be detected by measuring the rates of α and β synthesis or by using molecular biologic techniques. Deletion of two genes produces **α-thalassemia minor** with mild or no anemia and microcytosis. In individuals of African origin, the gene deletions occur on different chromosomes (trans), and the disorder is benign. In the Asian population, deletions may occur on the same chromosome (cis), and infants may inherit two number 16 chromosomes lacking three or even four genes. Deletion of all four genes leads to hydrops fetalis, severe intrauterine anemia, and death, unless intrauterine transfusions are administered. Deletion of three genes produces moderate hemolytic anemia with γ₄ tetramers (Bart hemoglobin) in the fetus and β₄ tetramers (hemoglobin H) in older children and adults (see Table 150-5).

**Beta chain hemoglobinopathies** in the United States are more prevalent than alpha chain disorders, possibly because these abnormalities are not symptomatic in utero. The major beta hemoglobinopathies include those that alter hemoglobin function, including **hemoglobin S, C, E, and D**, and those that alter beta chain production, the β-thalassemias. Because each RBC has two copies of chromosome 11 and they express both β-globin genes, most disorders of beta chains are not clinically severe, unless both beta chains are abnormal. By convention, when describing β-thalassemia genes, β⁰ indicates a thalassemic gene resulting in absent beta chain synthesis, whereas β⁺ indicates a thalassemic gene that permits reduced but not absent synthesis of normal β chains. Disorders of the beta chain usually manifest themselves clinically between 4 and 12 months of age, unless they have been detected prenatally or by cord blood screening.

**β-Thalassemia Major (Cooley Anemia)**

**Etiology and Epidemiology.** β-Thalassemia major is caused by mutations that impair **beta chain synthesis**. Because of unbalanced synthesis of alpha and beta chains, alpha chains precipitate within the cells, resulting in RBC destruction either in the bone marrow or in the spleen. β-Thalassemia major is seen most commonly in individuals of Mediterranean or Asian descent. The clinical severity of the illness varies on the basis of the molecular defect.

**Clinical Manifestations.** Signs and symptoms of β-thalassemia major result from the combination of chronic hemolytic disease, decreased or absent production of normal hemoglobin A, and ineffective erythropoiesis. The anemia is severe and leads to growth failure and high-output heart failure. **Ineffective erythropoiesis** causes increased expenditure of energy and expansion of the bone marrow cavities of all bones, leading to osteopenia, pathologic fractures, extramedullary erythropoiesis with resultant hepatosplenomegaly, and an increase in the rate of iron absorption.

**Treatment.** Treatment of β-thalassemia major is based on a **hypertransfusion program** that corrects the anemia and suppresses the patient’s own ineffective erythropoiesis, limiting the stimulus for increased iron absorption. This suppression permits the bones to heal, decreases metabolic expenditures, increases growth, and limits dietary iron absorption. Splenectomy may reduce the transfusion volume, but it adds to the risk of serious infection. Chelation therapy with deferoxamine or deferasirox should start when laboratory evidence of iron overload (hemochromatosis) is present and before there are clinical signs of iron overload (nonimmune diabetes mellitus, cirrhosis, heart failure, bronzing of the skin, and multiple endocrine abnormalities). Hematopoietic stem cell transplantation in childhood, before organ dysfunction induced by iron overload, has had a high success rate in β-thalassemia major and is the treatment of choice.

**Sickle Cell Disease**

**Etiology and Epidemiology.** The common sickle cell syndromes are **hemoglobin SS disease, hemoglobin S-C disease, hemoglobin S-β thalassemia**, and rare variants (Table 150-7). The specific hemoglobin phenotype must be identified because the clinical complications differ in frequency, type, and severity. As a result of a single **amino acid substitution**
(valine for glutamic acid at the β6 position), sickle hemoglobin crystallizes and forms a gel in the deoxygenated state. When reoxygenated, the sickle hemoglobin is normally soluble. The so-called reversible sickle cell is capable of entering the microcirculation. As the oxygen is extracted and saturation declines, sickling may occur, occluding the microvasculature. The surrounding tissue undergoes infarction, inducing pain and dysfunction. This sickling phenomenon is exacerbated by hypoxia, acidosis, fever, hypothermia, and dehydration.

**Clinical Manifestations and Treatment.** A child with sickle cell anemia is vulnerable to life-threatening infection by 4 months of age. By that time, splenic dysfunction is caused by sickling of the RBCs within the spleen, resulting in an inability to filter microorganisms from the bloodstream in most patients. Splenic dysfunction is followed, eventually, by splenic infarction, usually by 2 to 4 years of age. The loss of normal splenic function makes the patient susceptible to overwhelming infection by encapsulated organisms, especially *Streptococcus pneumoniae* and other pathogens (Table 150-8). The hallmark of infection is fever. A febrile patient with a sickle cell syndrome (temperature >38.5°C) must be evaluated immediately (see Chapter 96). Current precautions to prevent infections include prophylactic daily oral penicillin begun at diagnosis and vaccinations against pneumococcus, *Haemophilus influenzae* type b, hepatitis B virus, and influenza virus.

The anemia of hemoglobin SS disease is usually a chronic, moderately severe, hemolytic anemia that is not routinely transfusion dependent. The severity depends in part on the patient’s phenotype. Manifestations of chronic anemia include jaundice, pallor, variable splenomegaly in infancy, a cardiac flow murmur, and delayed growth and sexual maturation. Decisions about transfusion should be made on the basis of the patient’s clinical condition, the hemoglobin level, and the reticulocyte count.

Sickle cell disease is complicated by sudden, occasionally severe and life-threatening events caused by the acute intravascular sickling of the RBCs, with resultant pain or organ dysfunction (so-called crisis). In two different clinical situations, an acute, potentially life-threatening decline in the hemoglobin level may be superimposed on the chronic compensated anemia. **Splenic sequestration crisis** is a life-threatening, hyperacute drop in the hemoglobin level (blood volume) secondary to splenic pooling of the patient’s RBCs and sickling within the spleen. The spleen is moderately to markedly enlarged, and the reticulocyte count is elevated. In an aplastic crisis, parvovirus B19 infects RBC precursors in the bone marrow and induces transient RBC aplasia with reticulocytopenia and a rapid worsening of anemia because of the very short life span of sickle RBCs. Simple transfusion therapy is indicated for sequestration and aplastic crises when the anemia is symptomatic.

**Vasoocclusive painful events** may occur in any organ of the body and are manifested by pain and/or significant dysfunction (see Table 150-8). The **acute chest syndrome** is a vasoocclusive crisis within the lungs with evidence of a new infiltrate on chest radiograph. It is often associated with infection and infarction. The patient may first complain of chest pain but within a few hours develops cough, increasing respiratory and heart rates, hypoxia, and progressive respiratory distress. Physical examination reveals areas of decreased breath sounds and dullness on chest percussion. Treatment involves early recognition and prevention of arterial hypoxemia. Oxygen, fluids, judicious use of analgesic medications, antibiotics, bronchodilators, and RBC transfusion (rarely exchange transfusion) are indicated in therapy for acute chest syndrome. Incentive spirometry may help reduce the incidence of acute chest crisis in patients presenting with pain in the chest or abdomen.

**Pain crisis** is the most common type of vasoocclusive event. The pain usually localizes to the long bones of the arms or legs but may occur in smaller bones of the hands or feet in infancy (dactylitis) or in the abdomen. Painful crises usually last 2 to 7 days. Vasoocclusive crises within the femur may lead to avascular necrosis of the femoral head and chronic hip disease. Treatment of pain crises includes administration of fluids, analgesia (usually narcotics and nonsteroidal anti-inflammatory drugs), and oxygen if the patient is hypoxic. Although pain is often impossible to quantitate, the risk for drug dependency is highly overrated, and appropriate use of analgesics is necessary.

**Priapism** occurs in boys usually between 6 and 20 years old. The child experiences a sudden, painful onset of a

<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>CLINICAL CONDITION</th>
<th>Hb A</th>
<th>Hb S</th>
<th>Hb A2</th>
<th>Hb F</th>
<th>Hb C</th>
<th>OTHER FINDING(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA</td>
<td>Sickle cell trait</td>
<td>55–60</td>
<td>40–45</td>
<td>2–3</td>
<td>–</td>
<td>–</td>
<td>Usually asymptomatic</td>
</tr>
<tr>
<td>SS</td>
<td>Sickle cell anemia</td>
<td>0</td>
<td>85–95</td>
<td>2–3</td>
<td>5–15</td>
<td>–</td>
<td>Clinically severe anemia; Hb F heterogeneous in distribution</td>
</tr>
<tr>
<td>S-β° thalassemia</td>
<td>Sickle cell-β° thalassemia</td>
<td>0</td>
<td>70–80</td>
<td>3–5</td>
<td>10–20</td>
<td>–</td>
<td>Moderately severe anemia; splenomegaly in 50%; smear: hypochromic, microcytic anemia</td>
</tr>
<tr>
<td>S-β+ thalassemia</td>
<td>Sickle cell-β+ thalassemia</td>
<td>10–20</td>
<td>60–75</td>
<td>3–5</td>
<td>10–20</td>
<td>–</td>
<td>Hb F distributed heterogeneously; mild microcytic anemia</td>
</tr>
<tr>
<td>SC</td>
<td>Hb SC disease</td>
<td>0</td>
<td>45–50</td>
<td>–</td>
<td>–</td>
<td>45–50</td>
<td>Moderately severe anemia; splenomegaly; retinopathy; target cells</td>
</tr>
<tr>
<td>S-HPFH</td>
<td>Sickle-hereditary persistence of Hb F</td>
<td>0</td>
<td>70–80</td>
<td>1–2</td>
<td>20–30</td>
<td>–</td>
<td>Often asymptomatic; Hb F is uniformly distributed</td>
</tr>
</tbody>
</table>

Clinical Manifestations of Sickle Cell Anemia

<table>
<thead>
<tr>
<th>MANIFESTATION</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Chronic, onset 3-4 mo of age; may require folate therapy for chronic hemolysis; hemoglobin usually 6-10 g/dL</td>
</tr>
<tr>
<td>Aplastic crisis</td>
<td>Parovirus infection, reticulocytopenia; acute and reversible; may need transfusion</td>
</tr>
<tr>
<td>Sequestration crisis</td>
<td>Massive splenomegaly (may involve liver), shock; treat with transfusion</td>
</tr>
<tr>
<td>Hemolytic crisis</td>
<td>May be associated with G6PD deficiency</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>Hand-foot swelling in early infancy</td>
</tr>
<tr>
<td>Painful crisis</td>
<td>Microvascular painful vasoocclusive infarcts of muscle, bone, bone marrow, lung, intestines</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>Large and small vessel occlusion → thrombosis/bleeding (stroke); requires chronic transfusion</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>Infection, asthma, atelectasis, infarction, fat emboli, severe hypoxemia, infiltrate, dyspnea, absent breath sounds</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>Pulmonary fibrosis, restrictive lung disease, cor pulmonale, pulmonary hypertension</td>
</tr>
<tr>
<td>Priapism</td>
<td>Causes eventual impotence; treated with transfusion, oxygen, or corpora cavernosa-to-spongios a shunt</td>
</tr>
<tr>
<td>Ocular</td>
<td>Retinopathy</td>
</tr>
<tr>
<td>Gallbladder disease</td>
<td>Bilirubin stones; cholecystitis</td>
</tr>
<tr>
<td>Renal</td>
<td>Hematuria, papillary necrosis, renal concentrating defect; nephropathy</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Skeletal</td>
<td>Osteonecrosis (avascular) of femoral or humeral head</td>
</tr>
<tr>
<td>Leg ulceration</td>
<td>Seen in older patients</td>
</tr>
<tr>
<td>Infections</td>
<td>Functional asplenia, defects in properdin system; pneumococcal bacteremia, meningitis, and arthritis; deafness from meningitis; Salmonella and Staphylococcus aureus osteomyelitis; severe Mycoplasma pneumonia</td>
</tr>
<tr>
<td>Growth failure, delayed puberty</td>
<td>May respond to nutritional supplements</td>
</tr>
<tr>
<td>Psychological problems</td>
<td>Narcotic addiction (rare), dependence unusual; chronic illness, chronic pain syndrome</td>
</tr>
</tbody>
</table>

Etiology. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an abnormality in the hexose monophosphate shunt pathway of glycolysis that results in the depletion of reduced nicotinamide adenine dinucleotide phosphate (NADPH) and the inability to regenerate reduced glutathione. When a patient with G6PD is exposed to significant oxidant stress, hemoglobin F decreases the number and severity of vasoocclusive events and frequency of acute chest syndrome and priapism. Hydroxyurea, which increases hemoglobin F, decreases the number and severity of vasoocclusive events and frequency of acute chest syndrome in children as early as 1 year of age. Hematopoietic stem cell transplantation, using a haploidentical sibling match, has cured many children with sickle cell disease. HSCT using alternative donors for children, without a suitable sibling match, is being studied.

Enzymopathies

**Decision-Making Algorithms**
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G6PD, Glucose-6-phosphate dehydrogenase.
*Clinical manifestations with sickle cell trait are unusual but include renal papillary necrosis (hematuria), sudden death on exertion, intraocular hyphema extension, and sickling in unpressurized airplanes.

tumescent penis that will not relax. Therapeutic steps for priapism include the administration of oxygen, fluids, analgesia, and transfusion when appropriate to achieve a hemoglobin S less than 30% (often by partial exchange transfusion). Fluid management requires recognition that renal medullary infarction results in loss of the ability to concentrate urine.

Overt stroke occurs in approximately 8% to 10% of patients with SS disease. These events may present as the sudden onset of an altered state of consciousness, seizures, or focal paralysis. Silent stroke, which is defined as evidence of cerebral infarction on imaging studies but a normal neurologic examination, is more common and occurs in approximately 20% of patients with SS disease. A significant change in school performance or behavior has been associated with silent stroke. Children with Hg SS disease over 3 years of age should be screened for increased risk of stroke using transcranial Doppler (TCD).

**Laboratory Diagnosis.** The diagnosis of hemoglobinopathies is made by identifying the precise amount and type of hemoglobin using hemoglobin electrophoresis, isoelectric focusing, or high-performance liquid chromatography. Every member of an at-risk population should have a precise hemoglobin phenotype performed at birth (preferably) or during early infancy. Most states perform newborn screening for sickle cell disease.

**Treatment.** Direct therapy of sickle cell anemia is evolving. The mainstay of care is supportive measures. The use of chronic RBC transfusions to treat patients who have had a stroke has been very successful. Chronic RBC transfusions have also been used successfully for short time periods to prevent recurrent vasoocclusive painful events, including acute chest syndrome and priapism. Hydroxyurea, which increases hemoglobin F, decreases the number and severity of vasoocclusive events and frequency of acute chest syndrome in children as early as 1 year of age. Hematopoietic stem cell transplantation, using a haploidentical sibling match, has cured many children with sickle cell disease. HSCT using alternative donors for children, without a suitable sibling match, is being studied.
and Oriental Jews, and Arabs is termed the Mediterranean variant and is associated with chronic hemolysis and potentially life-threatening hemolytic disease. Because the gene for G6PD deficiency is carried on the X chromosome, clinical hemolysis is most common in males. Heterozygous females who have randomly inactivated a higher percentage of the normal gene may become symptomatic, as may homozygous females with the A– variant (0.5% to 1% of females of African descent).

**Clinical Manifestations.** G6PD deficiency has two common presentations. Individuals with the A– variant have normal hemoglobin values when well, but develop an acute episode of hemolysis triggered by serious (bacterial) infection or ingestion of an oxidant drug. The RBC morphology during episodes of acute hemolysis is striking, appearing to have “bites” taken out of them (cookie cells). These are areas of absent hemoglobin that are produced by phagocytosis of Heinz bodies by splenic macrophages; as a result, the RBCs appear blistered. Clinically evident jaundice, dark urine resulting from bilirubin pigments, hemoglobinuria when hemolysis is intravascular, and decreased haptoglobin levels are common during hemolytic episodes. Early on, the hemolysis usually exceeds the ability of the bone marrow to compensate, so the reticulocyte count may be low for 3 to 4 days.

**Laboratory Studies.** The diagnosis of G6PD deficiency is based on decreased NADPH formation. G6PD levels during an acute, severe hemolytic episode may be normal, however, because the most deficient cells have been destroyed and reticulocytes are enriched with G6PD. Repeating the test at a later time when the patient is in a steady-state condition, testing the mothers of boys with suspected G6PD deficiency, or performing electrophoresis to identify the precise variant present aids in diagnosis.

**Treatment and Prevention.** The treatment of G6PD deficiency is supportive. Transfusions are indicated when significant cardiovascular compromise is present. Maintaining hydration and urine alkalization protects the kidneys against damage from precipitated free hemoglobin. Hemolysis is prevented by avoidance of known oxidants, particularly long-acting sulfonamides, nitrofurantoin, primaquine, dimeracrol, and moth balls (naphthalene). Fava beans (favisim) have triggered hemolysis, particularly in patients with the Mediterranean variant. Serious infection also is a potential precipitant of hemolysis in G6PD-deficient young children.

**Pyruvate kinase deficiency** is much less common than G6PD deficiency and represents a clinical spectrum of disorders caused by the functional deficiency of pyruvate kinase. Some individuals have a true deficiency state, and others have abnormal enzyme kinetics. The metabolic consequence of pyruvate kinase deficiency is adenosine triphosphate (ATP) depletion, impairing RBC survival. Pyruvate kinase deficiency is usually an autosomal disorder, and most children who are affected (and are not products of consanguinity) are double heterozygotes for two abnormal enzymes. Hemolysis is not aggravated by oxidant stress due to the profound reticulocytosis in this condition. Aplastic crises are potentially life-threatening. The spleen is the site for RBC removal in pyruvate kinase deficiency. Most patients have amelioration of the anemia and a reduction of transfusion requirements after splenectomy.

**Membrane Disorders**

**Etiology.** The biochemical basis of hereditary spherocytosis and hereditary elliptocytosis are similar. Both conditions appear to have a defect in the protein lattice (spectrin, ankyrin, protein 4.2, band 3) that underlies the RBC lipid bilayer and provides stability of the membrane shape. In hereditary spherocytosis, pieces of membrane bud off as microvesicles because of abnormal vertical interaction of the cytoskeletal proteins and uncoupling of the lipid bilayer from the cytoskeleton. When the RBC loses membrane, cell shape changes from a biconcave disk to a spherocyte. The RBC is less deformable when passing through narrow passages in the spleen. Hereditary elliptocytosis is a disorder of spectrin dimer interactions that occurs primarily in individuals of African descent. The transmission of the two variants is usually autosomal dominant, but spontaneous mutations causing hereditary spherocytosis are common. Hereditary pyropoikilocytosis (unusual instability of the erythrocytes when they are exposed to heat at 45°C) is the result of a structural abnormality of spectrin.

**Clinical Manifestations.** Hereditary spherocytosis varies greatly in clinical severity, ranging from an asymptomatic, well-compensated, mild hemolytic anemia that may be discovered incidentally to a severe hemolytic anemia with growth failure, splenomegaly, and chronic transfusion requirements in infancy necessitating early splenectomy. The most common variant of hereditary elliptocytosis is a clinically insignificant morphologic abnormality without shortened RBC survival. The less common variant is associated with spherocytes, ovalocytes, and elliptocytes with a moderate, usually compensated, hemolysis. Far more significant hemolysis occurs in hereditary pyropoikilocytosis. The peripheral blood smear in hereditary pyropoikilocytosis often includes elliptocytes, spherocytes, fragmented RBCs, and striking microcytosis. Such patients may have bizarre blood smears in the newborn period with small, fragmented RBCs.

**Laboratory Diagnosis.** The clinical diagnosis of hereditary spherocytosis should be suspected in patients with even a few spherocytes found on the blood smear because the spleen preferentially removes spherocytes. An incubated osmotic fragility test confirms the presence of spherocytes and increases the likelihood of the diagnosis. The osmotic fragility test result is abnormal in any hemolytic disease in which spherocytes are present—for example, in antibody-mediated hemolysis.

**Treatment.** Splenectomy corrects the anemia and normalizes the RBC survival in patients with hereditary spherocytosis, but the morphologic abnormalities persist. Splenectomy should be considered for any child with symptoms referable to anemia or growth failure, but should be deferred until age 5 years, if possible, to minimize the risk of overwhelming postsplenectomy sepsis and to maximize the antibody response to the polyvalent pneumococcal vaccine. In several reports, partial splenectomy seems to improve the hemolytic anemia and maintain splenic function in host defense.
Hemolytic Anemia Caused by Disorders Extrinsic to the Red Blood Cell
Etiology and Clinical Manifestations

Isoimmune hemolysis is caused by active maternal immunization against fetal antigens that the mother's erythrocytes do not express (see Chapter 62). Examples are antibodies to the A, B, and Rh D antigens; other Rh antigens; and the Kell, Duffy, and other blood groups. Anti-A and anti-B hemolysis is caused by the placental transfer of naturally occurring maternal antibodies from mothers who lack A or B antigen (usually blood type O). Positive results of the direct antiglobulin (Coombs) test on the infant's RBCs (Fig. 150-4), the indirect antiglobulin test on the mother's serum, and the presence of spherocytes and immature erythroid precursors (erythroblastosis) on the infant's blood smear confirm this diagnosis. Isoimmune hemolytic disease varies in clinical severity. There may be no clinical manifestations, or the infant may exhibit jaundice, severe anemia, and hydrops fetalis.

Autoimmune hemolytic anemia is usually an acute, self-limited process that develops after an infection (Mycoplasma, Epstein-Barr, or other viral infections). Autoimmune hemolytic anemia may also be the presenting symptom of a chronic autoimmune disease (systemic lupus erythematosus, lymphoproliferative disorders, or immunodeficiency). Drugs may induce a Coombs-positive hemolytic anemia by forming a hapten on the RBC membrane (penicillin) or by forming immune complexes (quinidine) that attach to the RBC membrane. Antibodies then activate complement-induced intravascular hemolysis. The third type of drug-induced immune hemolysis occurs during treatment with α-methyl dopa and a few other drugs. In this type, prolonged drug exposure alters the RBC membrane, inducing neoantigen formation. Antibodies are produced that bind to the neoantigen; this produces a positive antiglobulin test result far more commonly than it actually induces hemolysis. In each of these conditions, the erythrocyte is an innocent bystander.

A second form of acquired hemolytic disease is caused by mechanical damage to the RBC membrane during circulation. In thrombotic microangiopathy, the RBCs are trapped by fibrin strands in the circulation and physically broken by shear stress as they pass through these strands. Hemolytic uremic syndrome, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura, malignant hypertension, toxemia, and hyperacute renal graft rejection can produce thrombotic microangiopathy. The platelets are usually large, indicating that they are young, but have a decreased survival even if the numbers are normal. Consumption of clotting factors is more prominent in DIC than in the other forms of thrombotic microangiopathy. The smear shows RBC fragments (schistocytes), microspherocytes, teardrop forms, and polychromasia. Other examples of mechanical injury to RBCs include damage by exposure to nonendothelialized surfaces (as in artificial heart valves) or as a result of high flow and shear rates in giant hemangiomas (Kasabach-Merritt syndrome).

Alterations in the plasma lipids, especially cholesterol, may lead to damage to the RBC membrane and shorten RBC survival. Lipids in the plasma are in equilibrium with lipids in the RBC membrane. High cholesterol levels increase the membrane cholesterol and the total membrane surface without affecting the volume of the cell. This condition produces spur cells that may be seen in abetalipoproteinemia and liver diseases. Hemolysis occurs in the spleen, where poor RBC deformability results in erythrocyte destruction. Circulating toxins (e.g., snake venoms and heavy metals) that bind sulfhydryl groups may damage the RBC membrane and induce hemolysis. Irregularly spiculated RBCs (burr cells) are seen in renal failure. Vitamin E deficiency can also cause an acquired hemolytic anemia as a result of abnormal sensitivity of membrane lipids to oxidant stress. Vitamin E deficiency may occur in premature infants who are not being supplemented with vitamin E or who have insufficient nutrition, in infants with severe malabsorption syndromes (including cystic fibrosis), and in infants with transfusional iron overload, which can lead to severe oxidant exposure.

Laboratory Diagnosis. The peripheral blood smear in autoimmune hemolytic anemia usually reveals spherocytes
and occasionally nucleated RBCs. The reticulocyte count varies because some patients have relatively low reticulocyte counts as a result of autoantibodies that cross-react with RBC precursors.

Treatment and Prognosis. Transfusion for the treatment of autoimmune hemolysis is challenging because crossmatching is difficult, as the autoantibodies react with virtually all RBCs. In addition to transfusion, which may be lifesaving, management of autoimmune hemolytic anemia depends on antibody type. Management may involve administration of corticosteroids and, at times, intravenous immunoglobulin. Corticosteroids reduce the clearance of sensitized RBCs in the spleen. In drug-induced hemolysis, withdrawal of the drug usually leads to resolution of the hemolytic process. More than 80% of children with autoimmune hemolytic anemia recover spontaneously.

Many think of coagulation as having intrinsic and extrinsic pathways, but the reality is that these pathways are closely interactive and do not react independently (Fig. 151-2). For ease of use, all coagulation factors are denoted using Arabic rather than Roman numerals to prevent misreading factor VII (7) as factor VIII (8). In vivo, factor 7 autocatalyzes to form small amounts of factor 7a. When tissue is injured, tissue factor is released and causes a burst of factor 7a generation. Tissue factor, in combination with calcium and factor 7a, activates factor 9 and factor 10. The activation of factor 9 by factor 7a results in eventual generation of thrombin, which feeds back on factor 11, generating factor 11a and accelerating thrombin formation. This process explains why deficiency of factor 8 or factor 9 leads to severe bleeding disorders, whereas deficiency of factor 11 is usually mild, and deficiency of factor 12 is asymptomatic.

A series of inhibitory factors serve to tightly regulate the activation of coagulation. Antithrombin III inactivates thrombin and factors 10a, 9a, and 11a. The protein C and protein S system inactivates activated factors 5 and 8, which are cofactors localized in the “tenase” and “prothrombinase” complexes. The tissue factor pathway inhibitor, an anticoagulant protein, limits activation of the coagulation cascade by factor 7a and factor 10a. Fibrinolysis is initiated by the action of tissue plasminogen activator on plasminogen, producing plasmin, the active enzyme that degrades fibrin into split products. Fibrinolysis eventually dissolves the clot and allows normal flow to resume. Deficiencies of anticoagulant proteins may predispose to thrombosis.
Patients with hemostatic disorders may have complaints of either bleeding or clotting. Age at onset of bleeding indicates whether the problem is congenital or acquired. The sites of bleeding (mucocutaneous or deep) and degree of trauma (spontaneous or significant) required to induce injury suggest the type and severity of the disorder. Certain medications (aspirin and valproic acid) are known to exacerbate preexisting bleeding disorders by interfering with platelet function.

The physical examination should characterize the presence of skin or mucous membrane bleeding and deeper sites of hemorrhage into the muscles and joints or internal bleeding sites. The term petechia refers to a non-blanching lesion less than 2 mm in size. Purpura is a group of adjoining petechiae, ecchymoses (bruises) are isolated lesions larger than petechiae, and hematomas are raised, palpable ecchymoses.

The physical examination should also search for manifestations of an underlying disease, lymphadenopathy, hepatosplenomegaly, vasculitic rash, or chronic hepatic or renal disease. Deep venous thrombi may cause warm, swollen (distended), tender, purplish discolored extremities or organs or no findings. Arterial clots cause acute, painful, pale, and poorly perfused extremities. Arterial thrombi of the internal organs present with signs and symptoms of infarction.

**Laboratory Testing**

Screening laboratory studies for bleeding patients include a platelet count, prothrombin time, partial thromboplastin time, fibrinogen, and bleeding time or other screening test of platelet function. Many laboratories have adopted the platelet function analyzer (PFA) to replace the bleeding time as a screening test for platelet function abnormalities and
**Chapter 151 • Hemostatic Disorders**

**Procoagulants**

- APTT
- F 12
- F 12a
- F 11
- F 11a
- F 9
- F 9a
- F 8
- F 8a
- F 10
- F 10a
- F 5
- F 5a
- Prothrombin (F 2)
- Thrombin (2a)
- Fibrinogen (1)
- Fibrin

**Anticoagulants**

- PT
- TF
- TFPI
- P-C/S
- AT-III
- Ca++

**Figure 151-2** Simplified pathways of blood coagulation. The area inside the solid black line is the intrinsic pathway measured by the activated partial thromboplastin time (APTT). The area inside the green line is the extrinsic pathway, measured by the prothrombin time (PT). The area encompassed by both lines is the common pathway. AT-III, Antithrombin III; F, factor; HMWK, high-molecular-weight kininogen; P-C/S, protein C/S; PL, phospholipid; TFPI, tissue factor pathway inhibitor. (Modified from Scott JP, Montgomery RR: Hemorrhagic and thrombotic diseases. In Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors: Nelson Textbook of Pediatrics, ed 18, Philadelphia, 2007, Saunders, p 2061.)

**Figure 151-3** Common causes of bleeding. TAR, Thrombocytopenia with absence of radius (syndrome).

**CAUSES OF BLEEDING**

**HEMATOLOGIC**

- **Thrombocytopenia**
  - Primary
    - Idiopathic thrombocytopenic purpura
    - Neonatal isoimmune
    - TAR syndrome
    - Wiskott-Aldrich syndrome
  - Secondary
    - Malignancy
    - Aplastic anemia
    - Disseminated intravascular coagulation
    - Sepsis
    - Drug-induced
    - Hemolytic-uremic syndrome
    - Hemangioma
    - Hypersplenism
    - Mechanical (artificial heart valve)
    - Autoimmune (systemic lupus erythematosus)
    - Human immunodeficiency virus

- **Coagulopathy**
  - Primary
    - von Willebrand disease
    - Hemophilia
    - Platelet function defect
  - Secondary
    - Disseminated intravascular coagulation
    - Anticoagulants
    - Vitamin K deficiency, including hemorrhagic disease of the newborn
    - Hepatic failure
    - Renal failure
    - Maternal anticonvulsants
    - Anticoagulant drug ingestion (e.g., warfarin, rat poison)

**VASCULAR-NONHEMATOLOGIC**

- Child abuse
- Vasculitis
- Other trauma
- Ulcer
- Varices
- Polyps, tumors
- Ehlers-Danlos syndrome
- Telangiectasia
- Angiodysplasia
von Willebrand disease. The PFA has variable sensitivity and specificity for common bleeding disorders. No single laboratory test can screen for all bleeding disorders. The findings on screening tests for bleeding vary with the specific disorder (Table 151-2).

### Differential Diagnosis

#### Disorders of Platelets

Platelet counts less than 150,000/mm³ constitute **thrombocytopenia**. Mucocutaneous bleeding is the hallmark of platelet disorders, including thrombocytopenia. The risk of bleeding correlates imperfectly with the platelet count. Children with platelet counts greater than 80,000/mm³ are able to withstand all but the most extreme hemostatic challenges, such as surgery or major trauma. Children with platelet counts less than 20,000/mm³ are at risk for spontaneous bleeding. These generalizations are modified by factors such as the age of the platelets (young, large platelets usually function better than old ones) and the presence of inhibitors of platelet function, such as antibodies, drugs (especially aspirin), fibrin degradation products, and toxins formed in the presence of hepatic or renal disease. The size of platelets is routinely measured as the mean platelet volume (MPV). The etiology of thrombocytopenia (Fig. 151-4) may be organized into three mechanisms:

1. Decreased platelet production
2. Increased destruction
3. Sequestration

#### Thrombocytopenia Resulting from Decreased Platelet Production

Primary disorders of megakaryopoiesis (platelet production) are rare in childhood, other than as part of an aplastic syndrome. **Thrombocytopenia with absent radii syndrome** is characterized by severe thrombocytopenia in association with orthopedic abnormalities, especially of the upper
extremity. The thrombocytopenia usually improves over time. Amegakaryocytic thrombocytopenia presents at birth or shortly thereafter with findings of severe thrombocytopenia, but no other congenital anomalies. The marrow is devoid of megakaryocytes and usually progresses to aplasia of all hematopoietic cell lines.

Acquired thrombocytopenia as a result of decreased production is rarely an isolated finding. It is seen more often in the context of pancytopenia resulting from bone marrow failure caused by infiltrative or aplastic processes. Certain chemotherapeutic agents may affect megakaryocytes selectively more than other marrow elements. Cyanotic congenital heart disease with polycythemia often is associated with thrombocytopenia, but this is rarely severe or associated with significant clinical bleeding. Congenital (TORCH [toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex]) and acquired viral infections (human immunodeficiency virus [HIV], Epstein-Barr virus, and measles) and some drugs (anti-convulsants, antibiotics, cytotoxic agents, heparin, and quinidine) may induce thrombocytopenia. Postnatal infections and drug reactions usually cause transient thrombocytopenia, whereas congenital infections may produce prolonged suppression of bone marrow function.

**Figure 151-4 Differential diagnosis of childhood thrombocytopenic syndromes.** The syndromes initially are separated by their clinical appearances. Clues leading to the diagnosis are presented in italics. The mechanisms and common disorders leading to these findings are shown in the lower part of the figure. Disorders that commonly affect neonates are listed in the shaded boxes. HSM, Hepatosplenomegaly; ITP, idiopathic immune thrombocytopenic purpura; NATP, neonatal alloimmune thrombocytopenic purpura; SLE, systemic lupus erythematosus; TAR, thrombocytopenia with absence of radius syndrome; TTP, thrombotic thrombocytopenic purpura; UAC, umbilical artery catheter; WBC, white blood cell. (From Scott JP: Bleeding and thrombosis. In Kliegman RM, Greenbaum LA, Lye PS, editors: Practical Strategies in Pediatric Diagnosis and Therapy, Philadelphia, 2004, Saunders, p 920.)

**Thrombocytopenia Resulting from Peripheral Destruction**

**Etiology.** In a child who appears well, immune-mediated mechanisms are the most common cause of thrombocytopenia resulting from rapid peripheral destruction of antibody-coated platelets by reticuloendothelial cells. Neonatal alloimmune thrombocytopenic purpura (NATP) occurs as a result of sensitization of the mother to antigens present on fetal platelets. Antibodies cross the placenta and attack the fetal platelet (see Chapter 59). Many platelet alloantigens have been identified and sequenced, permitting prenatal diagnosis of the condition in an at-risk fetus. Mothers with idiopathic thrombocytopenic purpura (maternal ITP) or with a history of ITP may have passive transfer of antiplatelet antibodies, with resultant neonatal thrombocytopenia (see Chapter 59). The maternal platelet count is sometimes a useful indicator of the probability that the infant will be affected.

**Clinical Manifestations.** The infant with NATP is at risk for intracranial hemorrhage in utero and during the immediate delivery process. In ITP, the greatest risk seems to be present during passage through the birth canal, during which molding of the head may induce intracranial hemorrhage. Fetal scalp sampling or percutaneous umbilical blood sampling may be performed to measure the fetal platelet count.

**Treatment.** Administration of intravenous immunoglobulin (IVIG) before delivery increases fetal platelet counts and may alleviate thrombocytopenia in infants with NATP and ITP. Delivery by cesarean section is recommended to prevent central nervous system (CNS) bleeding (see Chapter 59). Neonates with severe thrombocytopenia (platelet counts <20,000/mm³) may be treated with IVIG or corticosteroids or both until thrombocytopenia remits. If necessary, infants with NATP may receive washed maternal platelets.

**Idiopathic Thrombocytopenic Purpura**

**Etiology.** Autoimmune thrombocytopenic purpura of childhood (childhood ITP) is a common disorder that usually follows an acute viral infection. Childhood ITP is caused by an antibody (IgG or IgM) that binds to the platelet membrane. The condition results in Fc receptor–mediated splenic destruction of antibody-coated platelets. Rarely, ITP may be the presenting symptom of an autoimmune disease, such as systemic lupus erythematosus (SLE).

**Clinical Manifestations.** Young children typically exhibit ITP 1 to 4 weeks after viral illness, with abrupt onset of petechiae, purpura, and epistaxis. The thrombocytopenia usually is severe. Significant adenopathy or hepatosplenomegaly is
unusual, and the red blood cell (RBC) and white blood cell (WBC) counts are normal.

Diagnosis. The diagnosis of ITP usually is based on clinical presentation and the platelet count and does not often require a bone marrow examination. If atypical findings are noted, however, marrow examination is indicated to rule out an infiltrative disorder (leukemia) or an aplastic process (aplastic anemia). In ITP, an examination of the bone marrow reveals increased megakaryocytes and normal erythroid and myeloid elements.

Treatment and Prognosis. Therapy is seldom indicated for platelet counts greater than 30,000/mm3. Therapy does not affect the long-term outcome of ITP but is intended to increase the platelet count acutely. For moderate and severe clinical bleeding with severe thrombocytopenia (platelet count <10,000/mm3), therapeutic options include prednisone, 2 to 4 mg/kg/24 hours for 2 weeks or IVIG, 1 g/kg/24 hours for 1 to 2 days. All of these approaches seem to decrease the rate of clearance of sensitized platelets, rather than decreasing production of antibody. The optimal choice for therapy (if any) is controversial. Splenectomy is indicated in adult ITP only for life-threatening bleeding. Approximately 80% of children have a spontaneous resolution of ITP within 6 months after diagnosis. Serious bleeding, especially intracranial bleeding, occurs in fewer than 1% of patients with ITP. There is no evidence that early treatment prevents intracranial bleeding.

ITP that persists for 6 to 12 months is classified as chronic ITP. Repeated treatments with IVIG, IV anti-D, or high-dose pulse steroids are effective in delaying the need for splenectomy. Secondary causes of chronic ITP, especially SLE and HIV infection, should be ruled out. Splenectomy induces a remission in 70% to 80% of childhood chronic ITP cases. The risks of splenectomy (surgery, sepsis from encapsulated bacteria, pulmonary hypertension) must be weighed against the risk of severe bleeding.

Other Disorders

Wiskott-Aldrich syndrome is an X-linked disorder characterized by hypogammaglobulinemia, eczema, and thrombocytopenia caused by a molecular defect in a cytoskeletal protein common to lymphocytes and platelets (see Chapter 74). Small platelets are seen on a peripheral blood smear. Nevertheless, thrombocytopenia often is improved by splenectomy. Hematopoietic stem cell transplantation cures the immunodeficiency and thrombocytopenia. Familial X-linked thrombocytopenia can be seen as a variant of Wiskott-Aldrich syndrome or Glanzmann thrombasthenia. Mild abnormalities of platelet aggregation and release, detectable by platelet aggregometry, are far more common. Secondary disorders caused by toxins and drugs (uremia, valproic acid, aspirin, nonsteroidal anti-inflammatory drugs, and infections) may cause a broad spectrum of platelet dysfunction.

Clinical Manifestations. Disorders of platelet function present with mucocutaneous bleeding and a prolonged bleeding time or long PFA closure time and may be primary or secondary. The bleeding time is an insensitive screen for mild and moderate platelet function disorders but is usually prolonged in severe platelet function disorders, such as Bernard-Soulier syndrome or Glanzmann thrombasthenia.

Disorders of Clotting Factors

Etiology. Hereditary deficiencies of most procoagulant proteins lead to bleeding. The genes for factor 8 and factor 9 are on the X chromosome, whereas virtually all the other clotting factors are coded on autosomal chromosomes. Factor 8 and factor 9 deficiencies are the most common severe inherited bleeding disorders. von Willebrand disease is the most common congenital bleeding disorder. Of the procoagulant proteins, low levels of the so-called contact factors (prekallikrein, high-molecular-weight kininogen, and Hageman factor [factor 12]) cause a prolonged activated partial thromboplastin time but are not associated with a predisposition to bleeding.

Hemophilia

Etiology. Hemophilia A (factor 8 deficiency) occurs in 1 in 5000 males. Hemophilia B (factor 9 deficiency) occurs in approximately 1 in 25,000. Clinically the two disorders are indistinguishable other than by their therapy (Table 151-3). The lack of factor 8 or factor 9 delays the generation of thrombin, which is crucial to forming a normal, functional fibrin clot and solidifying the platelet plug that has formed in areas of vascular injury. The severity of the disorder is determined by the degree of clotting factor deficiency.
Clinical Manifestations. Patients with less than 1% (severe hemophilia) factor 8 or factor 9 may have spontaneous bleeding or bleeding with minor trauma. Patients with 1% to 5% (moderate hemophilia) factor 8 or factor 9 usually require moderate trauma to induce bleeding episodes. In mild hemophilia (>5% factor 8 or factor 9), significant trauma is necessary to induce bleeding; spontaneous bleeding does not occur. Mild hemophilia may go undiagnosed for many years, whereas severe hemophilia manifests in infancy when the child reaches the toddler stage. In severe hemophilia, spontaneous bleeding occurs, usually in the muscles or joints (hemarthroses).

Laboratory Studies. The diagnosis of hemophilia is based on a prolonged activated partial thromboplastin time (aPTT). In the aPTT, a surface-active agent activates the intrinsic system of coagulation, of which factors 8 and 9 are crucial components. In factor 8 or factor 9 deficiency, the aPTT is quite prolonged but should correct to normal when the patient’s plasma is mixed 1:1 with normal plasma. When an abnormal aPTT is obtained, specific factor assays are needed to make a precise diagnosis (see Table 151-2) to determine the appropriate factor replacement therapy. Prenatal diagnosis and carrier diagnosis are possible using molecular techniques.

Treatment. Early, appropriate replacement therapy is the hallmark of excellent hemophilia care. Acute bleeding episodes are best treated in the home when the patient has attained the appropriate age and the parents have learned home treatment. Bleeding associated with surgery, trauma, or dental extraction often can be anticipated, and excessive bleeding can be prevented with appropriate replacement therapy. Prophylactic therapy starting in infancy has greatly diminished the likelihood of chronic arthropathy in children with hemophilia. For life-threatening bleeding, levels of 80% to 100% of normal factor 8 or factor 9 are necessary. For mild to moderate bleeding episodes (hemarthroses), a 40% level for factor 8 or a 30% to 40% level for factor 9 is appropriate. The dose can be calculated using the knowledge that 1 U/kg body weight of factor 8 increases the plasma level 2%, whereas 1.5 U/kg of recombinant factor 9 increases the plasma level 1%:

Dose for factor 8 = desired level (\%) × weight (kg) × 0.5

Dose for recombinant factor 9 = desired level (\%) × weight (kg) × 1.5

Desmopressin acetate is a synthetic vasopressin analog with minimal vasopressor effect. Desmopressin triples or quadruples the initial factor 8 level of a patient with mild or moderate (not severe) hemophilia A, but has no effect on factor 9 levels. When adequate hemostatic levels can be attained, desmopressin is the treatment of choice for individuals with mild and moderate hemophilia A. Aminocaproic acid is an inhibitor of fibrinolysis that may be useful for oral bleeding.

Patients treated with older factor 8 or 9 concentrates derived from large pools of plasma donors were at high risk for hepatitis B, C, and D and HIV. Recombinant factor 8 and factor 9 concentrates are safe from virally transmitted illnesses. Acquired immunodeficiency syndrome (AIDS) is the most common cause of death in older hemophilia patients (who received plasma-derived factors). Many older patients also have chronic hepatitis C.

Inhibitors are IgG antibodies directed against transfused factor 8 or factor 9 in congenitally deficient patients. Inhibitors arise in 15% of severe factor 8 hemophiliacs but are less common in factor 9 hemophiliacs. They may be high or low titer and show an anamnestic response to treatment. The treatment of bleeding patients with an inhibitor is difficult. For low titer inhibitors, options include continuous factor 8 infusions. For high titer inhibitors, it is usually necessary to administer a product that bypasses the inhibitor, preferably recombinant factor 7a. Activated prothrombin complex concentrates, used in the past to treat inhibitor patients, paradoxically increased the risks of thrombosis, resulting in fatal complications, such as myocardial
von Willebrand Disease

Etiology. Von Willebrand disease is a common disorder (1% of the population) caused by a deficiency of vWF, an adhesive protein that serves two functions: acting as a bridge between subendothelial collagen and platelets and binding and protecting circulating factor 8 from rapid clearance from circulation. Von Willebrand disease usually is inherited as an autosomal dominant trait and rarely as an autosomal recessive trait. vWF may be either quantitatively deficient (partial = type 1 or absolute = type 3) or qualitatively abnormal (type 2 = dysproteinemia). Approximately 80% of patients with von Willebrand disease have classic (type 1) disease (i.e., a mild to moderate deficiency of vWF). Several other subtypes are clinically important, each requiring different therapy.

Clinical Manifestations. Mucocutaneous bleeding, epistaxis, gingival bleeding, cutaneous bruising, and menorrhagia occur in patients with von Willebrand disease. In severe disease, factor 8 deficiency may be profound, and the patient may also have manifestations similar to hemophilia A (hemarthrosis). Findings in classic von Willebrand disease differ from findings in hemophilia A and B (see Table 151-3).

Laboratory Testing. vWF testing involves measurement of the amount of protein, usually measured immunologically as the vWF antigen (vWF:Ag). vWF activity (vWF:Act) is measured functionally in the ristocetin cofactor assay (vWF:RCo), which uses the antibiotic ristocetin to induce vWF to bind to platelets.

Treatment. The treatment of von Willebrand disease depends on the severity of bleeding. Desmopressin is the treatment of choice for most bleeding episodes in patients with type 1 disease and some patients with type 2 disease. When high levels of vWF are needed but cannot be achieved satisfactorily with desmopressin, treatment with a virally attenuated, vWF-containing concentrate (Humate P) may be appropriate. The dosage can be calculated as for factor 8 in hemophilia. Cryoprecipitate should not be used because it is not virally attenuated. Hepatitis B vaccine should be given before the patient is exposed to plasma-derived products. As in all bleeding disorders, aspirin should be avoided.

Vitamin K Deficiency

For discussion of vitamin K deficiency, see Chapters 27 and 31.

Disseminated Intravascular Coagulation

Etiology. Disseminated intravascular coagulation (DIC) is a disorder in which widespread activation of the coagulation mechanism is usually associated with shock. Normal hemostasis is a balance between hemorrhage and thrombosis. In DIC, this balance is altered by the severe illness, so the patient has activation of coagulation (thrombosis) mediated by thrombin and fibrinolysis mediated by plasmin (bleeding). Coagulation factors—especially platelets, fibrinogen, and factors 2, 5, and 8—are consumed, as are the anticoagulant proteins, especially antithrombin, protein C, and plasminogen. Endothelial injury, tissue release of thromboplastic procoagulant factors, or, rarely, exogenous factors (snake venoms) directly activate the coagulation mechanism (Table 151-4).
Clinical Manifestations. The diagnosis of DIC usually is suspected clinically and is confirmed by laboratory findings of a decline in platelets and fibrinogen associated with elevated prothrombin time, partial thromboplastin time, and elevated levels of D-dimer, formed when fibrinogen is clotted and then degraded by plasmin (Table 151-5). In some patients, DIC may evolve more slowly and there may be a degree of compensation. In a severely ill patient, the sudden occurrence of bleeding from a venipuncture or incision site, gastrointestinal or pulmonary hemorrhage, petechiae, or ecchymosis or evidence of peripheral gangrene or thrombosis suggests the diagnosis of DIC.

Treatment. The treatment of DIC is challenging. General guidelines include the following: treat the disorder inducing the DIC first; support the patient by correcting hypoxia, acidosis, and poor perfusion; and replace depleted blood-clotting factors, platelets, and anticoagulant proteins by transfusion.

Heparin may be used to treat significant arterial or venous thrombotic disease unless sites of life-threatening bleeding coexist.

Thrombosis

Etiology. A hereditary predisposition to thrombosis (see Table 151-1) may be caused by a deficiency of an anticoagulant protein (protein C or S, antithrombin, or plasminogen) (Fig. 151-5), by an abnormality of a procoagulant protein making it resistant to proteolysis by its respective inhibitor (factor 5 Leiden), by a mutation resulting in an increased level of a procoagulant protein (prothrombin 20210), or by damage to endothelial cells (homocysteinemia). Neonates with deficiency syndromes may be particularly vulnerable to thrombosis. Neonates with homozygous protein C deficiency present with purpura fulminans or thrombosis of the major arteries and veins or both. Many individuals with an inherited predisposition to thrombosis exhibit symptoms in adolescence or early adulthood. Protein C deficiency presenting in adulthood usually is inherited as an autosomal dominant trait, whereas the homozygous form usually is autosomal recessive. Protein S and antithrombin III deficiencies are inherited as autosomal dominant traits. Factor 5 Leiden is the most common hereditary cause of a predisposition to thrombosis, appearing in 3% to 5% of whites. Acquired antiphospholipid antibodies (anticardiolipin and lupus anticoagulant) also predispose to thrombosis.

Clinical Manifestations. Neonates and adolescents are the most likely pediatric patients to present with thromboembolic disease. Indwelling catheters, vasculitis, sepsis, immobilization, nephrotic syndrome, coagulopathy, trauma, infection, surgery, inflammatory bowel disease, oral contraceptive agents, pregnancy, and abortion all predispose to thrombosis. The manifestations of pulmonary emboli vary from no findings to chest pain, diminished breath sounds, a loud S2, cyanosis, tachypea, and hypoxemia.

Diagnostic and Imaging Studies. Venous thrombosis can be detected noninvasively by ultrasound Doppler flow compression studies. The gold standard for diagnosis is the venogram. An abnormal (high probability) ventilation-perfusion scan or detection of an intravascular thrombus on helical computed tomography (CT) is diagnostic of pulmonary emboli. There are no appropriate screening studies for thrombotic disorders. Diagnosis of a congenital or acquired predisposition to thrombosis requires a battery of specific assays.

Treatment. Therapy of thrombotic disorders depends on the underlying condition and usually involves standard or low-molecular-weight heparin and then longer term anticoagulation with warfarin. Major vessel thrombosis or life-threatening thrombosis may necessitate treatment with fibrinolytic agents (recombinant tissue plasminogen activator). In newborns, inherited deficiency syndromes may present as emergencies and necessitate replacement with plasma, antithrombin III concentrates, or protein C concentrates.
Transfusion of red blood cells (RBCs), platelets, plasma, cryoprecipitate, and granulocytes can be life-saving or life-maintaining (Table 152-1). Whole blood is rarely indicated and is most useful to provide both oxygen-carrying capacity and functional procoagulant and anticoagulant factors. Otherwise, packed RBCs are used to treat anemia to increase oxygen-carrying capacity. RBC transfusions should not be used to treat asymptomatic nutritional deficiencies that can be corrected by administering the appropriate deficient nutrient (iron or folic acid).

Blood component therapy requires proper anticoagulation of the component unit, screening for infectious agents and blood group compatibility testing before administration. Typical transfusion reactions are listed in Table 152-2. Transfusion may also result in circulatory overload, especially in the presence of cardiopulmonary deficiency. Filtering of blood products to remove white blood cells (WBCs) may prevent febrile reactions. Long-term complications of transfusions...
include graft-versus-host disease and infectious diseases such as hepatitis B (<1:250,000 units) and C (1:1,600,000 units), human immunodeficiency virus (<1:1,800,000 units), malaria, syphilis, babesiosis, brucellosis, and Chagas disease. Patients who are chronically transfused are more prone to iron overload and alloimmunization to RBCs and platelets.

Suggested Reading
Childhood cancer is rare; only about 1% of new cancer cases in the United States occur among children younger than 19 years of age. Hematopoietic tumors (leukemia, lymphoma) are the most common childhood cancers, followed by brain/central nervous system (CNS) tumors and sarcomas of soft tissue and bone (Fig. 153-1). There is wide variability in the age-specific incidence of childhood cancers. Embryonal tumors, such as neuroblastoma and retinoblastoma, peak during the first 2 years of life; acute lymphoblastic leukemia peaks during early childhood (ages 2 to 5 years); osteosarcoma peaks during adolescence; and Hodgkin disease peaks during late adolescence (Fig. 153-2). The overall incidence of cancer among white children is higher than that among other ethnic groups and is twice that of African American children in the United States.

**HISTORY**

Many signs and symptoms of childhood cancer are nonspecific. Although most children with fever, fatigue, weight loss, or limp do not have cancer, each of these symptoms may be a manifestation of an underlying malignancy. Uncommonly a child with cancer will have no symptoms at all. An abdominal mass may be palpated on routine examination, or a complete blood count (CBC) may be unexpectedly abnormal. Some children have a genetic susceptibility to cancer and should be screened appropriately (Table 153-1).

It is important to explore quality, duration, location, severity, and precipitating events of the chief complaint. A prominent lymph node that does not resolve (with or without antibiotics) may warrant a biopsy. A limp that does not improve within weeks should prompt a CBC and a radiograph or a bone scan. Persistent headaches or morning vomiting should prompt a computed tomography (CT) or magnetic resonance imaging (MRI) scan of the head. Fever, night sweats, or weight loss should raise the concern for lymphoma. In addition it is important to obtain the birth history, medical and surgical history, growth history, developmental history, family history, and social history.

**PHYSICAL EXAMINATION**

Growth parameters and vital signs are important to obtain in all patients. Pulse oximetry should be obtained if respiratory symptoms are present. The overall appearance of the patient should be noted, particularly general appearance, pain, cachexia, pallor, and respiratory distress. Palpable masses should be measured. Lymphadenopathy and organomegaly should be quantified, if present. A thorough examination of the skin may reveal rashes, bruises, and petechiae. Careful neurologic and ophthalmologic examinations are crucial if headache or vomiting is present, because the vast majority of patients with CNS tumors have abnormal neurologic examinations.

**COMMON MANIFESTATIONS**

The most common manifestations of childhood cancer are fatigue, anorexia, malaise, pain, fever, abnormal lump or mass, pallor, bruising, petechiae, bleeding, headache, vomiting, visual changes, weight loss, and night sweats (Table 153-2). Lymphadenopathy and organomegaly are common in leukemia, particularly with T-cell acute lymphoblastic leukemia (ALL) or non-Hodgkin lymphoma. Patients with solid tumors usually have a palpable or measurable mass. Other signs and symptoms may include limp, cough, dyspnea, cranial nerve palsies, and papilledema. In general malignant masses are firm, fixed, and nontender, whereas masses that are infectious or inflammatory in nature are relatively softer, mobile, and tender to palpation.
DIFFERENTIAL DIAGNOSIS

Distinguishing a malignant process from another disease can be difficult. Ultimately a tissue diagnosis (from bone marrow or solid tumor biopsy) with pathologic confirmation is required to confirm a diagnosis of cancer. Infection commonly masquerades as a potential malignancy. In particular, Epstein-Barr virus, cytomegalovirus, and mycobacterial infections can mimic leukemia or lymphoma by causing fever, lymphadenopathy, organomegaly, weight loss, and abnormal blood counts. Trauma may produce swelling that can mimic solid tumors. Idiopathic thrombocytic purpura and iron deficiency can produce thrombocytopenia and anemia, respectively. Immune deficiencies or irregularities (autoimmune hemolytic anemia or neutropenia) can also produce cytopenias. Juvenile idiopathic arthritis and other collagen vascular disease can cause musculoskeletal pain and anemia, mimicking leukemia. Benign tumors are relatively common in children, including mature germ cell tumors/hamartomas, hemangiomas or other vascular tumors, mesoblastic nephromas, and bone cysts.

INITIAL DIAGNOSTIC EVALUATION

Screening Tests

A CBC with differential and review of the peripheral blood smear is the best screening test for many pediatric malignancies. Leukopenia (with or without neutropenia), anemia, or thrombocytopenia may be present in leukemia or any cancer that invades the bone marrow (e.g., neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma). Leukemia may also produce leukocytosis, usually with blasts present on the peripheral blood smear. An isolated cytopenia (neutropenia, anemia, or thrombocytopenia) widens the differential diagnosis but still could be the only abnormal laboratory finding. Of note, a
patient with leukemia may also have a normal CBC. Lactate dehydrogenase and uric acid are often elevated in fast-growing tumors (leukemia or lymphoma) and occasionally in sarcomas or neuroblastoma. In many cases, it is appropriate to assess electrolytes and renal and hepatic function in the screening process. Elevated blood pressure, if confirmed by repeat measurements, should prompt a urine analysis, as should the palpation of an abdominal mass.

**Diagnostic Imaging**

A chest x-ray (CXR) (posteroanterior and lateral) is the best screening radiographic study for a patient with suspicious cervical lymphadenopathy, fever, and weight loss. Mediastinal masses and pleural effusions can often be detected on CXR. Abdominal signs or symptoms warrant an ultrasound or CT. Persistent headache, vomiting, or abnormal neurologic findings should lead to a head CT or MRI. For suspected bone tumors, plain radiographs are indicated and will usually reveal the lesion(s), if present. Radiographs may be normal when a bony pelvic lesion is suspected; a CT or MRI should be obtained. Other imaging studies to delineate a mass and to search for suspected metastases are often indicated, but these decisions are usually best left to the pediatric oncology team. Table 153-3 shows the general use of diagnostic imaging following confirmation of a diagnosis of cancer, assessing the primary tumor and for metastases. Positron emission tomography (PET) has proved useful for staging and assessing response for some pediatric cancers, especially lymphomas. Metaiodobenzylguanidine (mIBG) scans are useful for neuroblastoma.

<table>
<thead>
<tr>
<th>CANCER TYPE</th>
<th>RISK FACTOR</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoid leukemia</td>
<td>Ionizing radiation</td>
<td>Prenatal diagnostic x-ray exposure increases risk. Therapeutic irradiation for cancer treatment also increases risk.</td>
</tr>
<tr>
<td></td>
<td>Genetic conditions</td>
<td>Down syndrome is associated with an estimated 10- to 20-fold increased risk. Neurofibromatosis 1, Bloom syndrome, and ataxia-telangiectasia, among others, are associated with an elevated risk.</td>
</tr>
<tr>
<td>Acute myeloid leukemias</td>
<td>Chemotherapeutic agents</td>
<td>Alkylating agents and epipodophyllotoxins increase risk.</td>
</tr>
<tr>
<td></td>
<td>Genetic factors</td>
<td>Down syndrome and neurofibromatosis 1 are strongly associated. Familial monosomy 7 and several other genetic syndromes are also associated with increased risk. Patients treated with radiation therapy for other cancers.</td>
</tr>
<tr>
<td>Brain cancers</td>
<td>Therapeutic ionizing radiation to the head</td>
<td>Neurofibromatosis 1 is strongly associated with optic gliomas and, to a lesser extent, with other central nervous system tumors. Tuberous sclerosis and several other genetic syndromes are associated with increased risk.</td>
</tr>
<tr>
<td></td>
<td>Genetic factors</td>
<td>Monozygotic twins and siblings are at increased risk.</td>
</tr>
<tr>
<td>Hodgkin disease</td>
<td>Family history</td>
<td>Epstein-Barr virus is associated with increased risk.</td>
</tr>
<tr>
<td></td>
<td>Infections</td>
<td>Acquired and congenital immunodeficiency disorders and immunosuppressive therapy increase risk.</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Immunodeficiency</td>
<td>Epstein-Barr virus is associated with increased risk.</td>
</tr>
<tr>
<td></td>
<td>Infections</td>
<td>Mutations in the Rb gene on chromosome 14</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>Ionizing radiation</td>
<td>Cancer radiation therapy and high radium exposure increase risk.</td>
</tr>
<tr>
<td></td>
<td>Genetic factors</td>
<td>Increased risk is apparent with Li-Fraumeni syndrome and hereditary retinoblastoma.</td>
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<tr>
<td>Ewing sarcoma</td>
<td>Race</td>
<td>Incidence is about nine times higher in white children than in black children in the United States.</td>
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<tr>
<td>Neuroblastoma</td>
<td>Genetic factors</td>
<td>Chromosome 6p22 variants and mutations in the ALK and PHOX genes are associated with increased risk.</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Genetic factors</td>
<td>Li-Fraumeni syndrome and neurofibromatosis 1 are associated with increased risk.</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>Congenital anomalies</td>
<td>Aniridia, Beckwith-Wiedemann syndrome, and other congenital and genetic conditions are associated with increased risk.</td>
</tr>
<tr>
<td>Renal medullary carcinoma</td>
<td>Sickle cell trait</td>
<td>Etiology is unknown.</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Congenital anomalies and genetic conditions</td>
<td>Li-Fraumeni syndrome and neurofibromatosis 1 are associated with increased risk.</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>Prematurity</td>
<td>Beckwith-Wiedemann syndrome, hemihypertrophy, Gardner syndrome, and familial adenomatous polyposis are associated with increased risk.</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Infections</td>
<td>Hepatitis B virus infection increases risk.</td>
</tr>
<tr>
<td>Malignant germ cell tumors</td>
<td>Cryptorchidism</td>
<td>Cryptorchidism is a risk factor for testicular germ cell tumors.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIGN/SYMPOTOM</th>
<th>SIGNIFICANCE</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pallor, anemia</td>
<td>Bone marrow infiltration</td>
<td>Leukemia, neuroblastoma</td>
</tr>
<tr>
<td>Petechiae, thrombocytopenia</td>
<td>Bone marrow infiltration</td>
<td>Leukemia, neuroblastoma</td>
</tr>
<tr>
<td>Fever, neutropenia</td>
<td>Bone marrow infiltration</td>
<td>Leukemia, neuroblastoma</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain, limp, arthralgia</td>
<td>Primary bone tumor, metastasis to bone</td>
<td>Osteosarcoma, Ewing sarcoma, leukemia, neuroblastoma</td>
</tr>
<tr>
<td>Fever of unknown origin, weight loss, night sweats</td>
<td>Lymphoreticular malignancy</td>
<td>Hodgkin disease, non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Painless lymphadenopathy</td>
<td>Lymphoreticular malignancy, metastatic solid tumor</td>
<td>Leukemia, Hodgkin disease, non-Hodgkin lymphoma, Burkitt lymphoma, thyroid carcinoma</td>
</tr>
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<td>Cutaneous lesion</td>
<td>Primary or metastatic disease</td>
<td>Neuroblastoma, leukemia, Langerhans cell histiocytosis, melanoma</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>Abdominal/pelvic organ</td>
<td>Neuroblastoma, Wilms tumor, lymphoma, hepatoblastoma, germ cell tumor</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Sympathetic nervous system tumor</td>
<td>Neuroblastoma, pheochromocytoma, Wilms tumor</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Vasoactive intestinal polypeptide</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Soft tissue mass</td>
<td>Local or metastatic tumor</td>
<td>Ewing sarcoma, osteosarcoma, neuroblastoma, thyroid carcinoma, rhabdomyosarcoma, germ cell tumor</td>
</tr>
<tr>
<td>Diabetes insipidus, galactorrhea, poor growth</td>
<td>Neuroendocrine involvement of hypothalamus or pituitary gland</td>
<td>Adenoma, craniopharyngioma, prolactinoma, Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>Emesis, visual disturbances, ataxia, headache, papilledema, cranial nerve palsies</td>
<td>Increased intrathecal pressure</td>
<td>Primary brain tumor; metastasis</td>
</tr>
<tr>
<td><strong>Ophthalmologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocoria</td>
<td>White pupil</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>Periorbital ecchymosis</td>
<td>Metastasis</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Miosis, ptosis, heterochromia</td>
<td>Horner syndrome: compression of cervical sympathetic nerves</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opsomyoclonus, ataxia</td>
<td>Neurotransmitters (?)</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Autoimmunity (?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exophthalmos, proptosis</td>
<td>Orbital tumor</td>
<td>Rhabdomyosarcoma, lymphoma</td>
</tr>
<tr>
<td><strong>Thoracic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior mediastinal mass</td>
<td>Cough, stridor, pneumonia, tracheal-bronchial compression</td>
<td>Germ cell tumor, T-cell lymphoma, Hodgkin disease, primary mediastinal large B-cell lymphoma</td>
</tr>
<tr>
<td>Posterior mediastinal mass</td>
<td>Vertebral or nerve root compression; dysphagia</td>
<td>Neuroblastoma, ganglioneuroblastoma, ganglioneuroma</td>
</tr>
</tbody>
</table>
Table 153-3

Minimum Workup Required for Common Pediatric Malignancies to Assess Primary Tumor and Potential Metastases

<table>
<thead>
<tr>
<th>MALIGNANCY</th>
<th>BMA/bx</th>
<th>CXR</th>
<th>CT SCAN</th>
<th>MRI</th>
<th>BONE SCAN</th>
<th>CSF ANALYSIS</th>
<th>MARKER(S)</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>PET or gallium scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS tumors</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>VMA, HVA</td>
<td>mIBG scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>Yes</td>
<td>Yes</td>
<td>(chest)</td>
<td>(primary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>Yes</td>
<td>Yes</td>
<td>(chest)</td>
<td>(primary)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germ cell tumors</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver tumors</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>±</td>
<td>Yes, if MRI not available</td>
<td>Yes (brain)</td>
<td>±</td>
<td></td>
<td>Rb gene analysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AFP, Alpha-fetoprotein; BMA/bx, bone marrow aspirate/biopsy; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; CXR, chest x-ray; β-hCG, beta-human chorionic gonadotropin; HVA, homovanillic acid; mIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; PET, positron emission tomography; Rb, retinoblastoma; VMA, vanillylmandelic acid.

*Individual cases may require additional studies.

Chapter 154

PRINCIPLES OF CANCER TREATMENT

The overall goal of pediatric oncology is to cure all patients with minimal toxicity. Treatment for children with cancer is often multimodal and may involve surgery, radiation therapy, and chemotherapy. Surgery and radiation are generally local treatment modalities (an exception is total body irradiation as part of a bone marrow or stem cell transplant), whereas chemotherapy has both local and systemic effects.

Primary prevention strategies for most pediatric malignancies are unknown. Two exceptions are the use of hepatitis B vaccine to lower the rates of hepatocellular carcinoma and the use of human papillomavirus vaccine to reduce the risk of cervical, vulvar, and vaginal cancers. Childhood malignancies are not associated with tobacco or alcohol use, dietary factors, or sun exposure. Treatment with certain chemotherapy agents and radiation therapy increases the rate of second malignancies. Secondary prevention may be accomplished by screening the at-risk child (e.g., a child with Beckwith-Wiedemann syndrome or twin of a leukemia patient), but these opportunities are rare.

ONCOLOGIC EMERGENCIES

Adverse effects of tumors and treatments may result in oncologic emergencies in children and adolescents (Table 154-1). Mediastinal masses from lymphoma can cause life-threatening airway obstruction. Tumors with a large tumor burden (e.g., lymphoma, leukemia) may affect renal function adversely from tubular deposition of uric acid crystals. Allopurinol or rasburicase can be administered before chemotherapy to minimize this effect.

A common metabolic emergency is tumor lysis syndrome, often seen in treatment of leukemia and lymphoma. Large amounts of phosphate, potassium, and uric acid are released into the circulation from lysed cells. Overwhelming infection and spinal cord compression with neurologic compromise are other oncologic emergencies.

SURGERY

Appropriate imaging (usually with computed tomography [CT] or magnetic resonance imaging [MRI]) for solid tumors presenting as a palpable mass or mass-related symptoms (pain, respiratory distress, intestinal obstruction) should be obtained and followed by resection (when possible) or biopsy (if complete resection is not feasible). An exception to this is a suspected lymphoma, for which a biopsy may be needed. However, almost all pediatric lymphomas are chemosensitive and do not require surgical resection.

It is crucial to determine the amount of tissue required and the appropriate distribution of the tissue for testing so that all necessary studies are performed. A general oncologic surgery principle is to resect not just the tumor, but also, in most cases, a surrounding margin of normal tissue to ensure the entire tumor has been resected.
CHEMOTHERAPY

Because most pediatric solid tumors have a high risk for micrometastatic disease at the time of diagnosis, chemotherapy is used in almost all cases (Table 154-2). Exceptions include low-stage neuroblastoma and Wilms tumor (particularly in infants) and low-grade central nervous system (CNS) tumors. For patients with localized solid tumors, chemotherapy administered after removal of the primary tumor is referred to as **adjuvant therapy**. Chemotherapy administered while the primary tumor is still present is referred to as **neoadjuvant chemotherapy**. Neoadjuvant chemotherapy has a number of potential benefits, including an early attack on...
<table>
<thead>
<tr>
<th><strong>DRUG</strong></th>
<th><strong>ACTION</strong></th>
<th><strong>METABOLISM</strong></th>
<th><strong>EXCRETION</strong></th>
<th><strong>INDICATION</strong></th>
<th><strong>ACUTE TOXICITY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Folic acid antagonist; inhibits dihydrofolate reductase</td>
<td>Hepatic</td>
<td>Renal, 50%–90% excreted unchanged; biliary</td>
<td>ALL, lymphoma, medulloblastoma, osteosarcoma</td>
<td>Myelosuppression (nadir 7–10 days), mucositis, dermatitis, hepatitis, renal and CNS effects with high-dose administration; prevent with hydration and leucovorin, monitor levels</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>Purine analog</td>
<td>Hepatic</td>
<td>Renal</td>
<td>ALL</td>
<td>Myelosuppression; hepatitis; mucositis; allopurinol increases toxicity</td>
</tr>
<tr>
<td>Cytosine arabinoside (Ara-C)</td>
<td>Pyrimidine analog; inhibits DNA polymerase</td>
<td>Hepatic</td>
<td>Renal</td>
<td>ALL, AML, lymphoma</td>
<td>Myelosuppression, conjunctivitis, mucositis, neurotoxicity</td>
</tr>
<tr>
<td><strong>Alkylating Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylates guanine; inhibits DNA synthesis</td>
<td>Hepatic</td>
<td>Renal</td>
<td>ALL, lymphoma, sarcoma, brain tumors</td>
<td>Myelosuppression; hemorrhagic cystitis</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Similar to cyclophosphamide</td>
<td>Hepatic</td>
<td>Renal</td>
<td>Lymphoma, Wilms tumor, sarcoma, germ cell and testicular tumors</td>
<td>Similar to cyclophosphamide; neurotoxicity, cardiac toxicity</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin and daunorubicin</td>
<td>Binds to DNA, intercalation</td>
<td>Hepatic</td>
<td>Biliary, renal</td>
<td>ALL, AML, osteosarcoma, Ewing sarcoma, lymphoma, neuroblastoma</td>
<td>Cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, radiation dermatitis, arrhythmia</td>
</tr>
<tr>
<td>Dactinomycin</td>
<td>Binds to DNA, inhibits transcription</td>
<td>Renal, stool, 30% excreted as unchanged drug</td>
<td>Wilms tumor, rhabdomyosarcoma, Ewing sarcoma</td>
<td>Tissue necrosis on extravasation, myelosuppression, hepatopathy with thrombocytopenia, stomatitis</td>
<td></td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Binds to DNA, cuts DNA</td>
<td>Hepatic</td>
<td>Renal</td>
<td>Hodgkin disease, lymphoma, germ cell tumors</td>
<td>Pneumonitis, stomatitis, Raynaud phenomenon, pulmonary fibrosis, dermatitis</td>
</tr>
<tr>
<td><strong>Vinca Alkaloids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>Inhibits microtubule formation</td>
<td>Hepatic</td>
<td>Biliary</td>
<td>ALL, lymphoma, Wilms tumor, Hodgkin disease, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, brain tumors</td>
<td>Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Inhibits microtubule formation</td>
<td>Hepatic</td>
<td>Biliary</td>
<td>Hodgkin disease, Langerhans cell histiocytosis</td>
<td>Local cellulitis, myelosuppression</td>
</tr>
<tr>
<td><strong>Enzymes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asparaginase</td>
<td>Depletion of asparagine</td>
<td>—</td>
<td>Reticuloendothelial system</td>
<td>ALL, AML</td>
<td>Allergic reaction; pancreatitis, hyperglycemia, platelet dysfunction and coagulopathy, encephalopathy, stroke, thrombosis</td>
</tr>
</tbody>
</table>
presumed micrometastatic disease, shrinkage of the primary tumor to facilitate local control, and additional time to plan for definitive surgery.

Resistance to a particular chemotherapeutic agent can develop in a number of ways: decreased influx into or increased efflux of the chemotherapeutic agent from the malignant cell; mutation in the target tissue so that it cannot be inhibited by the drug; amplification of a drug target to overcome inhibition; and blockade of normal cellular processes leading to programmed cell death or apoptosis. Because mutation is an ongoing process in malignant tumors, it follows that certain subpopulations of tumor cells within a tumor may be more or less sensitive to any particular chemotherapy drug. Given this fact, combinations of chemotherapy drugs are used, as opposed to sequential single agents, to treat the various forms of childhood cancer.

The blood-brain barrier prevents the penetration of chemotherapeutic drugs into the CNS; instillation of the chemotherapeutic agent directly into the cerebrospinal fluid (by lumbar puncture) may be necessary. Radiation therapy also circumvents the blood-brain barrier.

### Radiation Therapy

Radiation therapy is the process of delivering ionizing radiation to malignant cells in order to kill them directly or, more commonly, prevent them from dividing by interfering with DNA replication. Conventional radiation therapy uses photons, but atomic particles such as electrons, protons, and neutrons can also be used. Not all tumors are radiosensitive, and radiation therapy is not necessary in all tumors that are radiosensitive.

### Other Therapies

Certain cancers have been treated with cytokines, biologic response modifiers, or monoclonal antibodies in addition to standard treatments. **Targeted therapies** specifically target the tumor cells, sparing normal host cells. Imatinib mesylate is a protein kinase inhibitor that targets the effects of the t(9;22) translocation of chronic myeloid leukemia and acute lymphoblastic leukemia. Rituximab is a monoclonal antibody directed against the cell surface antigen CD20 expressed in some lymphomas. Ch14.18 is an anti-GD2 monoclonal antibody used for neuroblastoma.

Supportive care also plays an important role in pediatric oncology, including the use of appropriate antimicrobial agents, blood products, nutritional support, intensive care, and integrative therapies.

### Adverse Effects

Because chemotherapy agents are cellular toxins, numerous adverse effects are associated with their use. Bone marrow suppression, immunosuppression, nausea, vomiting, and alopecia are general adverse effects of commonly used chemotherapy drugs. Each chemotherapy drug also has specific toxicities. Doxorubicin can cause cardiac damage; cisplatin can cause renal damage and ototoxicity; cyclophosphamide and ifosfamide can cause hemorrhagic cystitis; and vincristine can cause peripheral neuropathy. Radiation therapy produces many adverse effects such as mucositis, growth retardation, organ dysfunction, and the later development of secondary cancers. Significant therapy-related **late effects** may develop in pediatric cancer patients (Table 154-3).
LEUKEMIA

ETIOLOGY
The etiology of childhood leukemia is unknown and is probably multifactorial. Genetics and environmental factors play important roles. There are many recurrent nonrandom chromosomal translocations in leukemia cells. A translocation may lead to the formation of a new gene, whose expression may lead to a novel protein with transforming capabilities. In chronic myelogenous leukemia (CML) and some cases of acute lymphoblastic leukemia (ALL), a translocation between chromosomes 9 and 22 results in a fusion gene incorporating parts of two genes, BCR and ABL. The protein formed by this novel gene plays an important role in the development of the leukemias. In addition, certain constitutional genotypes can predispose a child to the development of acute leukemia. Patients with Down syndrome, Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and neurofibromatosis I all have an increased risk of acute leukemia. Siblings of children with leukemia are at increased risk of developing leukemia (approximately twofold to fourfold above the childhood population). This risk increases for twin siblings (up to 25% for monozygotic twins). In certain patients with leukemia, the unique antigen receptor gene rearrangement or the specific chromosomal translocation characterizing the patient's leukemic clone can be demonstrated in cord blood cells and neonatal blood spots used for screening for metabolic diseases, suggesting a possible in utero etiology. There are reports of familial leukemia. Environmental factors that may increase the risk of leukemia include ionizing radiation and exposure to certain chemotherapy agents, particularly the topoisomerase II inhibitors.

EPIDEMIOLOGY
Each year 2500 to 3500 new cases of childhood leukemia occur in the United States. The disease affects about 40 per 1 million children under the age of 15 years. ALL accounts for approximately 75% of cases. Acute myelogenous leukemia (AML) accounts for 15% to 20%, and CML accounts for less than 5% of cases. Other chronic leukemias, including juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, and chronic lymphocytic leukemia, are rare in childhood.

ALL and AML are classified according to the World Health Organization system (Table 155-1), although many clinicians and pathologists still use the French-American-British system for AML. ALL is classified according to cell lineage as either B-lineage or T-lineage. The incidence of ALL peaks at 2 to 5 years of age and is higher in boys than in girls. T-cell ALL, in particular, is associated with male predominance as well as an older age of peak incidence. In the United States, ALL is more common in white than in African American children. The incidence of AML is relatively high in the neonatal period then drops and stabilizes until adolescence when there is a slight increase, which continues into adulthood, especially beyond 55 years of age. Males and females are equally affected by AML. Hispanic and African American children have slightly higher incidence rates than white children.

CLINICAL MANIFESTATIONS

<table>
<thead>
<tr>
<th>Problem</th>
<th>Etiologic Agent(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
<td>Alkylating agents; radiation</td>
</tr>
<tr>
<td>Second cancers</td>
<td>Genetic predisposition; radiation; alkylating agents, etoposide, topoisomerase II inhibitors</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Methotrexate, 6-mercaptopurine; radiation</td>
</tr>
<tr>
<td>Hepatic venoocclusive disease</td>
<td>High-dose, intensive chemotherapy (busulfan, cyclophosphamide) ± bone marrow transplant</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>Radiation</td>
</tr>
<tr>
<td>Pulmonary (fibrosis)</td>
<td>Radiation; bleomycin, busulfan</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Doxorubicin, daunorubicin; radiation</td>
</tr>
<tr>
<td>Leukoencephalopathy</td>
<td>Cranial radiation ± methotrexate</td>
</tr>
<tr>
<td>Cognition/intelligence</td>
<td>Cranial radiation ± methotrexate</td>
</tr>
<tr>
<td>Pituitary dysfunction</td>
<td>Cranial radiation</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>Stress, anxiety, death of peers; conditioned responses to chemotherapy</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>Radiation</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>

Signs and symptoms of acute leukemias are related to the infiltration of leukemic cells into normal tissues, resulting in either bone marrow failure (anemia, neutropenia, thrombocytopenia) or specific tissue infiltration (lymph nodes, liver, spleen, brain, bone, skin, gingiva, testes). Common presenting symptoms are fever, pallor, petechiae or ecchymoses, lethargy, malaise, anorexia, and bone or joint pain. Physical examination frequently reveals lymphadenopathy and hepatosplenomegaly. The tests and central nervous system (CNS) are common extramedullary sites for ALL; neurologic symptoms or a painless enlargement of one or both testes may be seen. Patients with T-cell ALL often have high white blood cell (WBC) counts, anterior mediastinal masses, bulky disease
patients have a WBC count greater than 50,000/mm3. Defin-

The WBC count may be low, normal, or high; 15% to 20% of

blood counts; anemia and thrombocytopenia are common.

bone marrow aspirate, or both. Most patients have abnormal

immature blast cells on either the peripheral blood smear,

The diagnosis of acute leukemia is confirmed by findings of

cytochemical staining patterns.

*The designations M0 to M7 are those of the French-American- British

classification system for AML, which predated the World Health Organization

system and is still used by many clinicians and pathologists.

Modified from World Health Organization Classification.

MLL, Mixed lineage leukemia.

*The designations M0 to M7 are those of the French-American- British

classification system for AML, which predated the World Health Organization

system and is still used by many clinicians and pathologists.

be undertaken in all cases of acute leukemia. Certain types of

both lymphoid and myeloid leukemias have specific chromo-

somal abnormalities. In ALL, the t(12;21) translocation is most

common (approximately 20% of all cases) and is associated

with a favorable prognosis. The t(9;22) translocation occurs in

less than 5% of cases and is associated with a poor prognosis.

The t(4;11) translocation (and other translocations involving

the MLL gene on chromosome 11) often occurs in infants and

patients with secondary AML and is generally associated with

a poor prognosis. Fluorescent in situ hybridization or poly-

merase chain reaction techniques are now used in most cases

of leukemia because many chromosomal abnormalities may

not be apparent on routine karyotypes. DNA microarray tech-

niques are gaining relevance and will likely become standard

in the future. A lumbar puncture should always be performed

at the time of diagnosis to evaluate the possibility of CNS

involvement. A chest x-ray should be obtained in all patients

to exclude an anterior mediastinal mass, which is commonly

seen in T-cell ALL. Electrolytes, calcium, phosphorus, uric

acid, and renal and hepatic function should be monitored in

all patients.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of acute leukemia includes non-
malignant and malignant diseases. Infection is probably the

most common mimic of acute leukemia, particularly the

Epstein-Barr virus infection. Other infections (cytomega-

lovirus, pertussis, mycobacteria) also can produce signs and

symptoms common to leukemia. Noninfectious diagnostic

considerations include aplastic anemia, histiocytosis, juvenile

rheumatoid arthritis, immune thrombocytopenic purpura,

and congenital or acquired conditions that lead to neutrope-

nia or anemia. Several malignant diagnoses also can mimic

leukemia, including neuroblastoma, rhabdomyosarcoma, and

Ewing sarcoma. Newborns with trisomy 21 may have a condi-

tion known as transient myeloproliferative disorder, which

produces elevated WBC counts with peripheral blasts, ane-

mia, and thrombocytopenia. It usually resolves with support-

ive care only, but these children have a significantly increased

risk (30%) of developing true acute leukemia (ALL or AML)

within the next few months and years of life.

**LABORATORY AND IMAGING STUDIES**

The diagnosis of acute leukemia is confirmed by findings of

immature blast cells on either the peripheral blood smear,

bone marrow aspirate, or both. Most patients have abnormal

blood counts; anemia and thrombocytopenia are common.

The WBC count may be low, normal, or high; 15% to 20% of

patients have a WBC count greater than 50,000/mm3. Defin-

tive diagnosis requires the evaluation of cell surface markers

(immunophenotype) by flow cytometry and evaluation of

cytochemical staining patterns. **Cytochemical analysis** should

with cervical lymphadenopathy, hepatosplenomegaly, and

CNS involvement. In patients with AML, extramedullary soft

tissue tumors may be found in various sites.

**TREATMENT**

Patients with ALL generally receive three- or four-agent

induction chemotherapy based on their initial risk group

assignment. Low- and standard-risk patients receive vinc-

ristine, prednisone, and L-asparaginase for 4 weeks; high-

risk patients also receive an anthracycline (daunorubicin or

doxorubicin). During induction, intrathecal instillation of

some combination of methotrexate, cytarabine, and hydro-
cortisone is given to treat existing CNS leukemia or prevent

its development. Following induction of successful remission,

which is achieved in nearly all patients with ALL, the remis-

sion is **consolidated** along with CNS-directed therapy. The

intensity of therapy depends on risk factors with higher risk

patients receiving more intensive chemotherapy. For patients

with CNS disease detected at diagnosis and those with T-cell

ALL, cranial radiation therapy is usually provided, although

the omission of radiation therapy for all pediatric leukemia

patients holds great promise. All patients receive **continuation**
therapy for a total duration of therapy of 2 to 3 years. Continuation therapy generally consists of intermittent vincristine and short courses (5 to 7 days) of oral corticosteroid therapy, plus daily oral 6-mercaptopurine, and weekly methotrexate (orally or intramuscularly).

The treatment of AML is quite different from that of ALL because nonmyelosuppressive drugs (vincristine, prednisone, and asparaginase) are not effective. Several cycles of extremely intensive myelosuppressive chemotherapy are necessary to cure childhood AML; there is little evidence that low-dose continuation therapy is helpful in AML (with the exception of acute promyelocytic leukemia).

Induction therapy for AML usually consists of cytarabine, daunomycin, and etoposide (or 6-thioguanine). If a patient has an HLA-matched sibling donor, most experts recommend a stem cell transplantation in the first remission, except in patients with Down syndrome and those with relatively favorable cytogenetics such as inv(16), t(15;17), and t(8;21). Bortezomib, sorafenib and haploidentical natural killer cell transplantation are being studied as an adjuvant therapy for newly diagnosed childhood AML.

COMPLICATIONS
Major short-term complications associated with the treatment of leukemia result from bone marrow suppression caused by chemotherapy. Patients may have bleeding and significant anemia that necessitates transfusion of platelets or blood. Neutropenia with fewer than 500 neutrophils/mm³, and especially fewer than 100 neutrophils/mm³, greatly predispose the patient to significant bacterial and fungal infection. Cell-mediated immunosuppression increases the risk of Pneumocystis jiroveci (carinii) pneumonia. Prophylaxis with oral trimethoprim-sulfamethoxazole or aerosolized pentamidine is recommended. Prophylaxis with antibiotics and antifungal agents is under investigation. Long-term sequelae of therapy are less common than in previous treatment eras but are prevalent in long-term survivors treated in the 1980s and earlier. These sequelae include neurocognitive impairment, short stature, obesity, cardiac dysfunction, infertility, second malignant neoplasms, and psychosocial problems (see Table 154-3).

PROGNOSIS
Patients with ALL are classified into four prognostic risk groups (low, standard, high, and very high) based on age, initial WBC count, genetic characteristics, and response to induction therapy. Classification systems are complex and evolving (Table 155-2). In general low-risk patients are 1 to 9 years old with an initial WBC count less than 50,000/mm³ and favorable cytogenetic findings such as t(12;21). High-risk patients are younger (<1 or >10 years) and asparaginase) are not effective. Several cycles of extremely intensive myelosuppressive chemotherapy are necessary to cure childhood AML; there is little evidence that low-dose continuation therapy is helpful in AML (with the exception of acute promyelocytic leukemia).

Induction therapy for AML usually consists of cytarabine, daunomycin, and etoposide (or 6-thioguanine). If a patient has an HLA-matched sibling donor, most experts recommend a stem cell transplantation in the first remission, except in patients with Down syndrome and those with relatively favorable cytogenetics such as inv(16), t(15;17), and t(8;21). Bortezomib, sorafenib and haploidentical natural killer cell transplantation are being studied as an adjuvant therapy for newly diagnosed childhood AML.

The overall cure rate for childhood ALL with current therapy approximates 80%. Relapse of ALL occurs most commonly in the bone marrow but also may occur in the CNS, testes, or other extramedullary sites. If relapse occurs while the patient is still receiving treatment, the prognosis is worse than if relapse occurs after discontinuation of therapy. Stem cell transplant from a matched sibling donor, matched unrelated donor, or cord blood currently is recommended for patients who have a relapse while receiving initial chemotherapy. The current overall cure rate for childhood AML is approximately 50%. It is slightly higher for patients who receive a matched sibling stem cell transplant in first remission than for patients treated with chemotherapy alone. The prognosis for relapsed AML is poor.

Table 155-2 General Prognostic Factors in Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>FAVORABLE (LOWER RISK)</th>
<th>UNFAVORABLE (HIGHER RISK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1-9.99 years</td>
<td>&lt;1 or &gt;10 years</td>
</tr>
<tr>
<td>Initial WBC count</td>
<td>&lt;50,000/mm³</td>
<td>&gt;50,000/mm³</td>
</tr>
<tr>
<td>CNS disease at diagnosis</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>DNA index</td>
<td>&gt;1.16</td>
<td>&lt;1.16</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>t(12;21)</td>
<td>t(4;11), t(9;22)</td>
</tr>
<tr>
<td>Response to therapy</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
</tbody>
</table>

CNS, Central nervous system; WBC, white blood cell.

LYMPHOMA

ETIOLOGY
Lymphomas, or malignancies of lymphoid tissues, are the most common malignancy in childhood, behind leukemias and central nervous system (CNS) tumors. There are two major types of lymphoma: Hodgkin disease and non-Hodgkin lymphoma (NHL). The etiologies are unknown, but evidence in many cases suggests that the Epstein-Barr virus (EBV) plays a causal role in both conditions.

Almost all cases of NHL in childhood are diffuse, highly malignant, and show little differentiation. NHL has three histologic subtypes: small noncleaved cell (Burkitt lymphoma), lymphoblastic, and large cell. For simplicity, these may be regarded as B cell, T cell, and large cell (which may be of either B-cell or T-cell origin) (Table 156-1). Chromosomal translocation may move an oncogene from its normal site to a new, unregulated site, leading to increased expression. In Burkitt lymphoma, translocation occurs
between chromosome 8 (c-myc oncogene) and the immunoglobulin gene locus on chromosome 2, 14, or 22, such that the c-myc oncogene comes to reside next to an immunoglobulin gene. The c-myc gene turns on the immunoglobulin gene, leading to a malignant B-cell lymphoma.

**CLINICAL MANIFESTATIONS**

The most common clinical presentation of Hodgkin disease is painless, firm lymphadenopathy often confined to one or two lymph node areas, usually the supraclavicular and cervical nodes. Mediastinal lymphadenopathy producing cough or shortness of breath is another frequent initial presentation. The presence of one of three B symptoms has prognostic value: fever (>38°C for 3 consecutive days), drenching night sweats, and unintentional weight loss of 10% or more within 6 months of diagnosis.

The sporadic (North American) form of Burkitt lymphoma more commonly has an abdominal presentation (typically with pain), whereas the endemic (African) form frequently presents with tumors of the jaw. The anterior mediastinum and cervical nodes are the usual primary sites for T-cell lymphomas. These lymphomas may cause airway or superior vena cava obstruction, pleural effusion, or both.

The diagnosis of lymphoma is established by tissue biopsy or examination of pleural or peritoneal fluid. Systemic symptoms, such as fever and weight loss, may be present and are particularly prominent in patients with anaplastic large cell lymphoma, which can be insidious in onset. If the bone marrow contains 25% or greater blasts, the disease is classified as acute leukemia (either B-cell acute lymphoblastic leukemia [ALL] or T-cell ALL). This distinction makes little prognostic or therapeutic difference because both require aggressive, systemic therapy in addition to CNS-directed therapy.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for lymphomas in children includes leukemia, rhabdomyosarcoma, nasopharyngeal carcinoma, germ cell tumors, and thymomas. Nonmalignant diagnoses include infectious mononucleosis (EBV infection), branchial cleft and thyroglossal duct cysts, cat scratch disease (*Bartonella henselae*), bacterial or viral lymphadenitis, mycobacterial infection, toxoplasmosis, and even tinea capitis, all of which can produce significant lymphadenopathy that can mimic lymphoma. Patients with acute abdominal pain from Burkitt lymphoma may be misdiagnosed as having appendicitis.

**TREATMENT**

The generally accepted treatment for childhood Hodgkin disease is a combination of chemotherapy and low-dose, involved-field radiation therapy. Chemotherapy usually consists of some

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**Table 156-1** Subtypes of Non-Hodgkin Lymphoma in Children

<table>
<thead>
<tr>
<th>HISTOLOGIC CATEGORY</th>
<th>IMMUNOPHENOTYPE</th>
<th>USUAL PRIMARY SITE</th>
<th>MOST COMMON TRANSLOCATION(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small noncleaved (Burkitt lymphoma)</td>
<td>Mature B-cell (surface immunoglobulin present)</td>
<td>Abdomen (sporadic form)</td>
<td>t(8;14)(q24;q32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head and neck (endemic form)</td>
<td>t(2;8)(p11;q24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t(8;22)(q24;q11)</td>
</tr>
<tr>
<td>Lymphoblastic</td>
<td>T-cell (rarely pre-B-cell)</td>
<td>Neck and/or anterior mediastinum</td>
<td>Many</td>
</tr>
<tr>
<td>Large cell</td>
<td>T-cell, B-cell, or indeterminate</td>
<td>Lymph nodes, skin, soft tissue, bone</td>
<td>t(2;5)p(23;q35)</td>
</tr>
</tbody>
</table>
combination of cyclophosphamide, vincristine, procarbazine, doxorubicin, bleomycin, vinblastine, prednisone, and etoposide. In general four to six courses of combination chemotherapy are given. Selected low-risk patients may be cured with chemotherapy alone, without radiation therapy.

Distant, noncontiguous metastases are common in childhood NHL. Systemic chemotherapy is mandatory and should be administered to all children with NHL, even those with clinically localized disease at diagnosis.

T-cell lymphoblastic lymphoma and anaplastic large cell lymphoma generally are treated with aggressive multidrug regimens similar to the regimens used in ALL. The main drugs used in the treatment of mature B-cell NHL are cyclophosphamide, moderate- to high-dose methotrexate, cytarabine, doxorubicin, ifosfamide, and etoposide. Surgery and radiation therapy rarely are used because the disease is rarely localized and is highly sensitive to chemotherapy.

COMPLICATIONS
The short-term complications from the treatment of lymphoma are similar to other pediatric malignancies and commonly include immunosuppression, related sequelae from myelosuppression, nausea, vomiting, and alopecia. Late adverse effects include second malignant neoplasms (acute myeloid leukemia or myelodysplasia, thyroid malignancies, and breast cancer), hypothyroidism, impaired soft tissue and bone growth, cardiac dysfunction, and pulmonary fibrosis.

PROGNOSIS
Children and adolescents with Hodgkin disease are classified as low, intermediate, or high risk according to stage and nodal bulk. The prognosis is generally excellent. There is an approximately 90% 5-year overall survival rate, approaching 100% for low-risk patients and 70% to 90% for high-risk patients. For NHL prognosis also is related to stage. The overall 3-year survival rates for B-cell, T-cell, and large cell NHL are 70% to 90%.

CENTRAL NERVOUS SYSTEM TUMORS

ETIOLOGY
Most central nervous system (CNS) tumors in children and adolescents are primary tumors that originate in the CNS and include low-grade astrocytomas or embryonic neoplasms (medulloblastoma, ependymoma, germ cell tumor). In contrast CNS tumors in adults are high-grade astrocytomas or secondary tumors that are metastatic from other carcinomas. CNS tumors also may arise in patients previously treated with radiation therapy. CNS tumors are likely multifactorial in etiology. The classification of CNS tumors is complex and evolving, with the World Health Organization classification being the most complete and accurate system.

EPIDEMIOLOGY
CNS tumors are the most common solid tumors in children and are second to leukemia in overall incidence during childhood. About 1700 new cases occur each year in the United States; the rate is approximately 33 cases per 1 million children under 15 years of age. The incidence peaks before age 10 years and then decreases until a second peak after age 70. For medulloblastoma and ependymoma, males are more affected than females; for other tumor types, no gender differences exist. In the first 2 to 3 years of life, whites are affected more than multiracial children; otherwise incidence rates are essentially equal for whites and multiracial children.

Children with certain inherited syndromes, including neurofibromatosis (types 1 and 2), Li-Fraumeni syndrome, tuberous sclerosis, Turcot syndrome, and von Hippel-Lindau syndrome, have an increased risk for developing a CNS tumor. Most CNS tumors arise in children with no known underlying disorder or risk factor.

CLINICAL MANIFESTATIONS

| Abnormal Head Size, Shape, and Fontanels |
| Visual Impairment and Leukocoria |
| Vomiting |
| Headaches |
Brain tumors can cause symptoms by impingement on normal tissue (usually cranial nerves) or by an increase in intracranial pressure caused either by obstruction of cerebrospinal fluid (CSF) flow or by a direct mass effect. Tumors that obstruct the flow of CSF become quickly symptomatic. Symptoms of increased intracranial pressure are lethargy, headache, and vomiting (particularly in the morning on awakening). Irritability, anorexia, poor school performance, and loss of developmental milestones all may be signs of slow-growing CNS tumors. In young children with open cranial sutures, an increase in head circumference may occur. Optic pathway tumors may lead to loss of visual acuity or visual field defects. Inability to abduct the eye as the result of sixth cranial nerve palsy is a common sign of increased intracranial pressure. Cranial nerve deficits other than sixth nerve palsy suggest involvement of the brainstem. Seizures occur in 20% to 50% of patients with supratentorial tumors; focal weakness or sensory changes also may be seen. Pituitary involvement produces neuroendocrine effects (galactorrhea with prolactinoma, excessive growth with growth hormone secretory tumors, precocious puberty). Cerebellar tumors are associated with ataxia and diminished coordination. A history and physical examination are fundamental for evaluation, which should include a careful neurologic assessment, including visual fields and a funduscopic examination.

LABORATORY/IMAGING STUDIES
If an intracranial lesion is suspected, magnetic resonance imaging (MRI) is currently the examination of choice (Fig. 157-1). Examination of CSF by cytocentrifuge histologic testing is essential to determine the presence of metastatic disease in primitive neuroectodermal tumors, germ cell tumors, and pineal region tumors. A lumbar puncture should not be performed before imaging has been obtained to evaluate for evidence of increased intracranial pressure. If a tumor is suspected to have metastatic potential (medulloblastoma), MRI of the entire spine should be obtained before surgery to assess for neuraxial dissemination. A postoperative MRI study of the brain should be obtained within 24 to 48 hours of surgery to assess the extent of resection. During follow-up, magnetic resonance spectroscopy can help distinguish recurrent tumor from radiation necrosis.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis of a CNS mass lesion includes malignant tumor, benign tumor, arteriovenous malformation, aneurysm, brain abscess, cysticercosis, granulomatous disease (tuberculosis, sarcoid), intracranial hemorrhage, pseudotumor cerebri, vasculitis, and, rarely, metastatic tumor.

TREATMENT
The therapy for children with CNS tumors is individualized and depends on the tumor type, location, size, and associated symptoms. High-dose dexamethasone often is administered immediately to reduce tumor-associated edema. Surgical objectives are complete excision, if possible, and maximal debulking if a complete excision is not possible. In children, radiation therapy often is combined with chemotherapy; in young children, radiation therapy may be delayed or avoided altogether. Primitive neuroectodermal tumors (including medulloblastoma) and germ cell tumors are sensitive to chemotherapy; gliomas are less sensitive to chemotherapy. Chemotherapy plays an especially important role, particularly in infants in whom the effects of high-dose CNS radiation may have devastating effects on growth and neurocognitive development.

COMPLICATIONS
Short-term adverse effects of therapy include nausea, vomiting, anorexia, fatigue, immunosuppression, and cushingoid features. Long-term adverse effects include neurocognitive deficits, endocrinologic sequelae, decreased bone growth, ototoxicity, renal insufficiency, cataracts, infertility, and second malignant neoplasms (including myelodysplasia). The neurocognitive deficits can be significant, particularly in infants and young children, and are the primary reason for the continued search for the lowest efficacious radiation therapy dose and the most conformal delivery methods for the radiation therapy boosts. Cerebellar mutism syndrome occurs in 25% of patients after resection of a posterior fossa tumor and is characterized by an acute decrease in speech (often mutism), behavioral changes (e.g., irritability; apathy; or both), diffuse cerebellar dysfunction, and other neurologic abnormalities. It may begin within hours to days of surgery and is usually self-resolving within weeks to months; cerebellar ataxia and dysmetria often persist. Somnolence syndrome, which is characterized by excessive fatigue and sleepiness, may occur in the months after completion of radiation therapy and is self-limited. Posterior fossa syndrome manifests as headache and aseptic meningitis days to weeks after surgery in this area.

PROGNOSIS
Improvements in neurodiagnosis, neurosurgical techniques, chemotherapy regimens, and radiation therapy techniques
Section 21  Oncology

Neuroblastoma is remarkable for its broad spectrum of clinical prognosis ranging from spontaneous regression to rapid progression and metastasis resulting in death. Children with localized disease are often asymptomatic at diagnosis, whereas children with metastases often appear ill and have systemic complaints, such as fever, weight loss, and pain. The most common presentation is abdominal pain or mass. The mass is often palpated in the flank and is hard, smooth, and nontender. In the abdomen, 45% of tumors arise in the adrenal gland, and 25% arise in the retroperitoneal sympathetic ganglia. Other sites of origin are the paravertebral ganglia of the chest and neck. Paraspinal tumors may invade through the neural foramina and cause spinal cord compression. Horner syndrome sometimes is seen with neck or apical masses. Several paraneoplastic syndromes, including secretory diarrhea, profuse sweating, and opsomyoclonus (dancing eyes and dancing feet), are associated with neuroblastoma.

Neuroblastoma may metastasize to multiple organs, including the liver, bone, bone marrow, and lymph nodes. Periorbital ecchymoses is a sign of orbital bone involvement. A unique category of neuroblastoma, stage 4S, is defined in infants (<1 year old) with a small primary tumor and metastasis limited to skin, liver, or bone marrow. It is associated with a favorable outcome.

Etiology

Neuroblastoma is derived from neural crest cells that form the adrenal medulla and the sympathetic nervous system. The cause is unknown. Most cases occur in young children, thus it is likely that neuroblastoma results from prenatal and perinatal events. Neuroblastoma may rarely (1% to 2% of cases) be hereditary. Mutations in the ALK and PHOX2B genes are associated with most familial cases. In sporadic cases, several genetic mutations have been identified.

Epidemiology

Neuroblastoma is the most common extracranial solid tumor of childhood and the most common malignancy in infancy. The median age at diagnosis is 20 months. There are approximately 650 new cases of neuroblastoma in the United States each year. The incidence is estimated to be 1 in 7000 live births. The tumor usually occurs sporadically, but, in 1% to 2% of cases, there is a family history of neuroblastoma.

Clinical Manifestations

Laboratory/Imaging Studies

A complete blood count and plain films may help identify patients with neuroblastoma. Calcification within abdominal neuroblastoma tumors is often observed on plain films of the abdomen. About 90% of neuroblastomas produce catecholamines (Vanillylmandelic acid; Homovanillic acid) that can be detected in the urine. Definitive diagnosis of neuroblastoma requires tissue for light microscopic, electron microscopic, and immunohistologic examination. A computed tomography (CT) scan of the chest, abdomen, and pelvis; a bone scan and/or metaiodobenzylguanidine scan; bilateral bone marrow aspiration and biopsies; and urinary catecholamines complete the evaluation.

Differential Diagnosis

The abdominal presentation of neuroblastoma must be differentiated from Wilms tumor, which also presents as an
abdominal flank mass. Ultrasound or CT examination usually differentiates the tumors. Periorbital ecchymoses from orbital metastases sometimes are mistaken for child abuse. Because children with bone marrow involvement may have anemia, thrombocytopenia, or neutropenia, leukemia is often considered in the differential.

**TREATMENT**

Treatment of neuroblastoma is based on surgical staging and biologic features (Table 158-1). Complete surgical excision is the initial treatment of choice for localized neuroblastoma. Children with favorable biology who undergo a gross total resection require no further therapy. In patients with advanced disease, combination chemotherapy usually is given after confirmation of the diagnosis. The most commonly used agents are vincristine, cyclophosphamide, doxorubicin, cisplatin, and etoposide. Delayed resection of the primary tumor is undertaken after numerous courses of chemotherapy. Radiation therapy often is administered to the primary tumor bed and areas of metastatic disease. **High-dose chemotherapy with autologous stem cell rescue** has improved the outcome for patients with high-risk neuroblastoma. Survival has also improved with the addition of **cis-retinoic acid** (isotretinoin) and anti-GD2 monoclonal antibody therapy after maximal reduction of tumor burden with chemotherapy, surgery, and radiation therapy.

**COMPLICATIONS**

Spinal cord compression from neuroblastoma may cause an irreversible neurologic deficit and is an oncologic emergency. Children with the opsomyoclonus syndrome may suffer from developmental delay or mental retardation. The aggressive chemotherapy and radiation therapies currently used to treat high-risk neuroblastoma may result in complications such as ototoxicity, nephrotoxicity, growth problems, and second malignancies.

**PROGNOSIS**

The prognosis for survival is affected by age at diagnosis, stage, primary site, presence or absence of metastasis, cytogenetics, DNA ploidy, MYCN status, and histopathology. Currently children with neuroblastoma can be divided into three groups: low, average, and high risk. Unfavorable biologic factors include lack of cell differentiation, amplification (>10 copies/cell) of the MYCN oncogene, lack of hyperdiploidy, and mutations of chromosome 1p, 11q, or 6p22. Patients with favorable biology tend to be younger and often have localized disease. Patients under 1 year of age generally have a better prognosis than older patients. Older patients with stage 4 disease most commonly have unfavorable biology, and more than 50% will relapse due to drug-resistant residual disease. Although neuroblastoma represents only 8% of cases of childhood cancer, it is responsible for 15% of cancer deaths in children.

**Table 158-1** Proposed Children’s Oncology Group Neuroblastoma Risk Stratification Schema, by Stage

<table>
<thead>
<tr>
<th>STAGE</th>
<th>AGE</th>
<th>MYCN</th>
<th>PLOIDY</th>
<th>HISTOLOGY</th>
<th>OTHER</th>
<th>RISK GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>2A/2B</td>
<td></td>
<td>Not amplified</td>
<td></td>
<td>&gt;50% resection</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not amplified</td>
<td></td>
<td>&lt;50% resection</td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not amplified</td>
<td></td>
<td>Biopsy only</td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amplified</td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>3</td>
<td>&lt;547 days</td>
<td>Not amplified</td>
<td></td>
<td></td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>≥547 days</td>
<td>Not amplified</td>
<td></td>
<td>Favorable</td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>≥547 days</td>
<td>Amplified</td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>4</td>
<td>&lt;365 days</td>
<td>Amplified</td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>&lt;365 days</td>
<td>Not amplified</td>
<td></td>
<td></td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>365–547 days</td>
<td>Amplified</td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>365–547 days</td>
<td>DI = 1</td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>365–547 days</td>
<td>Unfavorable</td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>365–547 days</td>
<td>DI &gt; 1</td>
<td></td>
<td>Favorable</td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>≥547 days</td>
<td>Amplified</td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>4S</td>
<td>&lt;365 days</td>
<td>Not amplified</td>
<td></td>
<td>DI &gt; 1</td>
<td>Favorable</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>&lt;365 days</td>
<td>Not amplified</td>
<td></td>
<td>DI = 1</td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>&lt;365 days</td>
<td>Missing</td>
<td></td>
<td>Missing</td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>&lt;365 days</td>
<td>Not amplified</td>
<td></td>
<td>Symptomatic</td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>&lt;365 days</td>
<td>Not amplified</td>
<td></td>
<td>Unfavorable</td>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>&lt;365 days</td>
<td>Amplified</td>
<td></td>
<td></td>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

DI, DNA index.
WILMS TUMOR

ETIOLOGY
Wilms tumor is thought to arise from primitive, metanephrine blastema, the precursor of a normal kidney. Nephrogenic rests are foci of embryonal cells that may be rarely (<1%) found in normal infant kidneys and are commonly (25% to 40%) found in Wilms tumor-bearing kidneys. They may be perilobar, intralobar, or both, and are widely considered to be precursors to Wilms tumors. Although the cause of Wilms tumor is unknown, children with certain congenital anomalies or genetic conditions are at increased risk of developing the disease.

Multiple Wilms tumor or WT genes have been identified. The WT1 gene at chromosomal band 11p13 is important in a minority of tumors, and other genes at 11p15, 16q, and 1p are also involved. The identification of several genes involved in the etiology or progression of Wilms tumor and the loss of heterozygosity (LOH) in normal tissues of some patients demonstrate that the genetic predisposition to Wilms tumor is heterogeneous.

EPIDEMIOLOGY
Wilms tumor is the most common malignant renal tumor of childhood, with approximately 500 new cases per year in the United States. The mean age at diagnosis is 3 to 3.5 years of age, and no gender predilection is apparent. A hereditary form of Wilms tumor may be associated with bilateral presentation and younger age at onset. Many congenital anomalies are associated with Wilms tumor, including sporadic aniridia, hemihypertrophy, and genitourinary abnormalities. Patients with the WAGR (Wilms tumor, aniridia, genitourinary malformation, mental retardation) syndrome have Wilms tumor as a manifestation of the syndrome itself, resulting from a germline deletion at chromosome 11p. Patients with Beckwith-Wiedemann syndrome and some other overgrowth syndromes are at increased risk for developing Wilms tumor and should be screened with periodic renal imaging.

CLINICAL MANIFESTATIONS

Most children with Wilms tumor are brought to medical attention because they have an abdominal mass that is discovered by their parents. Although many children do not have complaints at the time that the mass is first noted, associated symptoms may include abdominal pain, fever, hypertension, and hematuria.

LABORATORY/IMAGING STUDIES
An abdominal ultrasound or computed tomography (CT) scan can usually distinguish an intrarenal mass from a mass in the adrenal gland or other surrounding structures. Evaluation of the inferior vena cava is crucial because the tumor may extend from the kidney into the vena cava. A complete blood count, urinalysis, liver and renal function studies, and a chest radiograph (to identify pulmonary metastases) should be obtained. In most cases, a CT scan of the chest, abdomen, and pelvis is obtained. The diagnosis is confirmed by histologic examination of the tumor. Although most cases of Wilms tumor are classified as favorable histology, the presence of anaplasia is predictive of a worse prognosis and is considered unfavorable.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis of Wilms tumor includes hydronephrosis and polycystic disease of the kidney; benign renal tumors, such as mesoblastic nephroma and hamartoma; and other malignant tumors, such as renal cell carcinoma, neuroblastoma, lymphoma, and retroperitoneal rhabdomyosarcoma.

TREATMENT
The timing of nephrectomy for unilateral, resectable Wilms tumor remains controversial. The North American approach is for immediate nephrectomy followed by adjuvant chemotherapy, whereas the European approach is to make a diagnosis by imaging and sometimes a biopsy, give neoadjuvant chemotherapy followed by surgery and then adjuvant chemotherapy (plus radiation therapy, as indicated). The overall survival is comparable regardless of the approach. The Children's Oncology Group protocols for Wilms tumor with favorable histologic findings generally include vincristine and actinomycin, with or without doxorubicin. Radiation therapy is reserved for a minority of patients depending on stage, presence of metastases, response to therapy, and LOH status.

Bilateral Wilms tumor is present in about 5% of children on initial presentation, whereas recurrent disease affects the opposite kidney in 4% to 5% of patients. Treatment for patients with bilateral Wilms tumor should be individualized to retain as much normal kidney as possible.

COMPLICATIONS
Survivors of Wilms tumor are at risk for several late effects, including cardiomyopathy, scoliosis, hypertension and prehypertension, renal and bladder insufficiency, pulmonary dysfunction, hepatic dysfunction, infertility, and second malignancies. Patients with bilateral Wilms tumor are sometimes left with renal insufficiency or failure. Female survivors may have complicated pregnancies and deliveries.

PROGNOSIS
In general the prognosis for patients with Wilms tumor is very good. Prognostic factors include stage and histologic features. Anaplastic variants of Wilms tumor have a significantly worse outcome than classic Wilms tumor. In addition LOH at chromosomes 1p or 16q confers an increased risk of relapse and death compared to tumors without LOH at either site.
The 4-year relapse-free survival of patients with tumors of favorable histologic picture is directly related to stage. Cure rates for patients with localized Wilms tumor at diagnosis are greater than 85%, whereas patients with pulmonary metastases have event-free survival rates of approximately 70% to 80%.

SARCOMAS

Sarcomas are divided into soft tissue sarcomas and bone cancers. Soft tissue sarcomas arise primarily from the connective tissues of the body, such as muscle tissue, fibrous tissue, and adipose tissue. Rhabdomyosarcoma, the most common soft tissue sarcoma in children, is derived from mesenchymal cells that are committed to skeletal muscle lineage. Less common soft tissue sarcomas include fibrosarcoma, synovial sarcoma, and extraosseous Ewing sarcoma. The most common malignant bone cancers in children are osteosarcoma and Ewing sarcoma. Osteosarcomas derive from primitive bone-forming mesenchymal stem cells. Ewing sarcomas are thought to be of neural crest cell origin.

ETIOLOGY

The cause is unknown for most children diagnosed with sarcoma, although a few observations have been made regarding risks. Individuals with Li-Fraumeni syndrome (associated with a germline p53 mutation) and neurofibromatosis (associated with NF1 mutations) have an increased risk of soft tissue sarcomas. There is a 500-fold increased risk for osteosarcoma for individuals with hereditary retinoblastoma. Prior treatment for childhood cancer with radiation therapy or chemotherapy, specifically alkylating agents, or both, increases the risk for osteosarcoma as a second malignancy.

EPIDEMIOLOGY

In the United States, 850 to 900 children and adolescents under 20 years of age are diagnosed with soft tissue sarcomas each year; approximately 350 are rhabdomyosarcoma. The incidence of rhabdomyosarcoma peaks in children 2 to 6 years old and in adolescents. The early peak is associated with tumors in the genitourinary region, head, and neck; the later peak is associated with tumors in the extremities, trunk, and male genitourinary tract. Boys are affected 1.5 times more often than girls.

Of the 650 to 700 U.S. children and adolescents under 20 years of age diagnosed with bone tumors each year, approximately two thirds have osteosarcoma and one third have Ewing sarcoma. Osteosarcoma most commonly affects adolescents; the peak incidence occurs during the period of maximum growth velocity. The incidence of Ewing sarcoma peaks between ages 10 and 20 years but may occur at any age. Ewing sarcoma affects primarily whites; it rarely occurs in African American children or Asian children.

The clinical presentation of rhabdomyosarcoma varies, depending on the site of origin, subsequent mass effect, and presence of metastatic disease. Peri-orbital swelling, proptosis, and limitation of extraocular motion may be seen with an orbital tumor. Nasal mass, chronic otitis media, ear discharge, dysphagia, neck mass, and cranial nerve involvement may be noted with tumors in other head and neck sites. Urethral or vaginal masses, paratesticular swelling, hematuria, and urinary frequency or retention may be noted with tumors in the genitourinary tract. Trunk or extremity lesions tend to present as rapidly growing masses that may or may not be painful. If there is metastatic disease to bone or bone marrow, limb pain and evidence of marrow failure may be present.

Osteosarcoma often is located at the epiphysis or metaphysis of anatomic sites that are associated with maximum growth velocity (distal femur, proximal tibia, proximal humerus), but any bone may be involved. It presents with pain and may be associated with a palpable mass. Because the pain and swelling often are initially thought to be related to trauma, radiographs of the affected region frequently are obtained, which usually reveal a lytic lesion, often associated with calcification in the soft tissue surrounding the lesion. While 75% to 80% of patients with osteosarcoma have apparently localized disease at diagnosis, the majority of patients are believed to have micrometastatic disease as well.

Although Ewing sarcoma can occur in almost any bone in the body, the femur and pelvis are the most common sites. In addition to local pain and swelling, clinical manifestations may include systemic symptoms, such as fever and weight loss.

LABORATORY/IMAGING STUDIES

Tissue biopsy is needed for a definitive diagnosis of sarcomas. Selection of the biopsy site is important and has implications for future surgical resection and radiation therapy. Under light microscopy, rhabdomyosarcoma and Ewing sarcoma appear as small, round, blue cell tumors. Osteosarcomas are distinguishable by the presence of osteoid substance.

Immunohistochemical staining for muscle-specific proteins, such as actin and myosin, helps confirm the diagnosis of rhabdomyosarcoma. Two major histologic variants exist for rhabdomyosarcoma: embryonal and alveolar. Embryonal histologic variant is most common in younger children with head, neck, and genitourinary primary tumors. Alveolar histologic variant occurs in older patients and is seen most commonly in trunk and extremity tumors. Alveolar rhabdomyosarcoma often is characterized by specific translocations: t(2;13) or t(1;13). Metastatic evaluation for patients with rhabdomyosarcoma should include a computed tomography (CT) scan of the chest, abdomen, and pelvis; a bone scan; and bone scans.
marrow aspiration and biopsy. A lumbar puncture is required in patients with a parameningeal primary site.

Definitive diagnosis of osteosarcoma often is established by carefully placed needle biopsy. The presence of osteoid and immunohistochemical analysis confirms the diagnosis of osteosarcoma. The extent of the primary tumor should be delineated carefully with magnetic resonance imaging (MRI) before starting chemotherapy. Osteosarcoma tends to metastasize to the lung, most commonly, and rarely to other bones. Metastatic evaluation includes a chest CT scan and a bone scan.

The diagnosis of Ewing sarcoma is established with immunohistochemical analysis and cytogenetic and molecular diagnostic studies of the biopsy material. Ewing sarcoma is characterized by a specific chromosomal translocation, t(11;22), which is seen in 95% of tumors. MRI of the primary lesion should be performed to delineate extent of the lesion and any associated soft tissue mass. Metastatic evaluation involves a bone scan, chest CT scan, and bone marrow aspiration and biopsy.

DIFFERENTIAL DIAGNOSIS
Patients with Ewing sarcoma may be misdiagnosed as having osteomyelitis; children with osteogenic sarcoma often are thought initially to have pain and swelling related to trauma. The differential diagnosis for rhabdomyosarcoma depends on the location of the tumor. Tumors of the trunk and extremities often are unsuspected postoperatively. The differential diagnosis for intra-abdominal rhabdomyosarcoma includes other abdominal malignancies, such as Wilms tumor or neuroblastoma.

TREATMENT
Treatment of rhabdomyosarcoma is currently based on a staging system that incorporates both the primary site and histologic picture. The staging system also involves a local tumor group assessment based on the extent of disease and surgical result. In the intergroup rhabdomyosarcoma studies, the most common chemotherapy agents used are cyclophosphamide, vincristine, and actinomycin. Doxorubicin, etoposide, ifosfamide, topotecan, and irinotecan are also active against rhabdomyosarcoma. Radiation is administered to patients who have no residual disease after initial surgery or who have only had a primary biopsy of the tumor.

The current treatment of osteosarcoma involves neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy. Agents effective against osteosarcoma are doxorubicin, cisplatin, high-dose methotrexate, ifosfamide, and etoposide. The treatment for Ewing sarcoma is similar to that for osteosarcoma; preoperative chemotherapy is given, followed by local control measures, and then further chemotherapy. In contrast to osteosarcoma, Ewing sarcoma is radiation sensitive. Chemotherapy includes vincristine, cyclophosphamide, ifosfamide, etoposide, and doxorubicin.

COMPLICATIONS
In addition to the risk of late effects from the chemotherapy, children with sarcomas have potential complications related to local control of the tumor. If the local disease is controlled with surgery, the long-term sequelae may include loss of limb or limitation of function. If local control is accomplished with radiation therapy, the late effects depend on the dose of radiation given, the extent of the site radiated, and the development of the child at the time of radiation therapy. Irradiating tissues interfere with growth and development, so significant adverse consequences may occur in young children.

PROGNOSIS
For all children with sarcoma, presence or absence of metastatic disease at presentation is the most important prognostic factor. The outlook remains poor for patients who have distant metastasis from Ewing sarcoma, rhabdomyosarcoma, or osteosarcoma at diagnosis. Patients with localized rhabdomyosarcomas in favorable sites have an excellent prognosis when treated with surgery followed by vincristine and actinomycin. In patients with osteosarcoma and Ewing sarcoma, another important prognostic factor is the degree of tumor necrosis after preoperative chemotherapy. In general, patients whose tumor specimens show a high degree (>90%) of necrosis following preoperative chemotherapy have an event-free survival rate greater than 80%. Patients who still have large amounts of viable tumor after presurgical chemotherapy have a much worse prognosis. The cure rate for patients with localized osteosarcoma and Ewing sarcoma is approximately 60% to 70%. Patients who have lung metastasis at diagnosis have a cure rate of approximately 30% to 35%. Patients with metastases to other bones have a poor prognosis.

Suggested Reading
The kidneys preserve homeostasis through multiple mechanisms: maintain fluid and electrolyte balance, excrete metabolic waste products through glomerular filtration and tubular secretion, generate energy (gluconeogenesis), and produce important endocrine hormones (renin, vitamin D metabolites, erythropoietin). Renal disorders, by disturbing homeostasis, can affect growth and development and result in a variety of clinical manifestations (Table 161-1). Renal disorders in children may represent intrinsic renal diseases or derive from systemic conditions (Table 161-2).

HISTORY
Fetal urine production contributes to amniotic fluid volume, lung maturation, and somatic development. Congenital renal disorders may be associated with reduced (oligohydramnios) or increased amniotic fluid volume (polyhydramnios). Pulmonary hypoplasia and fetal maldevelopment of the face and extremities may result from insufficient amniotic fluid (Potter syndrome) (see Chapters 58 and 60).

Risk factors for renal disease (e.g., perinatal hypoxia-ischemia, acute tubular necrosis, renal vein thrombosis) can be detected by a careful history. A detailed family history may identify hereditary renal conditions. Poor growth and/or feeding, abnormal fluid intake and/or output may indicate underlying renal dysfunction. Other common manifestations of renal and/or urinary tract disorders are listed in Table 161-1.

PHYSICAL EXAMINATION
Renal diseases in children may be initially asymptomatic and detected during routine visits. Abnormal growth, hypertension (HTN), dehydration, or edema may suggest occult renal disease (see Chapter 33). Abnormal facial features may suggest syndromes associated with renal disorders (fetal alcohol syndrome, Down syndrome). Preauricular tags, deformities of the external ear, or ophthalmologic abnormalities (keratoconus, aniridia, iridocyclitis, cataracts) can be associated with congenital renal defects. Abdominal examination may reveal renal masses. Bladder distention may suggest a urine-concentrating defect or urinary tract obstruction.

RENAL PHYSIOLOGY
Normal renal function depends on intact glomerular filtration and tubular function (proximal tubule [PT], loop of Henle, and distal tubule [DT]) that results in urine formation (Fig. 161-1). The net glomerular pressure favors movement of fluid out of the capillaries into Bowman’s space. Intraglomerular pressure is regulated by afferent and, particularly, efferent arteriolar tone. Renin is generated by cells in the juxtaglomerular apparatus, located at the base of each glomerulus in proximity to the afferent/efferent arterioles and DT of that nephron and released in response to glomerular flow and perfusion.

The PT conducts isosmotic reabsorption (see Fig. 161-1) to reabsorb two thirds of the filtered volume, sodium, and chloride. Glucose, amino acids, potassium, and phosphate are almost completely reabsorbed. Approximately 75% of filtered bicarbonate is reabsorbed in the PT. When filtered bicarbonate exceeds the PT threshold, bicarbonate is spilled into the urine. The PT also secretes compounds such as organic acids, penicillins, and other drugs. The most potent vitamin D analog—1,25(OH)2-cholecalciferol (calcitriol)—is produced by PT cells in response to parathyroid hormone and intracellular calcium/phosphorus concentrations.

The loop of Henle is the site of reabsorption of 25% of sodium chloride filtered in the glomerulus (see Fig. 161-1). Active chloride transport drives the countercurrent multiplier and composes the medullary interstitial hypertonic gradient required for urinary concentration.

The DT is composed of the distal convoluted tubule (DCT) and collecting ducts (CD). The DCT is water impermeable and contributes to urine dilution by active sodium chloride absorption. The CD is the primary site of antidiuretic hormone (vasopressin) response, which leads to urine concentration. Sodium-potassium and sodium-hydrogen exchange in the CD is regulated by aldosterone. Active hydrogen ion secretion, which is responsible for the final acidification of the urine, also occurs in the CD.

Renal ammonia production and intraluminal generation of ammonium (NH₄⁺) facilitate urine hydrogen ion excretion. Urinary NH₄⁺ is not measured easily but can be inferred by calculation of the urinary anion gap. The gap between measured anions and cations largely consists of NH₄⁺. Problems with renal acid excretion or ammonia production decrease the
The maximum urinary concentrating capacity in a preterm newborn (~400 mOsm/L) is less than that in a full-term newborn (600 to 800 mOsm/L), which is less than that in older children and adults (~1200 mOsm/L). Neonates can dilute urine similar to adults (75 to 90 mOsm/L), but, because the glomerular filtration rate (GFR) is lower, the capacity to excrete a water load is less in infants. GFR reaches adult levels by 1 to 2 years of age. Tubular reabsorption of sodium, potassium, bicarbonate, and phosphate and excretion of hydrogen are all reduced in infants relative to adults. These functions mature independently and at different ages, so a neonate rapidly develops the ability to reabsorb sodium efficiently, but it takes 2 years for bicarbonate reabsorption to mature.

Erythropoietin is secreted by interstitial cells in the renal medulla in response to low oxygen delivery and helps regulate bone marrow red blood cell production.

### COMMON MANIFESTATIONS

Renal disorders can be classified as primary or secondary (due to systemic illnesses) (see Table 161-2). Renal diseases may present with obvious signs, such as hematuria or edema, or with subtle signs detected on screening examinations (abdominal or flank mass, HTN, proteinuria). Fever, urinary anion gap. A urinary gap of approximately 1 mEq/kg body weight is reasonable in normal children.
irritability, and vomiting may be presenting symptoms in neonates and infants with **urinary tract infections** (UTIs), whereas frequency and dysuria suggest UTI in older children. Chronic kidney disease often is associated with poor growth and feeding but may be first detected on screening examinations (HTN, hematuria). An abnormal urine stream may indicate posterior urethral valves, other bladder disorders, or obstructive lesions.

**DIAGNOSTIC STUDIES**

**Laboratory Studies**

The GFR is measured most accurately by infusion of a substance that is **freely** filtered by the glomerulus but is not metabolized, reabsorbed, or secreted in or by the tubules. The GFR is calculated as follows:

$$\text{GFR} = \frac{[U] \cdot V}{[P]}$$

where $[U]$ is urine concentration, $[P]$ is serum concentration of a substance (mg/dL) used to measure clearance, and $V$ is urine flow rate (mL/min).

By convention, GFR is corrected to a body surface area of 1.73 m$^2$ to allow comparison between different sized individuals. In a full-term newborn, an uncorrected GFR of 4 to 5 mL/min corrects to approximately 40 mL/min/1.73 m$^2$. GFR increases rapidly during the first 2 years of life when it achieves adult values (100 to 120 mL/min/1.73 m$^2$). After that, GFR and body size increase proportionately, and GFR remains stable.

**Plasma creatinine** reflects muscle mass, increases with age, and is used to approximate GFR. Creatinine is also secreted by PT, resulting in a less accurate measurement of GFR with immature kidneys or with decreased renal function. **Blood urea nitrogen** is affected by renal function but is greatly altered by hydration, nutrition, catabolism, and tissue breakdown. The correlation between creatinine and GFR can be used to estimate GFR. The revised Schwartz formula is the following:

$$\text{GFR} = \frac{0.413 \times \text{Ht}}{\text{Cr}_{\text{serum}}}$$

Height is measured in centimeters. Serum creatinine is measured in milligram per deciliter. This formula is most useful when body habitus and muscle mass are reasonably normal and when renal function is relatively stable. This formula may be most accurate in the range of 15 to 75 mL/min per 1.73 m$^2$. Values greater than 75 should be reported as such rather than as a specific number. **Creatinine clearance** ([U$_{\text{Cr}}$] V/[P$_{\text{Cr}}$]) estimates GFR but overestimates GFR when renal function is decreased.

**Urinalysis** is a useful screen for renal abnormalities. In addition to urine color and turbidity, **macroscopic urinalysis** uses a urine **dipstick** for pH and the presence of protein, glucose, ketones, blood, and leukocytes. Dilute urine may result in a false-negative result for protein; false-positive results may occur with extremely alkaline or concentrated urine or if there is a delay in reading the test. Dipsticks are exquisitely sensitive to the presence of hemoglobin (or myoglobin); there are few false-negative test results but many false-positive results. **Glucose** is detected via a glucose oxidase-peroxidase reaction, and leukocytes are detected via a **leukocyte esterase** reaction. The **nitrite test** may detect bacteriuria if the bacteria reduce nitrate to nitrite and have long contact time with the urine. False-negative results occur with frequent voiding, low urine bacterial count, urinary tract obstruction, and infection with bacteria unable to generate nitrite. Gross hematuria or prolonged
contact (uncircumcised boys) may result in a false-positive nitrite test. Microscopic urinalysis is used to confirm pyuria and hematuria and detect casts and crystals.

Proteinuria can be further defined by determination of a spot urine protein/creatinine ($U_{Pr}/Cr$) in a single urine specimen. This unit-less value correlates very well with 24-hour urine protein excretion: spot $U_{Pr}/Cr$ approximates 24-hour urine protein/m$^2$/day (normal <0.20; nephrotic range >2.0 in children).

**IMAGING STUDIES**

Ultrasound reliably assesses kidney size, determines degree of dilation, and differentiates cortex and medulla. The bladder also can be visualized. Pulsed Doppler studies assess arterial and venous blood flow and can be used to calculate the kidneys’ resistive index.

A voiding cystourethrogram involves repeated filling of the bladder to detect vesicoureteral reflux and to evaluate the urethra. Computed tomography and magnetic resonance imaging have mostly replaced the intravenous pyelogram to evaluate kidney structure and function. Radionuclide studies can define renal size, scars, and renal function/excretion.

**NEPHROTIC SYNDROME AND PROTEINURIA**

**ETIOLOGY AND EPIDEMIOLOGY**

Small amounts of protein are found in the urine of healthy children (<4 mg/m$^2$/hour or $U_{Pr}/Cr <0.20$). Nephrotic proteinuria in children is defined as protein greater than 40 mg/m$^2$/hour or $U_{Pr}/Cr >2.0$. Proteinuria between these levels is mildly to moderately elevated but not nephrotic.

Proteinuria may be transient or persistent, asymptomatic or symptomatic, and orthostatic (present in the upright position but not in the recumbent position) or fixed (present in all positions). Proteinuria may be glomerular (disruptions of the normal glomerular barrier to protein filtration) or tubular (increased filtration, impaired reabsorption, or secretion of proteins).

Nephrotic syndrome (NS) is characterized by persistent heavy proteinuria (mainly albuminuria) (>2 g/m$^2$/24 h); hypoproteinemia (serum albumin <3.0 g/dL); hypercholesterolemia (>250 mg/dL); and edema. Age, race, and geography affect the incidence of NS. Certain HLA types (HLA-DR7, HLA-B8, and HLA-B12) are associated with an increased incidence of NS. Increased glomerular permeability is due to alterations in the normal glomerular cellular and basement membrane barrier that restrict filtration of serum proteins. The resultant massive proteinuria leads to decreased serum proteins, especially albumin. Plasma oncotic pressure is diminished, leading to fluid shifts from vascular to interstitial compartments and plasma volume contraction. Renal blood flow and the glomerular filtration rate are not usually diminished. Edema results from reduction in effective circulating blood volume and increase in tubular sodium chloride reabsorption secondary to activation of the renin-angiotensin-aldoosterone system. Hypoproteinemia stimulates hepatic lipoprotein synthesis and diminishes lipoprotein metabolism, leading to elevated serum lipids (cholesterol, triglycerides) and lipoproteins.

NS may be primary or secondary (Table 162-1). A child with apparent primary NS, prior to renal biopsy, is considered to have idiopathic nephrotic syndrome. Minimal change nephrotic syndrome (MCNS) is the most common histologic form of primary NS in children. More than 80% of children less than 7 years of age with NS have MCNS. Children 7 to 16 years old with NS have a 50% chance of having MCNS. Males are affected more frequently than females (2:1).

Focal segmental glomerulosclerosis (FSGS) accounts for approximately 10% to 20% of children with primary NS. It may present like MCNS or with less impressive proteinuria. FSGS may develop from MCNS or represent a separate entity. A circulating factor that increases glomerular permeability is found in some patients with FSGS. More than 35% of children with FSGS progress to renal failure.

Membranoproliferative glomerulonephritis (MPGN) is characterized by hypocomplementemia with signs of glomerular renal disease. MPGN represents 5% to 15% of children with primary NS, is typically persistent, and has a high likelihood of progression to renal failure over time.

Membranous nephropathy represents less than 5% of children with primary NS. It is seen most commonly in adolescents and children with systemic infections, such as hepatitis B, syphilis, malaria, and toxoplasmosis, or on specific medications (gold, penicillamine).

Congenital NS presents during the first 2 months of life. There are two common types. The Finnish type is an autosomal recessive disorder most common in persons of Scandinavian descent and is due to a mutation in the nephrin protein component in the glomerular filtration slit. The second type is a heterogeneous group of abnormalities, including diffuse mesangial sclerosis and conditions associated with drugs or infections.
infections. Prenatal onset is supported by elevated levels of maternal alpha-fetoprotein.

Secondary NS may result from many different causes in children and are listed in Table 162-1.

**CLINICAL MANIFESTATIONS**

The sudden onset of dependent pitting edema or ascites is the most common presentation for children with NS. Anorexia, malaise, and abdominal pain are often present. Blood pressure may be elevated in up to 25% of children on presentation; acute tubular necrosis and significant hypotension may occur with sudden decline in serum albumin and significant volume depletion. Diarrhea (intestinal edema) and respiratory distress (pulmonary edema or pleural effusion) may be present. Typical MCNS is characterized by the absence of gross hematuria, renal insufficiency, hypertension (HTN), and hypocomplementemia.

**DIAGNOSTIC STUDIES**

Proteinuria of 1+ or higher on 2 to 3 random urine specimens suggests persistent proteinuria that should be further quantified. A $U_{pr}/Cr > 0.2$ on a first morning specimen excludes significant proteinuria. $U_{pr}/Cr > 2.0$ indicates nephrotic range proteinuria.

In addition to a demonstration of proteinuria, hypercholesterolemia, and hypoalbuminemia, routine testing typically includes a serum C3 complement. A low serum C3 implies a lesion other than MCNS, and a renal biopsy is indicated before trial of steroid therapy. Microscopic hematuria may be present in up to 25% of cases of MCNS but does not predict response to steroids. Additional laboratory tests, including electrolytes, blood urea nitrogen, creatinine, total protein, and serum albumin level, are performed based on history and physical examination features. Renal ultrasound is often useful. Biopsy is performed when MCNS is not suspected.

**DIFFERENTIAL DIAGNOSIS**

Transient proteinuria can be seen after vigorous exercise, fever, dehydration, seizures, and adrenergic agonist therapy. Proteinuria usually is mild ($U_{pr}/Cr < 1$), glomerular in origin, and always resolves within a few days. It does not indicate renal disease.

Postural (orthostatic) proteinuria is a benign condition defined by normal protein excretion while recumbent but significant proteinuria when upright. It is glomerular in nature, more common in adolescents and tall, thin individuals, and not associated with progressive renal disease. Many children with orthostatic proteinuria continue this process into adulthood.

**Tubular proteinuria** is characterized by preponderance of low-molecular-weight proteins in the urine and is suspected with acute tubular necrosis, pyelonephritis, structural renal disorders, polycystic kidney disease, and tubular toxins such as antibiotics or chemotherapeutic agents. The combination of tubular proteinuria with evidence of tubular electrolyte wasting and glycosuria is termed Fanconi syndrome.

**Glomerular proteinuria** is characterized by a combination of large- and small-molecular-weight proteins in the urine, variable levels of proteinuria, and often evidence of glomerular disease (hematuria, red blood cell casts, HTN, and renal insufficiency). Causes of glomerular proteinuria include glomerular capillary disruption (hemolytic uremic syndrome, crescentic glomerulonephritis); glomerular capillary immune complex deposition (poststreptococcal glomerulonephritis and lupus nephritis); and altered glomerular capillary permeability (MCNS, congenital NS).

**TREATMENT**

Because greater than 80% of children less than 13 years of age with primary NS have steroid-responsive forms (chiefly MCNS), steroid therapy may be initiated without a renal biopsy if a child has typical features of NS. Typical therapy for MCNS is prednisone, 2 mg/kg/day (60 mg/m²/24 h, maximum 60 mg/day), provided once a day or split into multiple doses. Over 90% of children who respond to steroids do so within 4 weeks. Responders should receive steroids for 12 weeks. A renal biopsy is indicated for nonresponders because steroid resistance decreases the chance that MCNS is the underlying disease. Frequent relapses or steroid resistance may necessitate additional immunosuppressive therapy.

No clearly effective therapy for FSGS has been identified. Approximately 35% respond to steroid therapy; others may respond to immunosuppressive therapy. MPGN and membranous glomerulonephritis may improve with chronic steroid or immunosuppressive therapy but do not reliably remit with standard NS steroid therapy. Aggressive medical therapy of familial congenital NS, with early nephrectomy, dialysis, and transplantation, is the only effective approach to this syndrome.

NS edema is treated by restricting salt intake. Severe edema may require the use of loop diuretics. When these therapies do not alleviate severe edema, cautious parenteral administration of 25% albumin (0.5 to 1.0 g/kg intravenously over 1 to 2 hours) with an intravenous loop diuretic usually results in diuresis. The administered albumin is excreted rapidly, and, thus, salt restriction and diuretics must be continued. Significant pleural effusions may require drainage. Acute HTN is treated with β-blockers or calcium channel blockers. Persistent HTN usually responds to angiotensin-converting enzyme inhibitors.

**COMPLICATIONS**

An increased incidence of serious infections, particularly bacteremia and peritonitis (particularly *Streptococcus pneumoniae, Escherichia coli*, or *Klebsiella*), is due to urinary loss of immunoglobulins and complement. Side effects of steroids are most common in steroid-dependent and frequently relapsing patients. Hypovolemia may result from diarrhea or diuretic use. The loss of coagulation factors, antithrombin, and plasminogen may lead to a hypercoagulable state with a risk of
thromboembolism (TE). Warfarin, Lovenox, low-dose aspirin, or dipyridamole may minimize the risk of clots in NS patients with a history of TE or high risk for TE. Hyperlipidemia promotes increased atherosclerotic vascular disease.

**PROGNOSIS**

Most children with NS eventually go into remission. Nearly 80% of children with MCNS experience NS relapse, defined as heavy proteinuria that persists for 3 or more consecutive days. Transient (up to 3 days) proteinuria may occur with intercurrent infection in children with MCNS and is not considered a relapse. Steroid therapy is typically effective for true relapse. Steroid-resistant patients have little risk of chronic renal failure. Patients with FSGS may initially respond to steroids but later develop resistance. Many children with FSGS progress to end-stage kidney failure (see Chapter 165). Recurrence of FSGS occurs in 30% of children who undergo renal transplantation.

**GLOMERULONEPHRITIS AND HEMATURIA**

**ETIOLOGY AND EPIDEMIOLOGY**

A child with gross hematuria may have a serious disease and requires prompt evaluation. Microscopic hematuria, defined as more than 3 to 5 red blood cells (RBCs) per high-power field on freshly voided and centrifuged urine, is often benign. Isolated asymptomatic microscopic hematuria is found in up to 4% of healthy children. In most cases this is a transient finding. Hematuria may originate from glomerular disease, tubulointerstitial processes, and lower urinary tract disorders (Table 163-1).

Immune-mediated inflammation is the mechanism of glomerulonephritis (GN). Poststreptococcal glomerulonephritis (PSGN) is the most common form of acute GN, and IgA nephropathy is the most common chronic GN, but many other types of GN can occur. The most common identifiable lower urinary tract causes of hematuria include urinary tract infection (UTI), kidney stones, and hypercalciuria.

**CLINICAL MANIFESTATIONS**

Children with acute GN commonly present with hematuria (gross or microscopic) along with other cardinal features of glomerular injury (proteinuria, hypertension, edema, oliguria, renal insufficiency). PSGN occurs most frequently in children 2 to 12 years of age and is more common in boys. Manifestations of PSGN are typical of acute GN listed previously and develop 5 to 21 days (average 10 days) after streptococcal pharyngitis infections and 4 to 6 weeks after impetigo. Acute postinfectious GN presents in the same manner as PSGN and can occur following infections with other bacterial and viral pathogens. PSGN can develop regardless of whether the child was treated with antibiotics at the time of infection. Special attention must be paid to the blood pressure because hypertension may be severe enough to lead to complications such as heart failure, seizures, and encephalopathy.

The presentation of IgA nephropathy is more variable and may take the form of acute GN, asymptomatic microscopic hematuria, or recurrent gross hematuria concurrent with an upper respiratory infection as opposed to several days later, as with PSGN. Children with hematuria secondary to systemic disorders such as Henoch-Schönlein purpura nephritis, lupus nephritis, and vasculitis-associated GN will present with other systemic features typical of the respective disease.

A special form of GN is rapidly progressive glomerulonephritis (RPGN) that presents with typical features of acute GN, but the renal insufficiency progresses more quickly and severely. Renal biopsy shows glomerular epithelial cell proliferation with crescents. RPGN may be idiopathic or secondary to any of the known types of GN. Early recognition of RPGN is crucial to prevent the progression to end-stage renal disease (ESRD) that occurs without prompt treatment.

Alport syndrome is typically caused by X-chromosome mutations in type IV collagen leading to an abnormal glomerular basement membrane (GBM) and may present with either asymptomatic microscopic or gross hematuria. Males typically...
Chapter 163  Glomerulonephritis and Hematuria

Develop progressive renal failure and sensorineural hearing loss during adolescence and young adulthood. Females typically have a more benign course but usually have at least microscopic hematuria. Thin basement membrane disease (benign familial hematuria) is caused by more benign mutations leading to a thinning of the GBM. The mutation is often autosomal dominant, and therefore hematuria is often noted in first-degree relatives. As opposed to Alport syndrome, thin basement membrane disease is typically not progressive and usually has an excellent prognosis.

The presentation of nonglomerular causes of hematuria is more variable and related to the underlying etiology. Hematuria due to tubular disorders is usually only microscopic and may be associated with proteinuria, glycosuria, and polyuria. These children typically do not have hypertension and only develop renal insufficiency with more severe disease. Painless gross hematuria may be seen with sickle cell trait/disease, Wilms tumor, and strenuous exercise. Hematuria may or may not be associated with pain when due to cystic bleeding and Nutcracker syndrome. Gross hematuria following trauma may signify more severe renal or lower urinary tract injury. UTI is associated with typical symptoms such as dysuria and urinary frequency. Urolithiasis may be associated with asymptomatic hematuria or with flank or abdominal pain. Hypercalciiuria can cause both gross and microscopic hematuria and may be associated with urinary tract symptoms such as dysuria and urinary frequency or may be asymptomatic.

**DIAGNOSTIC STUDIES**
All patients with hematuria should have a careful history and physical (including blood pressure) along with a urinalysis, including microscopic examination to identify RBCs. Glomerular hematuria is suggested by a brownish (tea- or cola-colored) appearance of the urine and the presence of RBC casts and/or dysmorphic RBCs on urine microscopy. A urine color that is more bright red in appearance without RBC casts or dysmorphic RBCs is more suggestive of a lower urinary tract source. However there may be overlap of these findings.

A suggested algorithm for the evaluation of hematuria is given in Figure 163-1. Gross hematuria and microscopic hematuria with associated concerning findings should have additional laboratory evaluation. The presence of low C3 complement narrows the differential diagnosis to PSGN, membranoproliferative GN, and lupus nephritis. Children with isolated asymptomatic microscopic hematuria may be observed with repeat urinalyses. If the hematuria is persistent, additional evaluation may be appropriate.

**THERAPY**
Therapy for PSGN is supportive and involves dietary sodium restriction, diuretics, and antihypertensive agents as needed. Although treating the streptococcal infection does not prevent PSGN, antibiotic treatment is still warranted with active streptococcal infection. Therapies for children with other forms of GN depend on the underlying cause and severity. In some cases, anti-inflammatory therapy involving corticosteroids and/or other immunosuppressive agents may be used. Treatment with angiotensin-converting enzyme inhibitors may reduce proteinuria and glomerular hyperperfusion but should be used with caution in the setting of acute kidney injury.
PROGNOSIS AND PREVENTION

PSGN usually has a benign outcome. In typical cases, the gross hematuria, proteinuria, and edema decline quickly (in 5 to 10 days). Microscopic hematuria may persist for months or even years; over 95% of children recover completely with no long-term sequelae.

Children with IgA nephropathy and other forms of chronic GN have a greater risk of progression to ESRD. The prognosis for renal recovery in chronic GN and in RPGN is variable and related to the underlying disorder and disease severity. The presence of persistent, heavy proteinuria, hypertension, decreased kidney function, and severe glomerular lesions on biopsy is associated with poor outcomes.

Children with idiopathic isolated asymptomatic microscopic hematuria or suspected thin basement membrane disease typically have an excellent renal prognosis. Long-term follow-up, including yearly urinalysis (to rule out proteinuria) and blood pressure, is required to exclude progressive forms of renal disease.

HEMOLYTIC UREMIC SYNDROME

ETIOLOGY AND EPIDEMIOLOGY

Hemolytic uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal injury and is an important cause of acute kidney injury in children. HUS typically occurs in children less than 5 years of age but can occur in older children. The most common type of HUS is associated with a prodromal diarrheal illness (D+HUS). Contamination of meat, fruit, vegetables, or water with verotoxin (VT)-producing Escherichia coli (most commonly E. coli O157:H7) is responsible for many outbreaks. VT may be produced by other bacteria such as Shigella. VT causes hemorrhagic enterocolitis of variable severity and results in HUS in 5% to 15% of affected children.

HUS presenting without a prodrome of diarrhea (atypical HUS) may occur at any age. The clinical course is usually more severe than that of D+HUS. Atypical HUS can be secondary to infection (Streptococcus pneumoniae, human immunodeficiency virus), genetic and acquired defects in complement regulation, medications, malignancy, systemic lupus erythematosus, and pregnancy.

CLINICAL MANIFESTATIONS

Classic D+HUS begins with enterocolitis, often with bloody stools, followed in 7 to 10 days by weakness, lethargy, and oliguria/anuria. Physical examination reveals irritability, pallor, and petechiae. Dehydration is often present; however some children have volume overload. Hypertension may be due to volume overload and/or renal injury. Central nervous system (CNS) involvement, including seizures, occurs in up to 25% of cases. Other potential organ involvement includes pancreatitis, cardiac dysfunction, and colonic perforation.

Children without evidence of a diarrheal prodrome may have a similar microangiopathic syndrome, identified as thrombotic thrombocytopenic purpura (TTP). Children with TTP typically have predominant CNS symptoms but may also have significant renal disease. Recurrent episodes are common. Because CNS involvement is also seen in HUS, TTP can be difficult to distinguish from HUS in some cases. Deficiencies of ADAMTS13, a von Willebrand factor-cleaving protease, have been identified in children affected with TTP.

DIAGNOSTIC STUDIES

Common laboratory findings in HUS are listed in Table 164-1. Peripheral blood smear reveals evidence of microangiopathic hemolysis. Coombs test is negative. The diarrhea and presence of toxin-producing E. coli may have resolved by the time HUS is diagnosed.

TREATMENT AND PROGNOSIS

Therapy for HUS is supportive and includes volume repletion, control of hypertension, and managing complications of renal insufficiency, including dialysis when indicated. Red blood cell transfusions are provided as needed. Platelet transfusions should be avoided because they may add to the thrombotic microangiopathy and are indicated only by active hemorrhage or in anticipation of a procedure. Antibiotics and anti diarrheal agents may increase the risk of developing HUS. Early hydration during the diarrheal phase may lessen the severity of renal insufficiency. Most children (>95%) with D+HUS survive the acute phase and recover normal renal function, although some may have evidence of long-term morbidity.
ACUTE AND CHRONIC RENAL FAILURE

ACUTE KIDNEY INJURY

Etiology
Acute kidney injury (AKI), formerly termed acute renal failure, refers to an abrupt decrease in glomerular filtration rate (GFR) and tubular function. This may lead to decreased excretion of waste products (e.g., urea) and a disturbance in fluid and electrolyte homeostasis. Early recognition and management of AKI are crucial.

AKI may be oliguric (<1 mL/kg/h in neonates and infants, <0.5 mL/kg/h in children) or nonoliguric, which is more difficult to recognize. Although urine output in nonoliguric AKI is normal or polyuric, electrolyte disturbances and uremia may become significant. The major causes of AKI may be divided into prerenal (renal hypoperfusion), intrinsic renal (tubular, glomerular, or vascular injury), and postrenal (urinary tract obstruction) categories (Table 165-1). In many cases the cause of AKI is multifactorial.

Prerenal azotemia is most commonly due to dehydration but may be secondary to other mechanisms of glomerular hypoperfusion. Tubular injury encompasses the most common causes of intrinsic AKI in children. Tubular injury may occur from hypoxia-ischemia (acute tubular necrosis), infection (sepsis), nephrotoxic agents (medications, contrast, myoglobin) and inflammation (interstitial nephritis). Postrenal AKI may be due to either structural or functional urinary tract obstruction.

Clinical Manifestations

History, physical examination, and basic studies usually allow proper classification of the child with AKI (Table 165-2). Prerenal azotemia is characterized by precipitating factors and oliguria. Intrinsic tubular injury is associated with precipitating factors but urine output may be low, normal, or high, depending on the severity of the injury. Glomerular and vascular disorders may present with hematuria, edema, hypertension, and oliguria. The urine output with postrenal AKI may be low or normal and may be associated with flank masses or a distended bladder on examination. Depending on the underlying cause and severity of illness, AKI can be associated with signs of dehydration or volume overload.

Diagnostic Studies
A urinalysis (UA) should be obtained in all children with AKI. In prerenal azotemia, the UA is unremarkable with a high specific gravity reflecting appropriate renal retention of water in the setting of renal hypoperfusion. However neonates are not able to concentrate urine as well. With intrinsic tubular injury and postrenal AKI, the UA may show mild hematuria and/or proteinuria with a specific gravity of 1.015 or less. With glomerular and vascular injury, the amount of hematuria and proteinuria is usually moderate to severe. In oliguric states, differentiation between prerenal azotemia and acute tubular necrosis may be aided by determining the urine osmolality and fractional excretion of sodium (see Table 165-2). Renal ultrasound is often helpful in determining the AKI category (see Table 165-2). Renal biopsy is indicated in select cases only.

Common electrolyte abnormalities seen with AKI include hyperkalemia, metabolic acidosis, hypocalcemia, and hyperphosphatemia. These labs may need to be monitored frequently, depending on the initial results and clinical course. A complete blood count should be obtained as anemia is frequently observed. Other studies may be obtained as clinically indicated.

Treatment
In some cases the underlying disorder can be treated. Examples include volume repletion in dehydration, stopping an offending nephrotoxic medication, and relieving urinary tract obstruction. In all cases efforts should be made to limit additional renal injury (e.g., ensuring adequate renal perfusion and avoiding nephrotoxic medications). Medication dosages should be adjusted for decreased renal function as appropriate.

Fluid therapy depends on the volume status and urine output. If hypovolemic is present, intravascular volume should be expanded by intravenous administration of saline. If hypervolemia is present, 1 to 2 mg/kg of furosemide and fluid restriction may be attempted. If the patient is relatively euvolemic, then the total fluid input should be adjusted to meet the total...
output, which may be higher or lower than normal, depending on the urine output. Assessment of intake and output should be augmented with serial measurements of body weight.

A large part of AKI treatment involves management of its complications. Electrolyte disorders are treated as appropriate. Potassium intake and medications that increase potassium should be restricted. Intravenous calcium will lower risk of arrhythmia while measures are initiated to shift potassium into cells (bicarbonate, beta-agonists, insulin/dextrose) and hasten removal (diuretics, sodium-potassium exchange resins, dialysis).

Preferred treatment of hypocalcemia involves oral supplementation and calcitriol, and IV supplementation is reserved for severe cases. Hypertension may be treated with diuretics, calcium channel blockers, and vasodilators. Angiotensin-converting enzyme (ACE) inhibitors are usually avoided in the setting of AKI. Preferred treatment of hypocalcemia involves oral supplementation and calcitriol, and IV supplementation is reserved for severe cases. Hypertension may be treated with diuretics, calcium channel blockers, and vasodilators. Angiotensin-converting enzyme (ACE) inhibitors are usually avoided in the setting of AKI.

Major indications for acute dialysis are listed in Table 165-3. Medical therapy may be attempted before initiating renal replacement therapy. There is no set blood urea nitrogen or creatinine level at which dialysis is started for uremia. Renal replacement options in children include peritoneal dialysis, hemodialysis, and continuous renal replacement therapy. The mode used is chosen on an individual basis.

**Prognosis**

Recovery from AKI depends on the etiology, severity, availability of specific treatments, and other aspects of the patient's course. Nonoliguric AKI usually recovers well, whereas the outcome with oliguric AKI is more variable. Even with a seemingly good recovery, history of AKI may place the child at increased risk for future renal complications, including chronic kidney disease (CKD).

**CHRONIC KIDNEY DISEASE**

**Etiology and Epidemiology**

Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common causes of CKD that present between birth and 10 years of age. After age 10 acquired diseases, such as focal segmental glomerulosclerosis and glomerulonephritis (GN), are more common causes of incident CKD. The risk of progression to end-stage renal disease (ESRD) is related to the underlying cause and severity of CKD. During puberty, renal function may deteriorate if the damaged kidneys are not able to grow and adapt to increased demands. CKD is staged to facilitate appropriate evaluation and monitoring (Table 165-4). The GFR can be estimated in children using the Schwartz formula (see Chapter 161). Most complications of CKD do not manifest until at least stage 3 CKD. In stage 4 CKD, the complications become more numerous and severe. Children with stage 5 CKD (ESRD) are typically treated with either dialysis or renal transplantation.

**Clinical Manifestations**

The clinical presentation of a child with CKD may be related to both the underlying diagnosis and complications of CKD. A child with CAKUT may have polyuria, polydipsia, and recurrent urinary tract infections. A child with glomerular disease may have hematuria, proteinuria, edema, and hypertension. Common complications of CKD in children are listed in Table 165-5. Most of these complications are multifactorial in etiology. For example, factors associated with growth failure include poor nutrition, renal osteodystrophy (ROP), metabolic acidosis, hormonal abnormalities, and resistance to growth hormone. Anemia results primarily from a failure to produce adequate erythropoietin and iron deficiency. ROD is usually due to secondary hyperparathyroidism as a result of diminished 1,25-dihydroxyvitamin D production in the kidney, hypocalcemia, and hyperphosphatemia (from decreased renal excretion). If prolonged and/or severe, ROD may eventually lead to rickets and bone deformities. Hypertension and

### Table 165-2

<table>
<thead>
<tr>
<th>LABORATORY/CLINICAL FEATURE</th>
<th>CHILD</th>
<th>NEONATE</th>
<th>CHILD</th>
<th>NEONATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine output</td>
<td>Low</td>
<td></td>
<td>Low, normal, or high</td>
<td>Low or normal</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Normal</td>
<td>RBCs, WBCs, protein, casts</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Urine Na(^+) (mEq/L)</td>
<td>&lt;15</td>
<td>&lt;20–30</td>
<td>&gt;40</td>
<td>&gt;50</td>
</tr>
<tr>
<td>(\text{FE}_{\text{Na}}) (%)</td>
<td>&lt;1</td>
<td>&lt;2.5</td>
<td>&gt;2</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/L)</td>
<td>&gt;500</td>
<td>&gt;350</td>
<td>~300</td>
<td>~300</td>
</tr>
<tr>
<td>Renal ultrasound</td>
<td>Normal</td>
<td>Increased echogenicity, decreased corticomedullary differentiation</td>
<td>Hydronephrosis</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{FE}_{\text{Na}}\) Fractional excretion of sodium; RBCs, red blood cells; WBCs, white blood cells.

\(\text{FE}_{\text{Na}}\) (%) = \(\left[\frac{\text{urine sodium/plasma sodium}}{\text{urine creatinine/plasma creatinine}}\right] \times 100\).

### Table 165-3

<table>
<thead>
<tr>
<th>ACUTE AND/OR CHRONIC DIALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume overload</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>Uremia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACUTE DIALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain ingestions</td>
</tr>
<tr>
<td>Hyperammonemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHRONIC DIALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor growth</td>
</tr>
<tr>
<td>Stage 5 chronic kidney disease (end-stage renal disease)</td>
</tr>
</tbody>
</table>

The clinical presentation of a child with CKD may be related to both the underlying diagnosis and complications of CKD. A child with a CAKUT may have polyuria, polydipsia, and recurrent urinary tract infections. A child with glomerular disease may have hematuria, proteinuria, edema, and hypertension. Common complications of CKD in children are listed in Table 165-5. Most of these complications are multifactorial in etiology. For example, factors associated with growth failure include poor nutrition, renal osteodystrophy (ROP), metabolic acidosis, hormonal abnormalities, and resistance to growth hormone. Anemia results primarily from a failure to produce adequate erythropoietin and iron deficiency. ROD is usually due to secondary hyperparathyroidism as a result of diminished 1,25-dihydroxyvitamin D production in the kidney, hypocalcemia, and hyperphosphatemia (from decreased renal excretion). If prolonged and/or severe, ROD may eventually lead to rickets and bone deformities. Hypertension and
left ventricular hypertrophy are commonly seen cardiovascular complications. Delayed puberty results from altered gonadotropin secretion and feedback patterns. Learning and school performance may also be impaired in CKD.

Treatment
The management of children with advanced CKD requires a multidisciplinary team of pediatric practitioners. Adequate nutrition should be provided even if this requires dietary supplements and tube feedings. In infants a low-solute formula may be indicated. Unless a child is oliguric, fluid restriction is not necessary. Many children with CAKUT require supplemental salt due to urine sodium wasting. Conversely children with GN tend to retain sodium and may become hypertensive or edematous if given excess salt. Common treatment considerations for other CKD complications are given in Table 165-5.

Measures can be taken to preserve kidney function or slow down the progression of CKD. Hypertension and proteinuria can be treated with ACE inhibitors or angiotensin receptor blockers. Potentially nephrotoxic medications should be avoided when feasible, and medication adjustment for reduced kidney function should be made as appropriate. Protein intake is typically not restricted in pediatric CKD.

The optimal treatment of ESRD is renal transplantation. Both deceased and living donors can be used for renal transplantation, but living donors are preferred when available. Maintenance dialysis is effective for a child awaiting renal transplantation or for whom renal transplantation is not possible. Indications for chronic dialysis are given in Table 165-3. Peritoneal dialysis is done at home by the family. Hemodialysis is typically done three times a week at a dialysis facility.

Prognosis
Children with mild CKD (stages 1 and 2) may do well but need to be monitored for progressive loss of kidney function. Children with stages 3 and 4 CKD have a high likelihood of progressing to ESRD at some point, although the timing can vary. Children with kidney transplants generally do well but have to take immunosuppressive medications associated with a variety of side effects, including infections, nephrotoxicity, cardiovascular complications, and increased risk for certain malignancies. Unfortunately most transplanted kidneys fail over time but can last for several years. Children on maintenance dialysis have the highest morbidity and mortality, especially with longer time spent on dialysis. Thus, their primary goal is to receive a kidney transplant.

HYPERTENSION
DEFINITION
In children, hypertension (HTN) is defined as blood pressure (BP) greater than the 95th percentile for age, gender, and height on at least three different occasions. The context of the BP measurement (e.g., cuff size, pain, anxiety) is important. The staging of HTN is given in Table 166-1. Hypertensive emergency is defined as severe elevation in BP associated with target organ damage (encephalopathy, heart failure).

ETIOLOGY
Pediatric HTN has many causes (Table 166-2) that are either primary (essential) or secondary. Essential HTN is the most common cause of HTN in adolescents. Obese children are more likely to develop essential HTN. Secondary HTN should be suspected with younger age and more severely elevated BP. Renal disease is the most common cause of secondary HTN in children.

CLINICAL MANIFESTATIONS

<table>
<thead>
<tr>
<th>Red Urine and Hematuria</th>
<th>Hypertension</th>
<th>Headaches</th>
<th>Obesity</th>
<th>Alkalemia</th>
</tr>
</thead>
</table>

Table 165-4: Classification of the Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>STAGE</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;90</td>
<td>Minimal kidney damage</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>Kidney damage with mild reduction of GFR</td>
</tr>
<tr>
<td>3</td>
<td>30–59</td>
<td>Moderate reduction of GFR</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>Severe reduction of GFR</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 (or dialysis)</td>
<td>End-stage renal disease</td>
</tr>
</tbody>
</table>

Table 165-5: Common Complications and Treatments of CKD

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor growth</td>
<td>Increased caloric intake, treat acidosis, treat renal osteodystrophy, recombinant GH</td>
</tr>
<tr>
<td>Anemia</td>
<td>Erythropoietin, iron supplementation</td>
</tr>
<tr>
<td>Renal osteodystrophy/secondary hyperparathyroidism</td>
<td>1,25-Dihydroxyvitamin D supplementation, calcium supplementation, dietary phosphorous restriction, phosphate binders</td>
</tr>
<tr>
<td>Cardiovascular 4a. Hypertension</td>
<td>Antihypertensive medications</td>
</tr>
<tr>
<td>4b. Left ventricular hypertrophy</td>
<td>Volume control</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>Low K diet, furosemide, sodium polyethylene sulfonate</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Sodium supplementation</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Alkali replacement</td>
</tr>
</tbody>
</table>

GFR, Glomerular filtration rate. *GFR ranges apply for children 2 years of age and older.
Most children with HTN have no symptoms. Signs and symptoms associated with severe HTN include encephalopathy (headache, vomiting, seizures), heart failure, stroke, and retinopathy (blurred vision, flame hemorrhage, and cotton wool spots on retinal exam). Neonatal history (low birth weight or use of umbilical artery catheter); family history of HTN, stroke, or heart disease; and dietary history (excessive salt or caffeine, drugs) are important. Additional findings that may suggest specific causes include abdominal bruit; diminished leg pressure and weak femoral pulse (coarctation of aorta); cafe-au-lait spots (neurofibromatosis associated renal artery stenosis); flank mass (hydronephrosis, Wilms tumor); tachycardia with flushing and diaphoresis (pheochromocytoma); and truncal obesity, acne, striae, and buffalo hump (Cushing syndrome). Signs of underlying kidney disease may be present.

**DIAGNOSTIC STUDIES**

In addition to history and physical examination, the evaluation of children with confirmed HTN includes the following:

1. Baseline etiologic assessment (urinalysis, electrolytes, blood urea nitrogen, creatinine, and renal ultrasound)
2. Focused studies based on clinical suspicion (e.g., plasma metanephrines, thyroid studies, vascular imaging)
3. Assessment for target organ damage (echocardiogram for left ventricular hypertrophy)
4. Assessment of other cardiovascular risk factors (lipids, fasting glucose, uric acid)

**TREATMENT**

Therapeutic lifestyle changes (diet, exercise) should be initiated for asymptomatic stage 1 HTN without target organ damage or systemic disease. Medication should be started for stage 2 or symptomatic HTN and stage 1 HTN, which fails to respond to lifestyle changes. Calcium channel blockers or angiotensin-converting enzyme inhibitors are the most frequently chosen first-line options in children. Angiotensin receptor blockers, β-blockers, or diuretics are also recommended as first-line antihypertensive agents. More than one agent may be needed. Hypertensive emergency requires prompt hospitalization and may require parenteral antihypertensive treatment with nicardipine, labetalol, esmolol, or sodium nitroprusside.

**PROGNOSIS**

Prognosis depends on the underlying etiology and BP control. Essential HTN, when present in adolescents, is usually not associated with morbidity at presentation. Left untreated, however, even asymptomatic stage 1 HTN may increase risk for cardiovascular, central nervous system, and renal morbidity in adults.

### VESICOURETERAL REFLEX

#### ETIOLOGY AND EPIDEMIOLOGY

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder up to the ureter or even up to the kidney. Most VUR results from congenital incompetence of the ureterovesical (UV) junction, a structure that matures through early childhood. In a significant minority of children, structural UV abnormalities exist that never resolve. VUR may be
children with high-grade VUR and/or recurrent symptomatic UTI. VUR exposes the kidney to increased hydrodynamic pressure during voiding and increases the likelihood of renal infection due to incomplete emptying of the ureter and bladder (see Chapter 114). Reflux nephropathy refers to development and progression of renal scarring. This is a particular risk if VUR is associated with a urinary tract infection (UTI) or obstruction. Although a single UTI may result in renal scarring, the incidence is higher in children with recurrent UTIs. Renal dysplasia is associated with congenital VUR. Because of increasing use of maternal-fetal ultrasonography, a number of newborns are now identified with VUR before UTI has occurred, creating opportunities for early intervention and prevention strategies. Duplication of the ureters, with or without an associated ureterocele, may obstruct the upper collecting system. Often the ureter draining the lower pole of a duplicated renal unit has VUR. Neurogenic bladder is accompanied by VUR in up to 50% of affected children. VUR may also be due to increased intravesicular pressure when the bladder outlet is obstructed from inflammation of the bladder (cystitis) or by acquired bladder obstruction.

CLINICAL MANIFESTATIONS

VUR is most often identified during radiologic evaluation following a UTI (see Chapter 114). The younger the patient with UTI, the more likely VUR is present. No clinical signs reliably differentiate children with UTI with and without VUR.

DIAGNOSTIC STUDIES

An imaging study can be performed after initiation of UTI treatment with no need to wait days or weeks before performing the test. Renal ultrasound (RUS) is the best study to evaluate the urinary tract in children. A voiding cystourethrogram (VCUG) or radionuclide cystogram (NCG) is performed to detect urethral/bladder abnormalities and/or VUR. Recent American Academy of Pediatrics guidelines for infants with a first UTI between 2 and 24 months of age recommend a VCUG if an RUS reveals hydronephrosis, scarring, or other findings suggestive of either high grade VUR or obstructive uropathy and in other atypical or complex clinical circumstances. VCUG should also be performed if there is a recurrence of a febrile UTI. Although the VCUG provides additional anatomic detail, the NCG may detect more children with mild VUR and involves less radiation. An international grading system has been used to describe reflux (Fig. 167-1). The incidence of renal scarring in patients with low-grade VUR is low (15%) and increases with grade IV or V reflux (65%). Grade I or II VUR is likely to resolve without surgical intervention, but VUR resolves in less than 50% grade IV or V. Nuclear renal scanning best identifies renal scars.

TREATMENT

Controversy remains about whether long-term prophylactic antibiotic therapy (trimethoprim-sulfamethoxazole or nitrofurantoin) is indicated in mild to moderate VUR. It is optional in this population and may be particularly useful in children with high-grade VUR and/or recurrent symptomatic UTI. Pivotal studies are under way. Complications of reflux nephropathy are hypertension and chronic kidney disease (CKD). CKD is typically heralded by mild proteinuria and involves the development of focal and segmental glomerulosclerosis as well as interstitial scarring. Indications for surgical repair of VUR are controversial and have been made more complex by the development of dextranomer/hyaluronic acid copolymer (Deflux procedure), which appears to be a very successful minimally invasive correction of mild to moderate VUR.

CONGENITAL AND DEVELOPMENTAL ABNORMALITIES OF THE URINARY TRACT

ETIOLOGY AND EPIDEMIOLOGY

Anomalies of the urinary tract (UT) occur in up to 4% of infants. Bilateral renal agenesis occurs in 1 in 4000 births. Renal agenesis is a component of Potter syndrome (flat facies, clubfoot, and pulmonary hypoplasia). Any intraperitoneal UT disorder that results in little fetal urine and, therefore, little amniotic fluid can lead to Potter syndrome. Unilateral renal agenesis occurs in 1 in 3000 births and is more common in infants of diabetic mothers and African Americans. It is accompanied by normal or minimally reduced renal function. This condition can also be found with vesicoureteral reflux (VUR) and other anomalies of the genital tract, ear, skeletal system, and cardiovascular system. Unilateral renal agenesis can be a component of the Turner syndrome.
syndrome, Poland syndrome, or VACTERL association (vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula, renal agenesis and dysplasia, and limb defects).

Renal hypoplasia/dysplasia refers to kidneys that are congenitally small, malformed, or both. Over time many affected children progress to chronic kidney disease (CKD) because of reduced nephron number. The kidneys are often unable to fully reabsorb sodium and water, and these children require salt and water supplementation to optimize growth.

Multicystic renal dysplasia (MCD) is due to abnormal nephron development that occurs in 1 in 4000 births. There is minimal or no functioning renal tissue in the affected kidney; bilateral disease is lethal. There is an association with VUR in the contralateral kidney. MCD often spontaneously involutes over the first few years of life and is rarely associated with hypertension (HTN) or recurrent urinary tract infection (UTI).

Polycystic kidney diseases (PKDs) are a group of genetic diseases affecting the kidneys and other tissues. PKD may be primary (autosomal recessive or autosomal dominant) or associated with other syndromes. Autosomal recessive PKD occurs in 1 in 10,000 to 40,000 children and is due to genetic defects in fibrocystin. Autosomal dominant PKD, due to defects in polycystin 1 or 2, occurs in 1 in 1000 individuals, making it the most common inherited kidney disease. Although there is some overlap clinically, the two conditions differ morphologically. Both may appear in infancy or in older children. Renal cysts also are observed in other inherited disorders, such as von Hippel–Lindau syndrome, tuberous sclerosis, and Bardet–Biedl syndrome.

Urinary tract obstruction can occur at any anatomic level of the genitourinary system (Table 168-1). Early in gestation, severe obstruction results in renal dysplasia. Ureteral obstruction later in fetal life or after birth results in dilation of the ureter and collecting system, often with subsequent renal parenchymal alterations. An obstructed UT is susceptible to infections, which may worsen renal injury. Posterior urethral valves are the most common cause of bladder outlet obstruction in males, present in 1 in 50,000 boys. Parents may note a poor urine stream in affected children. The valves are sail-shaped membranes that arise from the verumontanum and attach to the urethral wall. The prostatic urethra becomes dilated, VUR may be present, and hypertrophied detrusor muscle develops. Renal dilation varies in severity. Some degree of renal dysplasia is often present. Severe obstruction may be associated with oligohydramnios, resulting in lethal pulmonary hypoplasia. Intrauterine rupture of the renal pelvis produces urinary ascites, which is the most common cause of ascites in the newborn period.

<table>
<thead>
<tr>
<th>SITE ETILOGIC CONDITION/DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infundibula/pelvis</td>
</tr>
<tr>
<td>Ureteropelvic junction</td>
</tr>
<tr>
<td>Ureter</td>
</tr>
<tr>
<td>Retropitoneal tumor (lymphoma), retropitoneal fibrosis, chronic granulomatous disease</td>
</tr>
<tr>
<td>Bladder</td>
</tr>
<tr>
<td>Urethra</td>
</tr>
</tbody>
</table>

*Relatively common.

Bilateral renal agenesis results in insufficient lung development and Potter syndrome. Respiratory distress is severe, pneumothoraces can occur, and severe pulmonary hypoplasia is fatal. Unilateral renal agenesis may be asymptomatic because the nonaffected kidney undergoes compensatory growth and provides normal renal function.

Autosomal recessive PKD is characterized by marked bilateral renal enlargement. Interstitial fibrosis and tubular atrophy progress over time. Kidney failure usually occurs in early childhood. Hepatic fibrosis is present and may lead to portal HTN. Bile duct ectasia and biliary dysgenesis occur. Many affected infants display flank masses, hepatomegaly, pneumothorax, proteinuria, and/or hematuria.

Autosomal dominant PKD typically presents in middle adulthood but may present in infancy or childhood. Infants may have a clinical picture similar to autosomal recessive PKD, but older children show a pattern similar to that of adults, with large isolated cysts developing over time. The defect may occur anywhere along the nephron unit. Hepatic cysts are often present, and pancreatic, splenic, and ovarian cysts can also develop. Cerebral aneurysms may develop, and the risk of hemorrhage depends on size, blood pressure, and family history of intracranial hemorrhage.

UT obstruction may be silent but usually is discovered during prenatal ultrasound or with UTI or flank mass in early childhood. In a newborn, the most common type of abdominal mass is renal (most commonly ureteropelvic junction obstruction).

<table>
<thead>
<tr>
<th>Decision-Making Algorithms Available @ StudentConsult.com</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Urine and Hematuria</td>
</tr>
<tr>
<td>Hyponatremia</td>
</tr>
</tbody>
</table>

DIAGNOSTIC IMAGING

Renal ultrasound (RUS) and radionuclide renography (usually with a diuretic administered) are the standard tests for diagnosis of UT obstruction. RUS allows identification of renal agenesis, hypoplasia, dysplasia, cysts, and UT dilatation. Obstruction may be suggested but a dilated UT may also result from VUR, ureteral hypoplasia, or neurogenic bladder. A voiding cystourethrogram (VCUG) is also a part of the evaluation. Many boys with posterior urethral valves are identified by prenatal ultrasound. Postnatally the
diagnosis and extent of renal damage are established by RUS and VCUG.

**TREATMENT**

Infants and children with bilateral dysplasia often require additional sodium and water due to renal wasting. With MCD surgical removal of the kidney is rarely indicated unless severe HTN or recurrent UTI occurs.

Treatment of HTN can prolong maintenance of renal function. General therapy of CKD (see Chapter 165) can improve growth and development.

UT obstruction often requires drainage or surgical correction. Treatment of posterior urethral valve consists of either primary valve ablation or diversion (usually via vesicostomy) if ablation is not possible. Ectopic ureters are frequently obstructed; when this happens, surgical intervention is required.

Children with neurogenic bladder are prone to UTI and renal impairment from poor urine emptying. Clean intermittent catheterization or a urinary diversion is used to help minimize these complications.

Acute obstruction of urine flow is the cause of renal colic, a severe sharp intermittent pain in the flank or lower abdomen often radiating to the groin. Vomiting, distress, and inability to relieve pain with position changes are characteristic. In younger children, classic symptoms may not be apparent; fussiness and vomiting may be the only symptoms. Hematuria may be gross or microscopic and typically clears rapidly with passage of gravel or stone material.

**Diagnostic Studies**

Renal ultrasound may identify kidney stones in the kidney but can easily miss UT stones. Computed tomography (CT), particularly a helical CT, can identify stones throughout the UT, but stones can be obscured by oral or intravenous contrast material. Etiologic diagnosis is facilitated when stone material can be obtained and sent for analysis. Spot or 24-hour urine studies for mineral and electrolyte determinations, obtained on a typical diet for the child, are important to characterize any underlying metabolic predisposition and are valuable even when a stone is available for analysis.

**Treatment**

Acute treatment of urinary calculi consists of hydration and analgesia. Chronic treatment for all types of metabolic stones involves vigorous fluid intake, usually twice maintenance rates. Infection-related stones require treatment of infection and often removal of the stone as well as correction of any predisposing anatomic abnormality. Specific metabolic conditions require specific treatments; for IHC, normal calcium intake with low sodium and low oxalate intake is prescribed. For some children with IHC, potassium citrate or thiazides are required to minimize stone recurrence. Lithotripsy or surgery by a pediatric urologist may be required for children with large, infected, or obstructing stones.

**URINARY TRACT STONES**

**Etiology**

Urinary tract calculi are called **nephrolithiasis** or **urolithiasis**. Primary bladder stones can be seen with recurrent urinary tract infections (UTIs), neurogenic bladder or bladder surgery (sutures serve as a nidus), and intestinal bladder augmentation. Renal stones can result from obstructive abnormalities or an underlying metabolic predisposition. In industrialized societies, most stones (>90%) in children arise in the urinary tract (UT) and become symptomatic with passage or if lodged (commonly at the ureteropelvic junction or the ureterovesical junction). Metabolic causes include idiopathic familial hypercalciuria (IHC), hyperoxaluria, uric acid disorders, distal renal tubular acidosis, cystinuria, hypercalcemic hypercalciuria, and primary hyperparathyroidism. Some children with UT abnormalities and stones have a concomitant metabolic predisposition.

**Clinical Manifestations**

Acute obstruction of urine flow is the cause of renal colic, a severe sharp intermittent pain in the flank or lower abdomen often radiating to the groin. Vomiting, distress, and inability to relieve pain with position changes are characteristic. In younger children, classic symptoms may not be apparent; fussiness and vomiting may be the only symptoms. Hematuria may be gross or microscopic and typically clears rapidly with passage of gravel or stone material.

**Voiding Dysfunction**

**Etiology**

Voiding difficulties are frequent in preschool age children due to delay in maturation of bladder and micturition pathways. Normal micturition and continence rely on structural UT integrity, neurologic maturation, and coordination between somatic and autonomic nervous system units, including the central nervous system, spinal cord pathways, nerves innervating the bladder/urinary sphincter, and the autonomic system. Daytime continence is usually achieved before nighttime continence. Most children are dry, day and night, by 4 to 5 years of age. Nocturnal enuresis is the involuntary loss of urine during sleep. Children with primary enuresis have never had a prolonged (usually >3 months) span of nighttime continence. Up to 10% of 5-year-old children have primary enuresis with 15% spontaneous resolution per year. Boys are affected more than girls with increased incidence in families (40% at 6 years of age if one affected parent, 70% if two affected parents). Secondary enuresis involves loss of nighttime control after an extended period of dryness and generally requires evaluation to uncover the cause.

**Clinical Manifestations**

Dysfunctional voiding (DV) may manifest as incontinence, frequency, urgency, hesitancy, dysuria, lower abdominal pain, or
recurring UTI. Symptoms may vary over time and be associated with obvious neurologic problems (spinal cord injury, encephalitis), constipation, and/or behavioral problems. DV symptoms may vary, depending on recent UTI or changes in family or school life/stressors. The majority of children with DV are anatomically, neurologically, and psychologically normal.

**Diagnostic Studies**

Evaluation for DV may be performed at any age, but isolated urinary incontinence in an otherwise normal child is not usually evaluated until 5 years of age. A urinalysis and urine culture should be done to exclude occult infection and renal disease. Children with daytime incontinence should undergo renal/bladder ultrasound to exclude structural abnormalities. Urodynamic evaluation is typically reserved for children with a suspicion of neurogenic bladder or known neurologic etiology.

**Treatment**

For children with recurrent UTI, prophylactic antibiotics may be useful. Timed voiding and anticholinergic medications are used to treat bladder hyperactivity and sensory defects. More complicated treatment regimens include biofeedback, α-blockers, and intermittent catheterization. For children with simple primary enuresis, the bed wetting alarm provides safe and effective resolution of the problem for greater than 70% of affected children; medical therapy with anticholinergics, imipramine, or DDAVP may also be used in selected children.

**DISORDERS AND ABNORMALITIES OF THE SCROTUM AND ITS CONTENTS**

**Etiology**

Undescended testes (cryptorchidism) are found in about 1% of boys after 1 year of age. It is more common in full-term newborns (3.4%) than in older children. In neonates, cryptorchidism is more common with shorter gestation (20% in 2000- to 2500-g infants and 100% in <900-g infants). Cryptorchidism is bilateral in 30% of cases. Spontaneous testicular descent does not tend to occur after 1 year of age, but failure to find one or both testes in the scrotum does not indicate undescended testicles. Retractile testes, absent testes, and ectopic testes may resemble cryptorchidism in presentation.

**Clinical Manifestations**

A history of maternal drug use (steroids) and family history are important in the evaluation of a child for apparent cryptorchidism. Whether the testis was ever noted in the scrotum should be asked. The true undescended testis is found along the normal embryologic path of descent, usually in the presence of a patent processus vaginalis. An undescended testis is often associated with an inguinal hernia; it is also subject to torsion. There is a high incidence of infertility in adulthood. When bilateral and untreated, infertility is uniform. There is an increased malignancy risk (five times the normal rate) with undescended testis, usually presenting between the ages of 20 and 30. The risk is greater in untreated males or those with surgical correction during or after puberty.

Retractile testes are normal testes that retract into the inguinal canal from an exaggerated cremasteric reflex. The diagnosis of retractile testes is likely if testes are palpable in the newborn period but not at later examination. Frequently parents describe seeing their son’s testes in his scrotum when he gets cold.
Complications

Torsion of the testis is an emergency requiring prompt diagnosis and treatment to save the affected testis. Torsion accounts for 40% of cases of acute scrotal pain and swelling and is the major cause of the acute scrotum in boys less than 6 years of age. It is thought to arise from abnormal fixation of the testis to the scrotum. On examination the testicle is swollen and tender, and the cremasteric reflex is absent. The absence of blood flow on nuclear scan or Doppler ultrasound is consistent with torsion.

The differential diagnosis of testicular pain includes trauma, an incarcerated hernia, and torsion of the testicular epididymal appendix. Torsion of the appendix testis is associated with point tenderness over the lesion and minimal swelling. In adolescents, the differential diagnosis of testicular torsion also must include epididymitis, the most common cause of acute scrotal pain and swelling in older adolescents. Diagnosis is aided by an antecedent history of sexual activity or UTI. Testicular torsion must be considered as the principal diagnosis when severe acute testicular pain is present.

Treatment

The undescended testis is usually histologically normal at birth. Atrophy and dysplasia are found after the first year of life. Some boys have congenital dysplasia in the contralateral descended testis. Surgical correction at an early age results in greater chance of adult fertility. Administration of human chorionic gonadotropin causes testosterone release from functioning testes and may result in descent of retractile testes.

Orchidopexy is usually done in the second year of life. Most extra-abdominal testes can be brought into the scrotum with correction of the associated hernia. If the testis is not palpable, ultrasound or magnetic resonance imaging may determine its location. The closer the testis is to the internal inguinal ring, the better the chance of successful orchidopexy.

Surgical correction of testicular torsion is called detorsion and fixation of the testis. If performed within 6 hours of torsion, there is greater than a 90% chance of testicular salvage. The contralateral testis usually is fixed to the scrotum to prevent possible torsion. If torsion of the appendix is found, the necrotic tissue is removed.

ACKNOWLEDGMENT

We gratefully acknowledge the invaluable contributions of Rama Jayanthi, MD, Pediatric Urology, Nationwide Children's Hospital, Columbus, Ohio.

Suggested Reading

The endocrine system regulates vital body functions by means of hormonal messengers. Hormones are defined as circulating messengers, with action at a distance from the organ (gland) of origin of the hormone. Hormones can be regulated by nerve cells; endocrine agents can serve as neural messengers. There is also a relationship between the endocrine system and the immune system; autoantibodies may cause an organ to produce an excess or deficiency of a hormone. Manifestations of an endocrine disorder are related to the response of the peripheral tissue to a hormone excess or deficiency. Hormone action also may be paracrine (acting on adjacent neighboring cells to the cell of origin of the hormone) or autocrine (acting on the cell of origin of the hormone itself); agents acting in these ways are called factors rather than hormones (Fig. 170-1). Hormones generally are regulated in a feedback loop so that the production of a hormone is linked to its effect or its circulating concentration. Endocrine disorders generally manifest from one of four ways:

1. By excess hormone: In Cushing syndrome, there is an excess of glucocorticoid present; if the excess is secondary to autonomous glucocorticoid secretion by the adrenal gland, the trophic hormone adrenocorticotropic hormone (ACTH) is suppressed.

2. By deficient hormone: In glucocorticoid deficiency, the level of cortisol is inadequate; if the deficiency is at the adrenal gland, the trophic hormone is elevated (ACTH).

3. By an abnormal response of end organ to hormone: In pseudohypoparathyroidism, defects in the gene (GNAS1) encoding the alpha subunit of the stimulatory G protein (Gsa) is manifested by elevated PTH levels in the face of deficient PTH function (PTH resistance).

4. By gland enlargement that may have effects as a result of size rather than function: With a large nonfunctioning pituitary adenoma, abnormal visual fields and other neurologic signs and symptoms result even though no hormone is produced by the tumor.

Peptide hormones act through specific cell membrane receptors; when the hormone is attached to the receptor, the complex triggers various intracellular second messengers that cause the biologic effects. Peptide hormone receptor number and avidity may be regulated by hormones. Steroid hormones exert their effects by attachment to intranuclear receptors, and the hormone-receptor complex translocates to the nucleus, where it binds with DNA, and leads to further gene activation.

The interpretation of serum hormone levels must be related to their controlling factors. For example, a given value of parathyroid hormone may be normal in a eucalcemic patient but inadequate in a hypocalcemic patient with partial hypoparathyroidism or excessive in a hypercalcemic patient with hyperparathyroidism.

**HYPOTHALAMIC-PITUITARY AXIS**

The hypothalamus controls many endocrine systems either directly or through the pituitary gland. Higher central nervous system (CNS) centers control the hypothalamus. Hypothalamic releasing or inhibiting factors travel through capillaries of the pituitary portal system to control the anterior pituitary gland, regulating the hormones specific for the factor (Fig. 170-2). The pituitary hormones enter the peripheral circulation and exert their effects on target glands, which produce other hormones that feed back to suppress their controlling hypothalamic and pituitary hormones. Insulin-like growth factor-1 (IGF-1), growth hormone (GH), cortisol, sex steroids, and thyroxine (T₄) all feed back on the hypothalamic-pituitary system. Prolactin is the only pituitary hormone that is suppressed by a hypothalamic factor, dopaminergic. The hypothalamus is also the location of vasopressin-secreting axons that either terminate in the posterior pituitary gland and exert their effect via vasopressin secretion.
from this area or terminate in the mediobasal hypothalamus, from which they can exert effects on water balance, even in the absence of the posterior pituitary gland.

The assessment of pituitary function may be determined by measuring some of the specific pituitary hormone in the basal state; other assessments require the measurement after stimulation. Indirect assessment of pituitary function can be obtained by measuring serum concentrations of the target gland hormones (Table 170-1). Several tests of pituitary function are listed in Table 170-2.

**DISORDERS OF THE HYPOTHALAMIC-PITUITARY AXIS**

**Decision-Making Algorithms**

Available @ StudentConsult.com

Visual Impairment and Leukocoria

Amenorrhea

Pubertal Delay

Polyuria
Hypothalamic deficiency leads to a decrease in most pituitary hormone secretions but may lead to an increase in prolactin secretion. Destructive lesions of the pituitary gland or hypothalamus are more common in childhood than increased pituitary secretion of various hormones. A cranio-phyngioma, a tumor of the Rathke pouch, may descend into the sella turcica, causing erosion of the bone and destruction of pituitary and hypothalamic tissue. Acquired hypopituitarism also may result from pituitary infections; from infiltration (Langerhans cell histiocytosis [histiocytosis X], lymphoma, and sarcoidosis); after radiation therapy or trauma to the CNS; and as a consequence of autoimmunity against the pituitary gland.

Congenital hypopituitarism can be caused by the absence of hypothalamic releasing factors. Without hypothalamic stimulation, the pituitary gland does not release its hormones. Congenital defects associated with hypopituitarism range from holoprosencephaly (cyclopia, cebocephaly, orbital hypotelorism), to cleft palate (6% of cases of cleft palate are associated with GH deficiency). Septo-optic dysplasia (optic nerve hypoplasia, absent septum pellucidum, or variations of both) may result in significant visual impairment with pendular (“roving”) nystagmus (inability to focus on a target) in addition to varying degrees of hypopituitarism. The magnetic resonance imaging (MRI) findings of congenital hypopituitarism may include an ectopic posterior pituitary gland bright spot, the appearance of a pituitary stalk transection, and/or small pituitary gland.

**Table 170-2** Anterior Pituitary Hormone Function Testing

<table>
<thead>
<tr>
<th>RANDOM HORMONE MEASUREMENTS</th>
<th>PROVOCATIVE OR OTHER TESTS</th>
<th>TARGET HORMONE MEASUREMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH (not useful as a random determination except in newborns, and in GH resistance or in pituitary gigantism)</td>
<td>Arginine (a weak stimulus) L-Dopa (useful clinically) Insulin-induced hypoglycemia (a dangerous but accurate test)</td>
<td>IGF-1, IGFBP3 (affected by malnutrition as well as GH excess)</td>
</tr>
<tr>
<td></td>
<td>Clonidine (useful clinically) GHRH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12- to 24-h integrated GH levels (of questionable utility)</td>
<td></td>
</tr>
<tr>
<td>ACTH (early AM sample useful only if in high-normal range)</td>
<td>Cortisol after insulin-induced hypoglycemia (a dangerous test but accurate)</td>
<td>8 AM cortisol</td>
</tr>
<tr>
<td></td>
<td>ACTH stimulation test (may differentiate ACTH deficiency from primary adrenal insufficiency)</td>
<td></td>
</tr>
<tr>
<td>TSH*, LH, FSH*</td>
<td>TRH GnRH (difficult to interpret in prepubertal subjects)</td>
<td>FT4 Testosterone/estradiol</td>
</tr>
<tr>
<td>Prolactin (elevated in hypothalamic disease and decreased in pituitary disease)</td>
<td>TRH</td>
<td>None</td>
</tr>
</tbody>
</table>

ACTH, Adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH, growth hormone; GnRH, gonadotropin-releasing hormone; GHRH, growth hormone-releasing hormone; IGF-1, insulin-like growth factor-1; IGFBP3, insulin-like growth factor-binding protein 3; L-dopa, L-dihydroxyphenylalanine; LH, luteinizing hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

*New supersensitive assays allow determination of abnormally low values found in hypopituitarism.

**DIABETES MELLITUS**

Diabetes mellitus (DM) is characterized by hyperglycemia and glycosuria and is an end point of a few disease processes (Table 171-1). The most common type occurring in childhood is type 1 DM (DM1), which is caused by autoimmune destruction of the insulin-producing beta cells (islets) of the pancreas leading to permanent insulin deficiency. Type 2 DM (DM2) results from insulin resistance and relative insulin deficiency, usually in the context of exogenous obesity. The incidence of DM1 and DM2 in the United States is increasing. Less common types of diabetes result from genetic defects of the insulin receptor or inherited abnormalities in sensing of ambient glucose concentration by pancreatic beta cells (see Table 171-1).

**DEFINITION**

A diagnosis of DM is made based on four glucose abnormalities that may need to be confirmed by repeat testing: (1) Fasting serum glucose concentration ≥126 mg/dL, (2) a random venous plasma glucose ≥200 mg/dL with symptoms of hyperglycemia, (3) an abnormal oral glucose tolerance test (OGTT) with a 2-hour postprandial serum glucose concentration ≥200 mg/dL, and (4) a HgbA1c ≥6.5%.

A patient is considered to have impaired fasting glucose if fasting serum glucose concentration is 100 to 125 mg/dL or impaired glucose tolerance if 2-hour plasma glucose following an OGTT is 140 to 199 mg/dL. Sporadic hyperglycemia can occur in children, usually in the setting of an intercurrent illness. When the hyperglycemic episode is clearly related to
Table 171-1 Classification of Diabetes Mellitus in Children and Adolescents

<table>
<thead>
<tr>
<th>TYPE</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient neonatal</td>
<td>Manifests immediately after birth; lasts 1–3 months</td>
</tr>
<tr>
<td>Permanent neonatal</td>
<td>Other pancreatic defects possible</td>
</tr>
<tr>
<td>Classic type 1</td>
<td>Glycosuria, ketonuria, hyperglycemia, islet cell positive; genetic component</td>
</tr>
<tr>
<td>TYPE 2 (NON-INSULIN-DEPENDENT)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>Cystic fibrosis, hemochromatosis, drugs (L-asparaginase, tacrolimus)</td>
</tr>
<tr>
<td>Adult type (classic)</td>
<td>Associated with obesity, insulin resistance; genetic component</td>
</tr>
<tr>
<td>OTHER</td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>Abnormal glucose tolerance during pregnancy only, which reverts to normal postpartum; increased risk for later onset of diabetes</td>
</tr>
<tr>
<td>Maturity-onset diabetest of youth</td>
<td>Autosomal dominant, onset before age of 25 years; not associated with obesity or autoimmunity</td>
</tr>
<tr>
<td>Mitochondrial diabetes</td>
<td>Single-gene mutations include hepatocyte nuclear factors 1,1a, 4a; glucokinase; insulin promoter factor 1</td>
</tr>
<tr>
<td></td>
<td>Associated with deafness and other neurologic defects, maternal transmission—mtDNA point mutations</td>
</tr>
</tbody>
</table>

Etiology
DM1 results from the autoimmune destruction of insulin-producing beta cells (islets) of the pancreas. In addition to the presence of diabetes susceptibility genes, an unknown environmental insult presumably triggers the autoimmune process. A variety of studies has produced conflicting data regarding a host of environmental factors. These include cow’s milk feeding at an early age, viral infectious agents (Coxsackie virus, cytomegalovirus, mumps, rubella), vitamin D deficiency, and perinatal factors. DM1 is thought to be primarily a T cell–mediated disease.

Antibodies to islet cell antigens may be seen months to years before the onset of beta cell dysfunction (Fig. 171-1). These include islet cell antibodies, insulin autoantibodies, antibodies to tyrosine phosphatase IA-2, antibodies to glutamic acid decarboxylase, and others. The risk for diabetes increases with the number of antibodies detected in the serum. In individuals with one detectable antibody only, the risk is only 10% to 15%; in individuals with three or more antibodies, the risk is 55% to 90%. When 80% to 90% of the beta cell mass have been destroyed, the remaining beta cell mass is insufficient to maintain euglycemia and clinical manifestations of diabetes result (see Fig. 171-1).

Clinical Manifestations
Hyperglycemia results when insulin secretory capacity becomes inadequate to enhance peripheral glucose uptake and to suppress hepatic and renal glucose production. Insulin deficiency usually first causes postprandial hyperglycemia and then fasting hyperglycemia. Ketogenesis is a sign of more complete insulin deficiency. Lack of suppression of gluconeogenesis and glycogenolysis further exacerbates hyperglycemia while fatty acid oxidation generates the ketone bodies: β-hydroxybutyrate, acetoacetate, and acetone. Protein stores in muscle and fat stores in adipose tissue are metabolized to provide substrates for gluconeogenesis and fatty acid oxidation.

Glycosuria occurs when the serum glucose concentration exceeds the renal threshold for glucose reabsorption (from 160 to 190 mg/dL). Glycosuria causes an osmotic diuresis (including obligate loss of sodium, potassium, and other electrolytes), leading to dehydration. Polydipsia occurs as the patient attempts to compensate for the excess fluid losses. Weight loss results from the persistent catabolic state and the loss of calories through glycosuria and ketonuria. The classic presentation of DM1 includes polyuria, polydipsia, polyphagia, and weight loss.

Epidemiology
The annual incidence of DM1 is increasing steadily but with significant geographic differences. In the United States, the annual incidence is approximately 20 in 100,000. The annual incidence in children ranges from a high of 40 in 100,000 among Scandinavian populations to less than 1 in 100,000 in China. The prevalence of DM1 in the United States is highest in non-Hispanic whites followed by African Americans, Hispanic, and American Indians.
Genetic determinants play a role in the susceptibility to DM1, although the mode of inheritance is complex and multigenic. Siblings or offspring of patients with diabetes have a risk of 2% to 8% for the development of diabetes; an identical twin has a 30% to 50% risk. The human leukocyte antigen (HLA) region on chromosome 6 provides the strongest determinant of susceptibility, accounting for approximately 40% of familial inheritance of DM1. Specific class II DR and DQ HLA alleles (HLA DR3 and HLA DR4) increase the risk of developing DM1, whereas other specific HLA alleles exert a protective effect. More than 90% of children with DM1 possess HLA DR3 alleles, HLA DR4 alleles, or both. The insulin gene region variable number tandem repeat on chromosome 11 is also linked to DM1 susceptibility. There is evidence for association, beyond HLA, of more than 100 other loci with DM1. Genetic factors do not fully account for susceptibility to DM1; environmental factors also play a role.

Insulin-dependent (Type 1) Diabetes Mellitus

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**Diabetic Ketoacidosis**

If the clinical features of new-onset DM1 are not detected, diabetic ketoacidosis (DKA) will occur. DKA may also occur in patients with known DM1 if insulin injections are omitted.
or during an intercurrent illness when greater insulin requirements are unmet in the presence of elevated concentrations of the counter-regulatory and stress hormones (glucagon, growth hormone [GH], cortisol, and catecholamines). DKA can be considered to be present if (1) the arterial pH is below 7.3, (2) the serum bicarbonate level is below 15 mEq/L, and (3) ketones are elevated in serum or urine.

**Pathophysiology**

In the absence of adequate insulin secretion, persistent partial hepatic oxidation of fatty acids to ketone bodies occurs. Two of these three ketone bodies are organic acids and lead to metabolic acidosis with an elevated anion gap. Lactic acid may contribute to the acidosis that is initially compensated for by increased fluid intake. As the hyperglycemia and diuresis worsen, most patients are unable to maintain the large fluid intake, and dehydration occurs. Vomiting, as a result of increasing acidosis, and increased insensible water losses caused by tachypnea can worsen the dehydration. Electrolyte abnormalities occur through a loss of electrolytes in the urine and transmembrane alterations resulting from acidosis. As hydrogen ions accumulate as a result of ketoacidosis, intracellular potassium is exchanged for hydrogen ions. Serum concentrations of potassium increase initially with acidosis then decrease as serum potassium is cleared by the kidney. Depending on the duration of ketoacidosis, serum potassium concentrations at diagnosis may be increased, normal, or decreased, but intracellular potassium concentrations are depleted. A decreased serum potassium concentration is an ominous sign of total body potassium depletion. Phosphate depletion also can occur as a result of the increased renal phosphate excretion required for elimination of excess hydrogen ions. Sodium depletion is also common ketoacidosis, resulting from renal losses of sodium caused by osmotic diuresis and from gastrointestinal losses from vomiting (Fig. 171-2).

Patients with DKA present initially with polyuria, polydipsia, nausea, and vomiting. Abdominal pain occurs frequently and can mimic an acute abdomen. The abdomen may be tender from vomiting or distended secondary to a paralytic ileus. The presence of polyuria, despite a state of clinical dehydration, differentiates patients with DKA from patients with gastroenteritis or other gastrointestinal disorders. Respiratory compensation for acidosis results in tachypnea with deep (Kussmaul) respirations. The fruity odor of acetone frequently can be detected on the patient's breath. An altered mental status can occur, ranging from disorientation to coma.

**Laboratory studies** reveal hyperglycemia (serum glucose concentrations ranging from 200 mg/dL to >1000 mg/dL). Arterial pH is below 7.30, and the serum bicarbonate concentration is less than 15 mEq/L. Serum sodium concentrations may be elevated, normal, or low, depending on the balance of sodium and free water losses. The measured serum sodium concentration is artificially low, however, because of hyperglycemia. Hyperlipidemia also contributes to the decrease in measured serum sodium. The level of blood urea nitrogen (BUN) can be elevated with prerenal azotemia secondary to dehydration. The white blood cell count is usually elevated and can be left-shifted without implying the presence of infection. Fever is unusual and should prompt a search for infectious sources that may have triggered the episode of DKA.
Treatment

Therapy for patients with DKA involves careful replacement of fluid deficits, correction of acidosis and hyperglycemia via insulin administration, correction of electrolyte imbalances, and monitoring for complications of treatment. The optimal approach to management of DKA must strike a balance between adequate correction of fluid losses and avoidance of rapid shifts in osmolality and fluid balance. The most serious complication of DKA and its treatment is cerebral edema and cerebral herniation.

A patient with severe DKA is assumed to be approximately 10% dehydrated. If a recent weight measurement is available, the precise extent of dehydration can be calculated. An initial intravenous (IV) fluid bolus of a glucose-free isotonic solution (normal saline, lactated Ringer solution) at 10 to 20 mL/kg should be given to restore intravascular volume and renal perfusion. The remaining fluid deficit after the initial bolus should be added to maintenance fluid requirements, and the total should be replaced slowly over 36 to 48 hours. Ongoing losses resulting from osmotic diuresis usually do not need to be replaced unless urine output is large or signs of poor perfusion are present. Osmotic diuresis is usually minimal when the serum glucose concentration decreases to less than 300 mg/dL. To avoid rapid shifts in serum osmolality, 0.9% sodium chloride can be used as the replacement fluid for the initial 4 to 6 hours, followed by 0.45% sodium chloride.

Hyperglycemia. Fast-acting soluble insulin should be administered as a continuous IV infusion (0.1 U/kg/hour). Serum glucose concentrations should decrease at a rate no faster than 100 mg/dL/hour. When serum glucose concentrations decrease to less than 250 to 300 mg/dL, glucose should be added to the IV fluids. If serum glucose concentrations decrease to less than 200 mg/dL before correction of acidosis, the glucose concentration of the IV fluids should be increased, but the insulin infusion should not be decreased by more than half, and it should never be discontinued before resolution of acidosis.

Acidosis. Insulin therapy decreases the production of free fatty acids and protein catabolism and enhances glucose usage in target tissues. These processes correct acidosis. Bicarbonate therapy should be avoided. Potential adverse effects of bicarbonate administration include paradoxical increases in central nervous system (CNS) acidosis caused by increased diffusion of carbon dioxide across the blood-brain barrier, potential tissue hypoxia caused by shifts in the oxyhemoglobin dissociation curve, abrupt osmotic changes, and increased risk of the development of cerebral edema.

As acidosis is corrected, urine ketone concentrations may appear to rise. β-Hydroxybutyrate, which is not detected in urine ketone assays, is converted with treatment to what the assay most detects, acetoacetate. Hence minute-to-minute urine ketone concentrations are not a required index of the adequacy of therapy.

Electrolyte imbalances. Regardless of the serum potassium concentration at presentation, total body potassium depletion is likely. Serum potassium concentrations can decrease rapidly as insulin and then glucose therapy improves acidosis, and potassium is exchanged for intracellular hydrogen ions. When adequate urine output is shown, potassium should be added to the IV fluids. Potassium replacement should be given as 50% potassium chloride and 50% potassium phosphate at a concentration of 20 to 40 mEq/L. This combination provides phosphate for replacement of deficits but avoids excess phosphate administration, which may precipitate hypocalcemia. If the serum potassium level is greater than 6 mEq/L, potassium should not be added to IV fluids until the potassium level decreases.
Monitoring. Initial laboratory measurements should include serum glucose, sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, phosphate and magnesium concentrations; arterial or venous pH; and a urinalysis. Serum glucose measurement should be repeated every hour during therapy; electrolyte concentrations should be repeated every 2 to 3 hours. Calcium, phosphate, and magnesium concentrations should be measured every 4 to 6 hours during therapy. Neurologic and mental status should be assessed at frequent intervals. Any complaints of headache or deterioration of mental status should prompt rapid evaluation for possible cerebral edema. Indicative symptoms include a decreased sensorium, sudden severe headache, vomiting, change in vital signs (bradycardia, hypertension, apnea), a dilated pupil, opthalmoplegia, or seizure.

Complications
Clinically apparent cerebral edema occurs in 1% to 5% of cases of DKA. Cerebral edema is the most serious complication of DKA, with a mortality rate of 20% to 80%. The pathogenesis of cerebral edema likely involves osmolar shift resulting in fluid accumulation in the intracellular compartment and cell swelling. Subclinical cerebral edema is common in patients with DKA, but the factors that exacerbate this process leading to symptomatic brain swelling and possible cerebral herniation are not clearly defined. Cerebral edema typically occurs 6 to 12 hours after therapy for DKA is begun, often following a period of apparent clinical improvement. Factors that correlate with increased risk for cerebral edema include higher initial BUN concentration, lower initial Pco₂, failure of the serum sodium concentration to increase as glucose concentration decreases during treatment, and treatment with bicarbonate.

Signs of advanced cerebral edema include obtundation, papilledema, pupillary dilation or inequality, hypertension, bradycardia, and apnea. Treatment involves the rapid use of IV mannitol, endotracheal intubation, and ventilation and may require the use of a subdural bolt. Other complications of DKA are intracranial thrombosis or infarction, acute tubular necrosis with acute renal failure caused by severe dehydration, pancreatitis, arrhythmias caused by electrolyte abnormalities, pulmonary edema, and bowel ischemia. Peripheral edema occurs commonly 24 to 48 hours after therapy is initiated and may be related to residual elevations in anti-diuretic hormone and aldosterone.

Transition to Outpatient Management
When the acidosis has been corrected and the patient tolerates oral feedings, the IV insulin infusion can be discontinued, and a regimen of subcutaneous (SC) insulin injections can be initiated. The first SC insulin dose should be given 30 to 45 minutes before discontinuation of the IV insulin infusion. Further adjustment of the insulin dose should be made over the following 2 to 3 days. A patient already diagnosed with DM1 may be restarted on the prior doses if they were adequate. For a patient with new-onset DM1, typical starting total daily doses are approximately 0.5 to 0.7 U/kg/24 hours for pubertal patients and approximately 0.7 to 1 U/kg/24 hours for adolescents, using any number of the available insulin combinations. The best and most common choice for making the transition to SC insulin is to begin by giving injections of fast-acting (bolus) insulin (lispro, aspart, or glulisine insulin) with each meal and long-acting (basal) insulin (glargine or detemir) at bedtime. This regimen of multiple daily injections provides the most flexibility but requires the patient to administer many injections per day and to count carbohydrates in food. An alternative is a fixed mixed split dosing regimen (neutral protamine Hagedorn [NPH] and fasting-acting insulin) with two daily injections.

Externally worn pumps that provide a continuous SC infusion of fast-acting insulin are available, although not usually used at the very onset of DM1. Insulin pumps provide fast-acting insulin in small basal amounts continuously every hour and will provide bolus insulin when instructed. Insulin pumps may be used by all age groups who are highly motivated to achieve tight control. The absence of SC depot insulin (glargine or detemir) can increase the risk of DKA.

Serum glucose concentrations should be assessed before each meal, at bedtime, and periodically at 2 to 3 AM to provide information for adjustment of the regimen. Patients and their families should begin learning the principles of diabetes care as soon as possible. Demonstration of the ability to administer insulin injections and test glucose concentrations using a glucose meter is necessary before discharge, as is knowledge of hypoglycemia management. Meal planning is crucial to control glucose in DM1. Nutrition services must be part of the care delivered to the families from diagnosis.

Honeymoon Period
In some patients with new onset of DM1, the beta cell mass has not been completely destroyed. The remaining functional beta cells seem to recover function with insulin treatment. When this occurs, exogenous insulin requirements decrease. This is a period of stable blood glucose control, often with nearly normal glucose concentrations. This phase of the disease, known as the honeymoon period, usually starts in the first weeks of therapy, often continues for 3 to 6 months, and can last 2 years.

Outpatient Type 1 Diabetes Mellitus Management
Management of DM1 in children requires a comprehensive approach with attention to medical, nutritional, and psychosocial issues. Therapeutic strategies should be flexible with the individual needs of each patient and the family taken into account. Optimal care involves a team of diabetes professionals, including a physician, a diabetes nurse educator, a dietitian, and a social worker or psychologist.

Goals
The Diabetes Control and Complications Trial established that intensive insulin therapy, with the goal of maintaining blood glucose concentrations as close to normal as possible, can delay the onset and slow the progression of complications of diabetes (retinopathy, nephropathy, neuropathy). Attaining this goal using intensive insulin therapy can increase the risk of hypoglycemia. The adverse effects of hypoglycemia in young children may be significant because the immature CNS may be more susceptible to glycopenia. Although the risk for diabetic complications increases with duration of diabetes,
there is controversy as to whether the increase of risk is slower in the prepubertal years than in adolescence and adulthood.

The goals of therapy differ, depending on the age of the patient. For children younger than 5 years old, an appropriate goal is maintenance of blood glucose concentrations between 80 and 180 mg/dL. For school-age children, 80 to 150 mg/dL is a reasonable target range. For adolescents, the goal is 70 to 130 mg/dL. Goals of therapy also should take into account other individual characteristics, such as a history of severe hypoglycemia and the abilities of the patient and family.

**Insulin Regimens**

Many types of insulin differ in duration of action and time to peak effect (Table 171-2). These insulins can be used in various combinations, depending on the needs and goals of the individual patient. The most commonly used regimen is that of multiple injections of fast-acting insulin given with meals in combination with long-acting basal insulin given at bedtime. This regimen provides flexibility but requires administration of many injections per day and will require assistance for young children. After the total daily dose of insulin is determined, 30% to 50% are given as long-acting insulin, and the remainder is given as fast-acting insulin, divided according to the need for corrections of high glucose levels and for meals. To correct for hyperglycemia, one can determine the insulin sensitivity using the 1800 rule; dividing 1800 by the total daily dose of insulin to determine how many milligrams per deciliter of glucose will decrease with one unit of insulin. The insulin:carbohydrate ratio is used to calculate insulin for the carbohydrate content of food; 450 divided by the total daily dose determines the number of grams of carbohydrate that requires one unit of insulin.

Pumps that provide a continuous SC infusion of short-acting insulin also are available and are being used by children and adolescents who are highly motivated to achieve tight control.

Lispro, aspart, and glulisine insulin are synthetic human insulin analogs in which amino acid alterations result in fast absorption and onset of action (see Table 171-2). Because of the short duration of action, these are used in combination with long-acting insulin. Glargine and detemir are insulin analogs with increased solubility at acidic pH and decreased solubility at physiologic pH. They have a duration of greater than 24 hours and act as a basal insulin.

Newly diagnosed patients in the honeymoon period may require 0.4 to 0.6 U/kg/24 hours. Prepubertal patients with diabetes longer than 1 to 2 years typically require 0.5 to 1 U/kg/24 hours. During middle adolescence when elevated GH concentrations produce relative insulin resistance, insulin requirements increase by 40% to 50%, and doses of 1 to 2 U/kg/24 hours are typical.

**Nutrition**

Balancing the daily meal plan with the dosages of insulin is crucial for maintaining serum glucose concentrations within the target range and avoiding hypoglycemia or hyperglycemia. The content and schedule of meals vary according to the type of insulin regimen used. It is recommended that carbohydrates contribute 50% to 65% of the total calories, protein 12% to 20%, and fat <30%. Saturated fat should contribute <10% of the total caloric intake, and cholesterol intake should be less than 300 mg/24 hours. High fiber content is recommended.

Patients using multiple daily injections or the insulin pump can maintain a more flexible meal schedule with regard to the timing of meals and the carbohydrate content. These patients give an injection of insulin before or immediately after each meal with the total dose calculated according to the carbohydrate content of the meal. Further adjustments in the dose can be made based on the measured serum glucose concentration and plans for activity during the day. Children using a twice-a-day combination of intermediate-acting and fast-acting insulins need to maintain a relatively consistent meal schedule so that carbohydrate absorption and insulin action peaks correspond. A typical meal schedule for a patient using this type of regimen involves three meals and three snacks daily. The total carbohydrate content of the meals and snacks should be kept constant.

**Blood Glucose Testing**

Blood glucose should be routinely monitored before each meal and at bedtime. Hypoglycemia during the night or excessive variability in the morning glucose concentrations should prompt additional testing at 2 or 3 AM to ensure that there is no consistent hypoglycemia or hyperglycemia. During periods of illness or when blood glucose concentrations are higher than 300 mg/dL, urine ketones also should be tested. Continuous glucose monitors, which provide minute-to-minute blood glucose concentration information, can be useful in following

<table>
<thead>
<tr>
<th>Table 171-2</th>
<th>Representative Profiles of Insulin</th>
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<tbody>
<tr>
<td>INSULIN</td>
<td>ONSET</td>
</tr>
<tr>
<td>Very Short Acting</td>
<td>Lispro, aspart, glulisine</td>
</tr>
<tr>
<td>Short Acting</td>
<td>Regular</td>
</tr>
<tr>
<td>Intermediate Acting</td>
<td>Neutral protamine Hagedorn (NPH) (isophane)</td>
</tr>
<tr>
<td>Long Acting</td>
<td>Glargine</td>
</tr>
<tr>
<td></td>
<td>Detemir</td>
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trends of blood glucose concentrations but should not be used in calculations of mealtime insulin doses.

**Long-Term Glycemic Control**
Measurements of glycohemoglobin or hemoglobin A₁c (HgbA1c) reflect the average blood glucose concentration over the preceding 3 months and provide a means for assessing long-term glycemic control. HgbA1c should be measured four times a year, and the results should be used for counseling of patients. The American Diabetes Association has set HgbA1c targets based on age with children less than 6 years having an HgbA1c target of 7.5% to 8.5%, ages 6 to 13 years HgbA1c target of less than 8%, and ages 13 to 18 years HgbA1c target of less than 7.5%. Measurements of HgbA1c are inaccurate in patients with hemoglobinopathies. Glycosylated albumin or fructosamine can be used in these cases.

**Complications**
Patients with DM1 for more than 3 to 5 years should receive an annual ophthalmologic examination for retinopathy. Urine should be collected annually for assessment of microalbuminuria, which suggests early renal dysfunction and indicates a high risk of progression to nephropathy. Treatment with angiotensin-converting enzyme inhibitors may halt the progression of microalbuminuria. In children with DM1, annual cholesterol measurements and periodic assessment of blood pressure are recommended. Early detection of hypertension and hypercholesterolemia with appropriate intervention can help limit future risk of coronary disease.

**Other Disorders**
Chronic autoimmune lymphocytic thyroiditis is particularly common and can result in hypothyroidism. Because symptoms can be subtle, thyroid function tests should be performed annually. Other disorders that occur with increased frequency in children with DM1 include celiac disease, IgA deficiency, Addison disease, and peptic ulcer disease.

**Special Problems: Hypoglycemia**
Hypoglycemia occurs commonly in patients with DM1. For patients in adequate or better control, it is expected to occur on average once or twice a week. Severe episodes of hypoglycemia, resulting in seizures or coma or requiring assistance from another person, occur in 10% to 25% of these patients per year.

Hypoglycemia in patients with DM1 results from a relative excess of insulin in relation to the serum glucose concentration. This excess can be caused by alterations in the dose, timing, or absorption of insulin; alterations of carbohydrate intake; or changes in insulin sensitivity resulting from activity. Defective counterregulatory responses also contribute to hypoglycemia. Abnormal glucagon responses to falling serum glucose concentrations develop within the first few years of the disease, and abnormalities in epinephrine release occur after a longer duration.

**Lack of awareness** of hypoglycemia occurs in approximately 25% of patients with diabetes. Recent episodes of hypoglycemia may play a role in the pathophysiology of hypoglycemia unawareness; after an episode of hypoglycemia, autonomic responses to subsequent episodes are reduced. A return of symptoms of hypoglycemia can be exhibited in these patients after 2 to 3 weeks of strict avoidance of hypoglycemic episodes.

Symptoms of hypoglycemia include symptoms resulting from neuroglycopenia (headache, visual changes, confusion, irritability, or seizures) and symptoms resulting from the catecholamine response (tremors, tachycardia, diaphoresis, or anxiety). Mild episodes can be treated with administration of rapidly absorbed oral glucose (glucose gel or tablets or fruit juices). More severe episodes that result in seizures or loss of consciousness at home should be treated with glucagon injections. IV glucose should be given in hospital settings.

**Prognosis**
Long-term complications of DM1 include retinopathy, nephropathy, neuropathy, and macrovascular disease. Evidence of organ damage caused by hyperglycemia is rare in patients with diabetes of less than 5 to 10 years’ duration; clinically apparent disease rarely occurs before 10 to 15 years’ duration. Diabetic retinopathy is the leading cause of blindness in the United States. Nephropathy eventually occurs in 30% to 40% and accounts for approximately 30% of all new adult cases of end-stage renal disease. Neuropathy occurs in 30% to 40% of postpubertal patients with DM1 and leads to sensory, motor, or autonomic deficits. Macrovascular disease results in an increased risk of myocardial infarction and stroke among individuals with diabetes.

Intensive control of diabetes, using frequent blood glucose testing and multiple daily injections of insulin or an insulin pump, can reduce the development or progression of diabetic complications, including a 76% reduction of risk for retinopathy, a 39% reduction in microalbuminuria, and a 60% reduction in clinical neuropathy. For pubertal and adult patients, the benefits of intensive therapy likely outweigh the increased risk for hypoglycemia. For younger patients, in whom the risks for hypoglycemia are greater and the benefits of tight glucose control may be lower, a less intensive regimen may be appropriate.

**NON-INSULIN-DEPENDENT (TYPE 2) DIABETES MELLITUS**

**Pathophysiology**
DM2 can occur as the result of various pathophysiologic processes; however the most common form results from peripheral insulin resistance and compensatory hyperinsulinemia, followed by failure of the pancreas to maintain adequate insulin secretion (see Table 171-1).

**Epidemiology**
The prevalence of DM2 in children is increasing in parallel with childhood obesity and is highest in children of ethnic groups with a high prevalence of DM2 in adults, including Native Americans, Hispanic Americans, and African Americans. Obesity, the metabolic syndrome, ethnicity, and a family history of DM2 are risk factors. Auto-antibodies to the pancreas are present among some clinically assumed to have DM2, compounding the difficulty in differentiating DM1 from DM2 at the time of diagnosis.
Clinical Manifestations and Differential Diagnosis

Fasting and postprandial glucose levels for diagnosis of DM2 are the same as those for DM1. The diagnosis of DM2 may be suspected on the basis of polynia and polydipsia in a background of the metabolic syndrome. Differentiating DM2 from DM1 in children on only clinical grounds can be challenging. The possibility of DM2 should be considered in patients who are obese, have a strong family history of DM2, have other characteristics of the metabolic syndrome, or have absence of antibodies to beta cell antigens at the time of diagnosis of diabetes. Acanthosis nigricans, a dermatologic manifestation of hyperinsulinism and insulin resistance, presents as hyperkertatotic pigmentation in the nape of the neck and in flexural areas and is noted as a sign in the metabolic syndrome. Although ketonuria occurs far more commonly in DM1, it also can occur in patients with DM2 under conditions of physiologic stress and cannot be used as an absolute differentiating factor. DM2 can be confirmed by the evaluation of insulin or C-peptide responses to stimulation with oral carbohydrate and in the absence of islet cell autoreactivity.

Therapy

DM2 is the result of a combination of insulin resistance, relative insulin deficiency, and a secretory beta cell defect. Asymptomatic patients with mildly elevated glucose values (slightly >126 mg/dL for fasting or slightly >200 mg/dL for random glucose) may be managed initially with lifestyle modifications, including nutrition therapy (dietary adjustments) and increased exercise. Exercise has been shown to decrease insulin resistance. In most children with new-onset, uncomplicated DM2, oral agents are usually the first line of therapy. Only metformin, an insulin secretagogue, is approved by the U.S. Food and Drug Administration for use in children. A rare side effect of metformin is lactic acidosis, occurring mainly in patients with compromised renal function. The most common side effect is gastrointestinal upset. If ketonuria or ketoacidosis occurs, insulin treatment is necessary to first achieve adequate glycemic control but may be discontinued within weeks with continuation of oral medications. Insulin therapy may be required if adequate glycemic control is not achieved with lifestyle modifications and metformin.

Because DM2 may have a long preclinical course, early diagnosis is possible in subjects at risk who have the metabolic syndrome. Significant lifestyle modifications, such as improved eating habits and increased exercise, have a role in preventing or decreasing the morbidity of DM2. Finally, it is critical to monitor and manage the other components of metabolic syndrome, such as advanced pubertal development, hypertension, hyperlipidemia, and polycystic ovary syndrome in females.

Maturity-onset diabetes of youth (MODY)

MODY comprises a group of dominantly inherited forms of relatively mild diabetes. Insulin resistance does not occur in these patients; instead the primary abnormality is an insufficient insulin secretory response to glycemic stimulation. Treatment depends on the type and can include the use of sulfonylureas.

HYPOGLYCEMIA

Hypoglycemia in infancy and childhood can result from a large variety of hormonal and metabolic defects (Table 172-1). Hypoglycemia occurs most frequently in the early neonatal period, often as a result of transient neonatal hyperinsulinemia in infants of diabetic mothers or as a result of inadequate energy stores to meet the disproportionately large metabolic needs of premature or small for gestational age newborns. Hypoglycemia during the first few days of life in an otherwise normal newborn is less frequent and warrants concern (see Chapter 6). After the initial 2 to 3 days of life, hypoglycemia is far less common and is more frequently the result of endocrine or metabolic disorders (although sepsis must always be ruled out).

DEFINITION

The diagnosis of hypoglycemia should be made on the basis of a low serum glucose concentration, symptoms compatible with hypoglycemia, and resolution of the symptoms after administration of glucose.

Serum glucose concentrations less than 45 mg/dL are considered to be abnormal and necessitate treatment. Serum glucose concentrations greater than 55 mg/dL occasionally can occur in normal individuals, especially with prolonged fasting, but should be considered suspect, particularly if there are concurrent symptoms of hypoglycemia (Table 172-2).

CLINICAL MANIFESTATIONS

The symptoms and signs of hypoglycemia result from direct depression of the central nervous system owing to lack of energy substrate and the counterregulatory adrenergic response to low glucose via catecholamine secretion designed to correct hypoglycemia (see Table 172-2). Compared with older children, infants do not usually show adrenergic symptoms. The signs and symptoms of hypoglycemia in infants are relatively nonspecific and include jitteriness, feeding difficulties, pallor, hypotonia, hypothermia, episodes of apnea and bradycardia, depressed levels of consciousness, and seizures. In older children, signs and symptoms include confusion, irritability, headaches, visual changes, tremors, pallor, sweating, tachycardia, weakness, seizures, and coma.

Failure to recognize and treat severe, prolonged hypoglycemia can result in serious long-term morbidity, including mental retardation and nonhypoglycemic seizures. Younger infants and patients with more severe or prolonged hypoglycemia are at greatest risk for adverse outcomes.
PATHOPHYSIOLOGICAL
Hormonal Signal
Normal regulation of serum glucose concentrations requires
appropriate interaction of a number of hormonal signals and
metabolic pathways (Figure 172-1). In a normal individual, a
decrease in serum glucose concentrations leads to a suppres-
sion of insulin secretion and increased secretion of the coun-
terregulatory hormones (growth hormone [GH], cortisol,
glucagon, and epinephrine) (see Fig. 172-1). This hormonal
signal promotes the release of amino acids (particularly ala-
nine) from muscle to fuel gluconeogenesis and the release of
triglyceride from adipose tissue stores to provide free fatty
acids (FFAs) for hepatic ketogenesis. FFAs and ketones serve
as alternate fuels for muscle. This hormonal signal also stimu-
lates the breakdown of hepatic glycogen and promotes gluco-
neogenesis. Failure of any of the components of this hormonal
signal can lead to hypoglycemia.

<table>
<thead>
<tr>
<th>Table 172-1</th>
<th>Classification of Hypoglycemia in Infants and Children</th>
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<tbody>
<tr>
<td><strong>ABNORMALITIES IN THE HORMONAL SIGNAL INDICATING HYPOGLYCEMIA</strong></td>
<td><strong>FATTY ACID OXIDATION</strong></td>
</tr>
<tr>
<td>COUNTERREGULATORY HORMONE DEFICIENCY</td>
<td>Long-, medium-, or short-chain fatty acid acyl-CoA dehydrogenase deficiency</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
<td>Carnitine deficiency (primary or secondary)</td>
</tr>
<tr>
<td>Isolated growth hormone deficiency</td>
<td>Carnitine palmitoyltransferase deficiency</td>
</tr>
<tr>
<td>ACTH deficiency</td>
<td>Other</td>
</tr>
<tr>
<td>Addison disease</td>
<td>Enzymatic defects</td>
</tr>
<tr>
<td>Glucagon deficiency</td>
<td>Galactosemia</td>
</tr>
<tr>
<td>Epinephrine deficiency</td>
<td>Hereditary fructose intolerance</td>
</tr>
<tr>
<td>HYPERINSULINISM</td>
<td>Propionic acidemia</td>
</tr>
<tr>
<td>Infant of a diabetic mother</td>
<td>Methylmalonic acidemia</td>
</tr>
<tr>
<td>Infant with erythroblastosis fetalis</td>
<td>Tyrosinosis</td>
</tr>
<tr>
<td>Persistent hyperinsulinemic hypoglycemia of infancy</td>
<td>Glutaric aciduria</td>
</tr>
<tr>
<td>Beta cell adenoma (insulinoma)</td>
<td>Global hepatic dysfunction</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome</td>
<td>Reye syndrome</td>
</tr>
<tr>
<td>Anti-insulin receptor antibodies</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>INADEQUATE SUBSTRATE</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Prematurity/small for gestational age infant</td>
<td>Sepsis, shock</td>
</tr>
<tr>
<td>Ketotic hypoglycemia</td>
<td>Carcinoma/sarcoma (IGF-2 secretion)</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>Malnutrition/starvation</td>
</tr>
<tr>
<td>DISORDERS OF METABOLIC RESPONSE PATHWAYS</td>
<td>Hyperviscosity syndrome</td>
</tr>
<tr>
<td>Glycogenolysis</td>
<td>DRUGS/INTOXICATIONS</td>
</tr>
<tr>
<td>Glucose-6-phosphatase deficiency</td>
<td>Oral hypoglycemic agents or insulin</td>
</tr>
<tr>
<td>Amylo-1,6-glucosidase deficiency</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Liver phosphorylase deficiency</td>
<td>Salicylates</td>
</tr>
<tr>
<td>Glycogen synthase deficiency</td>
<td>Propranolol</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Fructose-1,6-diphosphatase deficiency</td>
<td>Pentamidine</td>
</tr>
<tr>
<td>Pyruvate carboxylase deficiency</td>
<td>Akee fruit (unripe)</td>
</tr>
<tr>
<td>Phosphoenolpyruvate carboxykinase deficiency</td>
<td>Quinine</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim-sulfamethoxazole (with renal failure)</td>
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</tbody>
</table>

ACTH, Adrenocorticotropic hormone; acyl-CoA, acyl coenzyme A; IGF-2, insulin-like growth factor-2.
as nesidioblastosis, or persistent hyperinsulinemic hypoglycemia of the newborn. In these infants, hyperplasia of the pancreatic islet cells develops in the absence of excess stimulation by maternal diabetes. Some of these patients have genetic abnormalities of the islet cell sulfonylurea receptor or other genetic defects that alter the function of the adenosine triphosphate–sensitive potassium channel that regulates insulin secretion. Hyperinsulinism also can occur in Beckwith-Wiedemann syndrome, a condition characterized by neonatal somatic gigantism: macrosomia, macroglossia, omphalocele, visceromegaly, and earlobe creases.

Regardless of the cause, neonates with hyperinsulinism are characteristically large for gestational age (see Chapter 60). Hypoglycemia is severe and frequently occurs within 1 to 3 hours of a feeding. Glucose requirements are increased, often two to three times the normal basal glucose requirement of 6 to 8 mg/kg/min. The diagnosis of hyperinsulinism is confirmed by the detection of serum insulin concentrations greater than 5 μU/mL during an episode of hypoglycemia. The absence of serum and urine ketones at the time of hypoglycemia is an important diagnostic feature, distinguishing hyperinsulinism from defects in counterregulatory hormone secretion.

Treatment initially involves the infusion of intravenous (IV) glucose at high rates and of diazoxide to suppress insulin secretion. If diazoxide therapy is unsuccessful, long-acting somatostatin analogs can be tried. Often medical therapy for persistent hyperinsulinemic hypoglycemia of the newborn is unsuccessful, and subtotal (90%) pancreatectomy is required to prevent long-term neurologic sequelae of hypoglycemia. In children hyperinsulinemia is a rare condition characterized by a voracious appetite, obesity, and accelerated linear growth and usually results from an islet cell adenoma. Computed tomography, magnetic resonance imaging, or radioisotope imaging of the pancreas should be attempted, but visualization of an adenoma is usually difficult. Surgical removal of the adenoma is curative.

Factitious Hyperinsulinemia

In rare cases insulin or a hypoglycemic medication is administered by a parent or caregiver to a child as a form of child abuse, which is a condition referred to as Munchausen syndrome by proxy. This diagnosis should be suspected if extremely high insulin concentrations are detected (>100 μU/mL). C-peptide concentrations are low or undetectable, which confirms that the insulin is from an exogenous source.

Defects in Counterregulatory Hormones

Abnormalities in the secretion of counterregulatory hormones that produce hypoglycemia usually involve GH, cortisol, or both. Deficiencies in glucagon and epinephrine secretion are rare. GH and cortisol deficiency occur as a result of hypopituitarism. Hypopituitarism results from congenital hypoplasia or aplasia of the pituitary or, more commonly, from deficiency of hypothalamic releasing factors (see Chapter 173). Clues to this diagnosis in infants include the presence of hypoglycemia in association with midline facial or neurologic defects (e.g., cleft lip and palate or absence of the corpus callosum), pendular (roving) nystagmus (indicating visual impairment from possible abnormalities in the development of the optic nerves, Table 172-2

<table>
<thead>
<tr>
<th>FEATURES ASSOCIATED WITH EPINEPHRINE RELEASE*</th>
<th>FEATURES ASSOCIATED WITH CEREBRAL GLYCOGENOLYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perspiration</td>
<td>Headache</td>
</tr>
<tr>
<td>Palpitation (tachycardia)</td>
<td>Mental confusion</td>
</tr>
<tr>
<td>Pallor</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>Trembling</td>
<td>Personality changes</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Inability to concentrate</td>
</tr>
<tr>
<td>Weakness</td>
<td>Staring</td>
</tr>
<tr>
<td>Nausea</td>
<td>Hunger</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Convulsions</td>
</tr>
<tr>
<td>Ataxia</td>
<td>Coma</td>
</tr>
<tr>
<td>Coma</td>
<td>Diplopia</td>
</tr>
<tr>
<td>Diplopia</td>
<td>Stroke</td>
</tr>
</tbody>
</table>

*These features and perceptions of the features may be blunted if the patient is receiving β-blocking agents.

Figure 172-1 Regulation of serum glucose. ◦ represents inhibitions. EPI, Epinephrine; FFA, free fatty acid; GH, growth hormone; TG, triglyceride.
which can occur in septo-optic dysplasia), and the presence of microphallus and cryptorchidism in boys (indicating abnormalities in gonadotropin secretion). Jaundice and hepatomegaly also can occur, simulating neonatal hepatitis. Despite the presence of GH deficiency, these infants are usually of normal size at birth.

Deficient cortisol secretion also can occur in primary adrenal insufficiency, resulting from a variety of causes. In infants it often results from congenital adrenal hyperplasia, most frequently as a result of 21-hydroxylase deficiency (see Chapters 177 and 178). In older children, primary adrenal insufficiency is seen most frequently in Addison disease and other disorders (see Chapter 178).

Confirmation of GH or cortisol deficiency as the cause of hypoglycemia requires the detection of low serum GH and cortisol concentrations during an episode of hypoglycemia or after other stimulatory testing. In contrast to hyperinsulinism, serum and urine ketones are positive at the time of hypoglycemia and FFAs are elevated. Treatment involves supplementation of the deficient hormones in physiologic doses.

**ENERGY STORES**

Sufficient energy stores in the form of glycogen, adipose tissue, and muscle are necessary to respond appropriately to hypoglycemia. Deficiencies in these stores are a common cause of hypoglycemia in neonates who are small for gestational age or premature (see Chapter 60). Beyond the early neonatal period, energy stores are usually sufficient to meet the metabolic requirements except in malnourished children.

**IDIOPATHIC KETOTIC HYPOGLYCEMIA**

A common cause of new-onset hypoglycemia is idiopathic ketotic hypoglycemia, usually seen in children between 18 months and 5 years of age. Patients have symptoms of hypoglycemia after a period of prolonged fasting, often in the setting of an intercurrent illness with decreased feeding. Children with this disorder are often thin and small and may have a history of being small for gestational age. Defective mobilization of alanine from muscle to fuel gluconeogenesis is thought to be the cause, although the condition may derive mostly from having lower fuel reserves. Because there are no specific diagnostic tests for this disorder, ketotic hypoglycemia is a diagnosis of exclusion.

Treatment involves avoidance of fasting and frequent feedings of a high-protein, high-carbohydrate diet. Patients may require hospitalization for IV glucose infusion if they cannot maintain adequate oral intake during a period of illness. The disorder usually resolves spontaneously by 7 to 8 years of age.

**DISRUPTED METABOLIC RESPONSE PATHWAYS**

Maintenance of normal serum glucose concentrations in the fasting state requires glucose production via glycogenolysis and gluconeogenesis and the production of alternative energy sources (FFAs and ketones) via lipolysis and fatty acid oxidation.

**Glycogenolysis**

Glycogen storage diseases occur in a variety of subtypes that differ in severity (see Chapter 52). Among the subtypes that result in hypoglycemia, the most severe form is glucose-6-phosphatase deficiency, which is characterized by severe hypoglycemia, massive hepatomegaly, growth retardation, and lactic acidosis. In contrast, deficiencies in the glycogen phosphorylase enzymes may cause isolated hepatomegaly with or without hypoglycemia.

The diagnosis of glycogen storage disease is suggested by a finding of hepatomegaly without splenomegaly. Confirmation of the diagnosis requires specific biochemical studies of leukocytes or liver biopsy specimens. Treatment involves frequent high-carbohydrate feedings during the day and continuous feedings at night via nasogastric tube. Feedings of uncooked cornstarch overnight are sufficient to maintain serum glucose concentrations in some patients.

**Gluconeogenesis**

Defects in glucogenogenesis are uncommon and include fructose-1,6-diphosphatase deficiency and phosphoenolpyruvate carboxykinase deficiency. Affected patients exhibit fasting hypoglycemia, hepatomegaly, lactic acidosis, and hyperuricemia. Ketosis occurs, and FFA and alanine concentrations are high. Treatment involves frequent high-carbohydrate, low-protein feedings (see Chapter 52).

**Fatty Acid Oxidation**

Fatty acid oxidation disorders of ketogenesis include the fatty acid acyl-coenzyme A (CoA) dehydrogenase deficiencies; long-chain, medium-chain, and short-chain acyl-CoA dehydrogenase deficiencies; and hereditary carnitine deficiency (see Chapter 55). Of these disorders, medium-chain acyl-CoA dehydrogenase deficiency is the most common; it occurs in 1 in 9000 to 15,000 live births. Patients often are well in infancy and have the first episode of hypoglycemia at 2 years of age or older. Episodes of hypoglycemia usually occur with prolonged fasting or during episodes of intercurrent illness.

Mild hepatomegaly may be present along with mild hyperammonemia, hyperuricemia, and mild elevations in hepatic transaminases. Ketone concentrations are low or undetected. The diagnosis is confirmed by the finding of elevated concentrations of dicarboxylic acids in the urine. Treatment involves avoidance of fasting.

**OTHER METABOLIC DISORDERS**

Many metabolic disorders can lead to hypoglycemia, including galactosemia, hereditary fructose intolerance, and disorders of organic acid metabolism (see Table 172-1). Hypoglycemia in these disorders is usually a reflection of global hepatic dysfunction secondary to the buildup of hepatotoxic intermediates. Many of these disorders present with low concentrations of ketone bodies because ketogenesis also is affected. The finding of non–glucose-reducing substances in the urine suggests a diagnosis of galactosemia or hereditary fructose intolerance. Occurrence of symptoms after ingestion of fructose or sucrose suggests hereditary fructose intolerance. Treatment requires dietary restriction of the specific offending substances.

**MEDICATIONS AND INTOXICATION**

Hypoglycemia can occur as an adverse effect of numerous medications (see Table 172-1). Valproate toxicity can cause...
a disorder similar to that seen in the fatty acid oxidation defects. Ethanol ingestion also can cause hypoglycemia, especially in younger children, because the metabolism of ethanol results in the depletion of cofactors necessary for gluconeogenesis.

**DIAGNOSIS**

Although the list of causes of hypoglycemia is long and complex, establishing the etiology in a particular patient is important. Frequently it is difficult to make an accurate diagnosis until one can obtain a critical sample of blood and urine at the time of the hypoglycemic episode. In a child with unexplained hypoglycemia, a serum sample should be obtained before treatment for the measurement of glucose and insulin, GH, cortisol, FFAs, and β-hydroxybutyrate and acetoacetate. Measurement of serum lactate levels also should be considered. A urine specimen should be obtained for measuring ketones and reducing substances. Hypoglycemia without ketonuria suggests hyperinsulinism or a defect in fatty acid oxidation. The results of this initial testing can establish whether endocrine causes are responsible and, if not, provide initial information regarding which types of metabolic disorders are most likely. Whenever possible, additional samples of blood and urine should be frozen for further analysis, if necessary.

**EMERGENCY MANAGEMENT**

Acute care of a patient with hypoglycemia consists of rapid administration of IV glucose (2 mL/kg of 10% dextrose in water). After the initial bolus, an infusion of IV glucose should provide approximately 1.5 times the normal hepatic glucose production rate (8 to 12 mg/kg/min in infants, 6 to 8 mg/kg/min in children). This infusion allows for suppression of the catabolic state and prevents further decompensation in patients with certain metabolic disorders. If adrenal insufficiency is suspected, stress doses of glucocorticoids should be administered.

**Growth Hormone Physiology**

Growth hormone (GH) secretion is pulsatile, stimulated by hypothalamic GH-releasing factor (GRF) and inhibited by GH release inhibitory factor (somatostatin, somatotropin release-inhibiting factor [SRIF]), which interact with their individual receptors on the somatotrope in a noncompetitive manner. GH is also stimulated by ghrelin, produced in the stomach. GH circulates bound to a GH-binding protein (GHBP); GHBP abundance reflects the abundance of GH receptors. GH has direct effects on tissue and also causes production and secretion of insulin-like growth factor-1 (IGF-1) in many tissues. GH stimulates IGF-1 production in liver along with production of the acid-labile subunit and the IGF-binding protein (IGF-BP3); this forms the complex that delivers IGF-1 to tissue.

IGF-1 acts primarily as a paracrine and autocrine agent and is most closely associated with postnatal growth. When IGF-1 attaches to its membrane-bound receptor, second messengers are stimulated to change the physiology of the cell and produce growth effects. IGF-1 production is influenced by disease states such as malnutrition, chronic renal and liver disease, hypothyroidism, or obesity.

IGF-BP3 is measurable in clinical assays and is less influenced by nutrition and age than is IGF-1; measuring IGF-1 and IGF-BP3 is useful in evaluating GH adequacy, particularly in infancy and early childhood.

**Measurement of Growth**

The correct measurement of an infant's length requires one adult to hold the infant's head still and another adult to extend the feet with the soles perpendicular to the lower legs. A caliper-like device, such as an infantometer, or the movable plates on an infant scale are used so that the exact distance between the two calipers or plates can be determined. Marking the position of the head and feet of an infant lying on a sheet of paper on the examining table leads to inaccuracies and may miss true disorders of growth or create false concerns about a disorder of growth in a normal child. Accurate measurements of height (standing), or length (lying down), and weight should be plotted on the Centers for Disease Control and Prevention growth charts for the timely diagnosis of growth disorders (http://www.cdc.gov/growthcharts/).

After 2 years of age, the height of a child should be measured in the standing position. Children measured in the standing position should be barefoot against a hard surface. A Harpenden stadiometer or equivalent device is optimal for the measurement of stature. A decrease of roughly 1.25 cm in height measurement may occur when the child is measured in the standing position rather than in the lying position, leading to the inappropriate referral of many children who appear to be not growing to a subspecialist.

Measurement of the arm span is essential when the diagnoses of Marfan or Klinefelter syndrome, short-limbed dwarfism, or other dysmorphic conditions are considered. Arm span is measured as the distance between the tips of the fingers when the patient holds both arms outstretched horizontally while standing against a solid surface. The upper-to-lower segment ratio is the ratio of the upper segment (determined by subtraction of the measurement from the symphysis pubis to the floor [known as the lower segment] from the total height) to the lower segment. This ratio changes with age. A normal term...
infant has an upper-to-lower ratio of 1.7:1, a 1-year-old has a ratio of 1.4:1, and a 10-year-old has a ratio of 1:1. Conditions of hypogonadism, not commonly discerned or suspected until after the normal age for onset of puberty, lead to greatly decreased upper-to-lower ratio in an adult, whereas long-lasting and untreated hypothyroidism leads to a high upper-to-lower ratio in the child.

**Endocrine Evaluation of Growth Hormone Secretion**

GH is a 191-amino acid protein secreted by the pituitary gland under the control of GRF and SRIF (see Fig. 170-2). GH secretion is enhanced by α-adrenergic stimulation, hypoglycemia, starvation, exercise, early stages of sleep, and stress and inhibited by β-adrenergic stimulation and hyperglycemia. Because concentrations of GH are low throughout the day, except for brief secretory peaks in the middle of the night or early morning, the daytime ascertainment of GH deficiency or sufficiency on the basis of a single determination of a random GH concentration is impossible. Adequacy of GH secretion may be determined by a stimulation test to measure peak GH secretion. A normal response is a vigorous secretory peak after stimulation; the lack of such a peak is consistent with GH deficiency. However there is a high false-positive rate (on any day, about 10% or more of normal children may not reach the normal GH peak after even two stimulatory tests). Indirect measurements of GH secretion, such as serum concentrations of IGF-1 and IGF-BP3, are considered better screens for GH deficiency.

The factors responsible for postnatal growth are not the same as the factors that mediate fetal growth. **Thyroid hormone** is essential for normal postnatal growth, although a thyroid hormone–deficient fetus achieves a normal birth length; similarly a GH-deficient fetus has a normal birth length, although in IGF-1 deficiency resulting from GH resistance (Laron dwarfism), fetuses are shorter than control subjects. Adequate thyroid hormone is necessary to allow the secretion of GH. Hypothyroid patients may appear falsely to be GH deficient; with thyroid hormone repletion, GH secretion normalizes. Gonadal steroids are important in the pubertal growth spurt. The effects of other hormones on growth are noted in Table 173-1.

**ABNORMALITIES OF GROWTH**

**Short Stature of Nonendocrine Causes**

**Table 173-1 Hormonal Effects on Growth**

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>BONE AGE</th>
<th>GROWTH RATE</th>
<th>ADULT HEIGHT*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen excess</td>
<td>Advanced</td>
<td>Increased</td>
<td>Diminished</td>
</tr>
<tr>
<td>Androgen deficiency</td>
<td>Normal or delayed</td>
<td>Normal or decreased</td>
<td>Increased slightly or normal</td>
</tr>
<tr>
<td>Thyroxine excess</td>
<td>Advanced</td>
<td>Increased</td>
<td>Normal or diminished</td>
</tr>
<tr>
<td>Thyroxine deficiency</td>
<td>Retarded</td>
<td>Decreased</td>
<td>Diminished</td>
</tr>
<tr>
<td>Growth hormone excess</td>
<td>Normal or advanced</td>
<td>Increased</td>
<td>Excessive</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>Retarded</td>
<td>Decreased</td>
<td>Diminished</td>
</tr>
<tr>
<td>Cortisol excess</td>
<td>Retarded</td>
<td>Decreased</td>
<td>Diminished</td>
</tr>
<tr>
<td>Cortisol deficiency</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>


*Effect in most patients with treatment.

Short stature is defined as subnormal height relative to other children of the same gender and age, taking family heights into consideration. It can be caused by numerous conditions (Table 173-2). The Centers for Disease Control and Prevention growth charts use the 3rd percentile of the growth curve as the demarcation of the lower limit. **Growth failure** denotes a slow growth rate regardless of stature. Ultimately a slow growth rate leads to short stature, but a disease process is detected sooner if the decreased growth rate is noted before the stature becomes short. Plotted on a growth chart, growth failure appears as a curve that crosses percentiles downward and is associated with a height velocity below the 5th percentile of height velocity for age (Fig. 173-1). A corrected midparental, or genetic target, height helps determine whether the child is growing well for the family (see Chapter 6). To determine a range of normal height for the family under consideration, the corrected midparental height is bracketed by 2 standard deviations (SDs), which, for the United States, is approximately 10 cm (4 in.). The presence of a height 3.5 SDs below the mean, a height velocity below the 5th percentile for age, or a height below the target height corrected for midparental height requires a diagnostic evaluation.

Nutrition is the most important factor affecting growth on a worldwide basis (see Chapter 28). Failure to thrive may develop in the infant as a result of **maternal deprivation** (nutritional deficiency or aberrant psychosocial interaction) or as a result of organic illness (anorexia, nutrient losses through a form of malabsorption, or hypermetabolism caused...
Short Stature

Perhaps the most common cause of short stature is constitutional (delayed bone age) growth, which is usually of no clinical importance. Genetic (short familial height) also contributes to short stature, although not necessarily in a linear fashion.

**ENDOCRINE DISORDERS**

- GH deficiency
  - Congenital
  - Isolated GH deficiency
  - With other pituitary hormone deficiencies
  - With midline defects
  - Pituitary agenesis
  - With gene deficiency
  - Acquired
    - Hypothalamic/pituitary tumors
    - Langerhans cell histiocytosis (X cell histiocytosis)
    - CNS infections and granulomas
    - Head trauma (birth and later)
    - Hypothalamic/pituitary irradiation
    - CNS vascular accidents
    - Hydrocephalus
    - Autoimmune
    - Psychosocial dwarfism (functional GH deficiency)
    - Amphetamine treatment for hyperactivity
    - Laron dwarfism (increased GH and decreased IGF-1)
    - Pygmies (normal GH and IGF-2 but decreased IGF-1)
    - Hypothyroidism
    - Glucocorticoid excess
    - Endogenous
    - Exogenous
    - Diabetes mellitus under poor control
    - Diabetes insipidus (untreated)
    - Hypophosphatemic vitamin D-resistant rickets
    - Virilizing congenital adrenal hyperplasia (tall child, short adult)
    - P-450(21), P-450(11) deficiencies

**SKELETAL DYSPLASIAS**

- Osteogenesis imperfecta
- Osteochondrodysplasias

**LYSOSOMAL STORAGE DISEASES**

- Mucopolysaccharidoses
- Mucolipidoses

**SYNDROMES OF SHORT STATURE**

- Turner syndrome (syndrome of gonadal dysgenesis)
- Noonan syndrome (pseudo-Turner syndrome)
- Autosomal trisomy 13, 18, 21
- Laurence-Moon-Bardet-Biedl syndrome
- Prader-Willi syndrome
- Autosomal abnormalities
- Dysmorphic syndromes (e.g., Russell-Silver or Cornelia de Lange syndrome)
- Pseudohypoparathyroidism

**CHRONIC DISEASE**

- Cardiac disorders
  - Left-to-right shunt
  - Heart failure
- Pulmonary disorders
  - Cystic fibrosis
  - Asthma (severe steroid dependent)
- Gastrointestinal disorders
  - Malabsorption (e.g., celiac disease)
  - Disorders of swallowing
  - Inflammatory bowel disease
- Hepatic disorders
- Hematologic disorders
  - Sickle cell anemia
  - Thalassemia
- Renal disorders
  - Renal tubular acidosis
  - Chronic uremia
- Immunologic disorders
  - Connective tissue disease
  - Juvenile idiopathic arthritis
  - Chronic infection
  - AIDS
- Hereditary fructose intolerance
- Malnutrition
  - Kwashiorkor, marasmus
  - Iron deficiency
  - Zinc deficiency
  - Anorexia caused by chemotherapy for neoplasms
  - Cerebral palsy


AIDS, Acquired immunodeficiency syndrome; CNS, central nervous system; GH, growth hormone; IGF, insulin-like growth factor.

*Only if caloric intake is severely diminished.

by hyperthyroidism or other causes) (see Chapter 21). Psychological difficulties also can affect growth, as in psychosocial or deprivation dwarfism, in which the child develops functional temporary GH deficiency and poor growth as a result of psychological abuse; when placed in a different, healthier psychosocial environment, GH physiology normalizes, and growth occurs.

The common condition known as constitutional delay in growth or puberty or both is considered a variation of normal growth, caused by a reduced tempo, or cadence, of physiologic
development (see Fig. 173-1). Usually a family member had delayed growth or puberty but achieved a normal final height. The bone age is delayed, but the growth rate remains mostly within the lower limits of normal. Constitutional delay usually leads to a delay in secondary sexual development. Genetic or familial short stature (Table 173-3) refers to the stature of a child of short parents, who is expected to reach a lower than average height and yet normal for these parents. If the parents were malnourished as children, grew up in a zone of war, or suffered famine, the heights of the parents are less predictive. Although there are differences in height associated with ethnicity, the most significant difference in stature between ethnic groups is the result of nutrition.

Phenotypic features suggesting an underlying chromosomal disorder can occur in many syndromes. These syndromes can be suspected by attending to arm spans and upper-to-lower segment ratios. Genetic syndromes often combine obesity and decreased height, whereas otherwise normal obese children are usually taller than average and have advanced skeletal development and physical maturation (see Table 173-2). The Prader-Willi syndrome includes fetal and infantile hypotonia, small hands and feet (acromicria), postnatal acquired obesity with an insatiable appetite, developmental delay, hypogonadism, almond-shaped eyes, and abnormalities of the snRNP (small nuclear ribonucleic particle) portion of the 15th chromosome at 15q11-q13. Most cases have deletion of the paternal sequence, but about 20% to 25% have uniparental disomy, in which both chromosomes 15 derive from the mother. Laurence-Moon-Bardet-Biedl syndrome is characterized by retinitis pigmentosa, hypogonadism, and developmental delay with an autosomal dominant inheritance pattern. Laurence-Moon syndrome is associated with spastic paraplegia; Bardet-Biedl syndrome is associated with obesity and polydactyly. Pseudohypoparathyroidism leads to short stature and developmental delay with short fourth and fifth digits (Albright hereditary osteodystrophy phenotype), resistance to parathyroid hormone and resultant hypocalcemia, and elevated levels of serum phosphorus. Turner syndrome is characterized by a karyotype of 45XO or by a mosaic karyotype and clinically presents with short stature, shield chest, wide-spaced nipples, wide-carrying angle of the upper extremities, high-arched palate, gonadal failure, kidney dysplasias with normal function, and aortic arch abnormalities. Affected girls are often susceptible to autoimmune disorders.

Classic congenital or idiopathic GH deficiency occurs in about 1 in 4000 to 1 in 10,000 children. Idiopathic GH deficiency, of unidentified specific etiology, is the most common cause of both congenital and acquired GH deficiency. Less often GH deficiency is caused by anatomic defects of the pituitary gland, such as pituitary aplasia or other midline defects, with variable degrees of deficiency of other pituitary functions. Hereditary forms of GH deficiency that affect pituitary differentiation are the result of heterogeneous defects of the gene for GH, GRF, or GH receptor. Classic GH deficiency refers to very reduced to absent secretion of GH; numerous short children may have intermediate forms of decreased GH secretion. Acquired GH deficiency causing late-onset growth failure suggests the possibility of a tumor of the hypothalamus or pituitary causing compression of the area (see Tables 173-2 and 173-3).

Clinical Manifestations
Infants with congenital GH deficiency achieve a normal or near-normal birth length and weight at term, but the growth rate slows after birth, most noticeably after age 2 to 3 years. These children become progressively shorter for age and tend to have an elevated weight-to-height ratio, appearing chubby and short. Careful measurements in the first year of life may suggest the diagnosis, but most patients elude diagnosis until several years of age. A patient with classic GH deficiency has the appearance of a cherub (a chubby, immature appearance), with a high-pitched voice resulting from an immature
### Table 173-3  Differential Diagnosis and Therapy of Short Stature

<table>
<thead>
<tr>
<th>DIAGNOSTIC FEATURE</th>
<th>HYPOPITUITARISM GH DEFICIENCY*</th>
<th>CONSTITUTIONAL DELAY</th>
<th>FAMILIAL SHORT STATURE</th>
<th>DEPRIVATIONAL DWARFISM</th>
<th>TURNER SYNDROME</th>
<th>HYPOTHYROIDISM</th>
<th>CHRONIC DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history positive</td>
<td>Rare</td>
<td>Frequent</td>
<td>Always</td>
<td>No</td>
<td>No</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Gender</td>
<td>Both</td>
<td>Males more often affected than females</td>
<td>Both</td>
<td>Both</td>
<td>Female</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Facies</td>
<td>Immature or with midline defect (e.g., cleft palate or optic hypoplasias)</td>
<td>Immature</td>
<td>Normal</td>
<td>Normal</td>
<td>Turner facies or normal</td>
<td>Coarse (cretin if congenital)</td>
<td>Normal</td>
</tr>
<tr>
<td>Sexual development</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Normal</td>
<td>May be delayed</td>
<td>Female prepubertal</td>
<td>Usually delayed, may be precocious if hypothryoidism is severe</td>
<td>Delayed</td>
</tr>
<tr>
<td>Bone age</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Normal</td>
<td>Usually delayed; growth arrest lines present</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Delayed</td>
</tr>
<tr>
<td>Dentition</td>
<td>Delayed</td>
<td>Normal; delay usual</td>
<td>Normal</td>
<td>Variable</td>
<td>Normal</td>
<td>Delayed</td>
<td>Normal or delayed</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Variable</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>45,X or partial deletion of X chromosome or mosaic</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Free T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Low (with TRH deficiency) or normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal or low</td>
<td>Normal; hypothyroidism may be acquired</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Stimulated GH</td>
<td>Low</td>
<td>Normal for bone age</td>
<td>Normal</td>
<td>Possibly low, or high if patient malnourished</td>
<td>Usually normal</td>
<td>Low</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Insulin-like growth factor-1</td>
<td>Low</td>
<td>Normal or low for chronologic age</td>
<td>Normal</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
<td>Low or normal (depending on nutritional status)</td>
</tr>
<tr>
<td>Therapy</td>
<td>Replace deficiencies</td>
<td>Reassurance; sex steroids to initiate secondary sexual development in selected patients</td>
<td>None</td>
<td>Change or improve environment</td>
<td>Sex hormone replacement, GH; oxandrolone may be useful</td>
<td>T&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Treat malnutrition, organ failure (e.g., dialysis, transplant, cardiotonic drugs, insulin)</td>
</tr>
</tbody>
</table>

*Possibly with GnRH, CRH, or TRH deficiency.

ACTH, Adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; TRH, thyrotropin-releasing hormone; T<sub>4</sub>, thyroxine.
Growth Failure: Screening Tests

<table>
<thead>
<tr>
<th>TEST</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Anemia: nutritional, chronic disease, malignancy</td>
</tr>
<tr>
<td></td>
<td>Leukopenia: bone marrow failure syndromes</td>
</tr>
<tr>
<td>ESR, CRP</td>
<td>Inflammation of infection, inflammatory diseases, malignancy</td>
</tr>
<tr>
<td>Metabolic panel (electrolytes, liver enzymes, BUN)</td>
<td>Signs of acute or chronic hepatic, renal, adrenal dysfunction; hydration and acid-base status</td>
</tr>
<tr>
<td>Carotene, folate, and prothrombin time; celiac antibody panel</td>
<td>Assess malabsorption; detect celiac disease</td>
</tr>
<tr>
<td>Urinalysis with pH</td>
<td>Signs of renal dysfunction, hydration, water and salt homeostasis; renal tubular acidosis</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Determines Turner (XO) or other syndromes</td>
</tr>
<tr>
<td>Cranial imaging (MRI)</td>
<td>Assesses hypothalamic-pituitary tumors (craniopharyngioma, glioma, germinoma) or congenital midline defects</td>
</tr>
<tr>
<td>Bone age</td>
<td>Compare with height age and evaluate height potential</td>
</tr>
<tr>
<td>IGF-1, IGF-BP3</td>
<td>Reflects growth hormone status or nutrition</td>
</tr>
<tr>
<td>Free thyroxine</td>
<td>Detects panhypopituitarism or isolated hypothyroidism</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Elevated in hypothalamic dysfunction or destruction, suppressed in pituitary disease</td>
</tr>
</tbody>
</table>

BUN, Blood urea nitrogen; CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IGF-1, insulin-like growth factor-1; IGF-BP3, insulin-like growth factor-binding protein 3; MRI, magnetic resonance imaging.

A very rare cause of growth failure is GH resistance or GH insensitivity, caused by abnormal number or function of GH receptors or by a postreceptor defect. Patients with the autosomal recessive Laron syndrome, involving mutations of the GH receptor, have a prominent forehead, hypoplastic nasal bridge, delayed dentition, sparse hair, blue sclerae, delayed bone maturation and osteoporosis, progressive adiposity, hypercholesterolemia, and low blood glucose. They have elevated serum GH concentrations, although serum IGF-1 and IGF-BP3 concentrations are low. Malnutrition, medications (corticosteroids), or severe liver disease may cause acquired GH resistance because serum GH is elevated and IGF-1 is decreased.

Diagnosis

If family or other medical history does not provide a likely diagnosis, screening tests should include a metabolic panel to evaluate kidney and liver function, a complete blood count (CBC) to rule out anemia, a celiac panel to rule out celiac disease, and carotene and folate levels to reflect nutrition and rule out malabsorption. A urinalysis aids in the evaluation of renal function. Urinary pH and serum bicarbonate can assess for renal tubular acidosis. In a girl without another explanation for short stature, a karyotype may rule out Turner syndrome. A bone age will establish skeletal maturation.

If chronic disease or familial short stature are ruled out and routine laboratory testing is normal (Table 173-4), two GH stimulatory tests are commonly performed (see Table 170-2). GH testing should be offered to a patient who is short (<5th percentile and usually >3.5 SDs below the mean), growing poorly (<5th percentile growth rate for age), or whose height projection, based on bone age, is considerably below the target height when corrected for family height.

Classic GH-deficient patients do not show an increase in serum GH levels after stimulation. Some patients release GH in response to secretagogue testing but cannot release GH spontaneously during the day or night. Measuring serum IGF-1 and IGF-BP3 is suggested but not consistently helpful in establishing a diagnosis of GH deficiency. Tests for GH secretion are insensitive, not very specific, and fairly variable. In equivocal cases, an operational definition of GH deficiency might be that patients grow significantly faster when administered a normal dose of GH than before treatment.

Treatment

GH deficiency is treated with biosynthetic recombinant DNA–derived GH. Dosage is titrated to the growth rate. Treatment with GH carries the risk of an increased incidence of slipped capital femoral epiphysis, especially in rapidly growing adolescents, and of pseudotumor cerebri.

Administration of GH to patients with normal GH responsiveness to secretagogues is controversial, but, as noted earlier, diagnostic tests are imperfect; if the patient is growing extremely slowly without alternative explanation, GH therapy is sometimes used. GH is effective in increasing the growth rate and final height in Turner syndrome and in chronic renal failure; GH also is used for treatment of short stature and muscle weakness of Prader-Willi syndrome. Other indications include children born small for gestational age who have not exhibited catch-up growth by 2 years of age and the long-term treatment of idiopathic short stature with height 2.25 SDs or less below the mean. Psychological support of children with severe short stature is important. Although there is controversy, marital status, satisfaction with life, and vocational achievement may be decreased in children of short stature who are not given supportive measures.
**DISORDERS OF PUBERTY**

**PHYSIOLOGY**

The staging of pubertal changes and the sequence of events are discussed in Chapter 67. The onset of puberty is marked by pubarche and gonadarche. Pubarche results from adrenal maturation or adrenarche and is marked with the appearance of pubic hair; other features include oiliness of hair and skin, acne, axillary hair, and body odor. Gonadarche is characterized by increasing secretion of gonadal sex steroids as a result of the maturation of the hypothalamic-pituitary-gonadal axis. These sex steroids differ by gender, consisting of testosterone from the testes and estradiol and progesterone from the ovaries. In males physical signs are pubic hair, axillary hair, facial hair, increased musculature, deeper voice, increased penile size, and increased testicular volume. In females the physical signs are breast development, development of the female body habitus, increased size of the uterus, and menarche with regular menstrual cycles. The third component is the growth spurt of puberty.

Hypothalamic gonadotropin-releasing hormone (GnRH), produced by cells in the arcuate nucleus, is secreted from the median eminence of the hypothalamus into the pituitary portal system and reaches the membrane receptors on the pituitary gonadotropes to cause the production and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the circulation. The hypothalamic-pituitary-gonadal axis is active in the fetus and newborn but is suppressed in the childhood years until activity increases again at the onset of puberty.

In females FSH stimulates the ovarian production of estrogen and, later in puberty, causes the formation and support of corpus luteum. In males LH stimulates the production of testosterone from the Leydig cells; later in puberty, FSH stimulates the development and support of the seminiferous tubules. The gonads also produce the protein inhibin. Both sex steroids and inhibin suppress the secretion of gonadotropins. The interplay of the products of the gonads and GnRH modulates the serum concentrations of gonadotropins. GnRH is released in episodic pulses that vary during development and during the menstrual period. These pulses ensure that gonadotropins are released in a pulsatile manner. With the onset of puberty, the amplitude of the pulses of gonadotropins and, in turn, the sex steroids increases, first at night and then throughout the day. Adrenarche generally occurs several years earlier than gonadarche and is heralded by increasing circulating dehydroepiandrosterone (DHEA) or androstenedione. Serum DHEA increases years before the appearance of its effects.

The normal developmental sequence in girls is thelarche (due to gonadarche) followed closely by pubarche (due to adrenarche) and finally menarche, 2 to 3 years later. In boys the first normal event is scrotal thinning followed by the enlargement of testes and by the appearance of pubic hair (long diameter of the testis greater than 2.5 cm, volume greater than 4 mL). Most of the enlargement of testes during puberty is the result of seminiferous tubule maturation.

**DELAYED PUBERTY**

Puberty is delayed when there is no sign of pubertal development by age 13 years in girls and 14 years in boys living in the United States (Tables 174-1 and 174-2).

**Constitutional Delay in Growth and Adolescence**

Patients with constitutional delay have delayed onset of pubertal development and significant bone age delay (2 standard deviations below the mean, which is equal to a 1.5- to 2-year delay as a teenager). The height of the patient should remain close to the genetic potential, based on the parental heights, when reinterpreted for bone age (see Chapter 173). Usually height gain is below, although fairly parallel to, the normal percentiles on the growth curve. The prepubertal nadir, or deceleration before their pubertal growth spurt, is prolonged or protracted. A family history of delayed puberty in a parent or sibling is reassuring. Spontaneous puberty usually begins in these patients by the time the bone age reaches 12 years in boys and 11 years in girls. Other causes of delayed puberty must be eliminated before a diagnosis of constitutional delay in puberty is made. Observation and reassurance are appropriate. Adult height normal for the genetic potential is generally attained. In some cases, boys may be treated with low-dose testosterone for a few months if the bone age is at least 11 to 12 years. Treatment is not required for longer than 4 to 8 months because endogenous hormone production usually ensues. Boys who do not initiate endogenous hormone production should be evaluated for other causes of hypogonadism. Estrogen treatment has been used in girls with constitutional delay, but there are no clear studies showing the added benefits. Young women with delayed puberty may need to be evaluated for primary amenorrhea.

**Hypogonadotropic Hypogonadism**

As a cause of delayed or absent puberty, hypogonadotropic hypogonadism may be difficult to distinguish from constitutional delay (see Tables 174-1 and 174-2). Hypogonadotropic hypogonadism precludes spontaneous entry into gonadarche; adrenarche usually occurs to some degree. Throughout childhood and in early puberty, patients with hypogonadotropic hypogonadism have normal proportions and growth. When these patients reach adulthood, eunuchoid proportions may ensue because their long bones grow for longer than normal, producing an upper-to-lower ratio below the lower limit of normal of 0.9 and an arm span greater than their height. If a patient has concurrent growth hormone (GH) deficiency, however, stature is exceptionally short, and the condition may have been diagnosed in infancy with a microphallus.
Disorders that can cause hypogonadism include congenital hypopituitarism, such as midline defects, tumors, infiltrative disease (hemochromatosis), and many syndromes, including Laurence-Moon-Bardet-Biedl, Prader-Willi, and Kallmann syndromes. If there is an inability to release gonadotropins but no other pituitary abnormality, the patient has isolated gonadotropin deficiency (almost universally a result of absent GnRH). Patients grow normally until the time of the pubertal growth spurt, when they fail to experience the accelerated growth characteristic of the normal growth spurt.

**Kallmann syndrome** combines isolated gonadotropin deficiency with disorders of olfaction. There is genetic heterogeneity; some patients have a decreased sense of smell, others have abnormal reproduction, and some have both. Most cases are sporadic but a number of patients may have mutations in the \( KAL1 \) gene at Xp 22.3 (X chromosome) or \( KAL2 \) gene. The mutation causes the GnRH neurons to remain ineffectually located in the primitive nasal area, rather than migrating to the correct location at the medial basal hypothalamus. Olfactory bulbs and olfactory sulci are often absent on magnetic resonance imaging (MRI). Other symptoms include disorders of the hand, with one hand copying the movements of the other hand, shortened fourth metacarpal bone, and an absent kidney.

## Abnormalities of the Central Nervous System

Central nervous system (CNS) tumors, including pituitary adenoma, glioma, prolactinoma, or craniopharyngioma, are important causes of gonadotropin deficiency. Craniopharyngiomas have a peak incidence in the teenage years and may cause any type of anterior or posterior hormone deficiency. Craniopharyngiomas usually calcify, eroding the sella turcica when they expand. They may impinge on the optic chiasm, leading to bitemporal hemianopsia and optic atrophy. Other tumors that may affect pubertal development include astrocytomas and gliomas.

**Idiopathic hypopituitarism** is the congenital absence of various combinations of pituitary hormones. Although this disorder may occur in family constellations, in X-linked or autosomal recessive patterns, sporadic types of congenital idiopathic hypopituitarism are more common. Congenital hypopituitarism may manifest in a male with GH deficiency and associated gonadotropin deficiency with a microphallus or with hypoglycemia with seizures, especially if adrenocorticotropic hormone and GH deficiency occurs as well.

### Isolated Gonadotropin Deficiency

<table>
<thead>
<tr>
<th>Table 174-1</th>
<th>Classification of Delayed Puberty and Sexual Infantilism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional delay in growth and puberty</td>
<td></td>
</tr>
<tr>
<td>Hypogonadotropic hypogonadism</td>
<td></td>
</tr>
<tr>
<td>CNS disorders</td>
<td></td>
</tr>
<tr>
<td>Tumors (craniopharyngioma, germinoma, glioma, prolactinoma)</td>
<td></td>
</tr>
<tr>
<td>Congenital malformations</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
</tr>
<tr>
<td>Other causes</td>
<td></td>
</tr>
<tr>
<td>Isolated gonadotropin deficiency</td>
<td></td>
</tr>
<tr>
<td>Kallmann syndrome (anosmia-hyposmia)</td>
<td></td>
</tr>
<tr>
<td>Other disorders</td>
<td></td>
</tr>
<tr>
<td>Idiopathic and genetic forms of multiple pituitary hormone deficiencies</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous disorders</td>
<td></td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td></td>
</tr>
<tr>
<td>Laurence-Moon-Bardet-Biedl syndrome</td>
<td></td>
</tr>
<tr>
<td>Functional gonadotropin deficiency</td>
<td></td>
</tr>
<tr>
<td>Chronic systemic disease and malnutrition</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Cushing disease</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td></td>
</tr>
<tr>
<td>Anorexia nervosa</td>
<td></td>
</tr>
<tr>
<td>Psychogenic amenorrhea</td>
<td></td>
</tr>
<tr>
<td>Impaired puberty and delayed menarche in female athletes and ballet dancers (exercise amenorrhea)</td>
<td></td>
</tr>
<tr>
<td>Hypergonadotropic hypogonadism</td>
<td></td>
</tr>
<tr>
<td>Klinefelter syndrome (syndrome of seminiferous tubular dysgenesis) and its variants</td>
<td></td>
</tr>
<tr>
<td>Other forms of primary testicular failure</td>
<td></td>
</tr>
<tr>
<td>Anorchia and cryptorchidism</td>
<td></td>
</tr>
<tr>
<td>Syndrome of gonadal dysgenesis and its variants (Turner syndrome)</td>
<td></td>
</tr>
<tr>
<td>Other forms of primary ovarian failure</td>
<td></td>
</tr>
<tr>
<td>XX and XY gonadal dysgenesis</td>
<td></td>
</tr>
<tr>
<td>Familial and sporadic XX gonadal dysgenesis and its variants</td>
<td></td>
</tr>
<tr>
<td>Familial and sporadic XY gonadal dysgenesis and its variants</td>
<td></td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td></td>
</tr>
<tr>
<td>Galactosemia</td>
<td></td>
</tr>
</tbody>
</table>


CNS, Central nervous system.
Decreased gonadotropin function occurs when voluntary dieting, malnutrition, or chronic disease results in weight loss to less than 80% of ideal weight. Anorexia nervosa is characterized by striking weight loss and psychiatric disorders (see Chapter 70). Primary or secondary amenorrhea frequently is found in affected girls, and pubertal development is absent or minimal, depending on the level of weight loss and the age at onset. Regaining weight to the ideal level may not immediately reverse the condition. Increased physical activity, even without weight loss, can lead to decreased menstrual frequency and gonadotropin deficiency in athletic amenorrhea; when physical activity is interrupted, menstrual function may return. Chronic or systemic illness (e.g., cystic fibrosis, diabetes mellitus, inflammatory bowel disease, or hematologic diseases) can lead to pubertal delay or to amenorrhea from hypothalamic dysfunction. Hypothyroidism inhibits the onset of puberty and delays menstrual periods. Conversely severe primary hypothyroidism may lead to precocious puberty.

### Table 174-2: Differential Diagnostic Features of Delayed Puberty and Sexual Infantilism

<table>
<thead>
<tr>
<th>CAUSATIVE CONDITION/DISORDER</th>
<th>STATURE</th>
<th>PLASMA GONADOTROPINS</th>
<th>GnRH TEST: LH RESPONSE</th>
<th>PLASMA GONADAL STEROIDS</th>
<th>PLASMA DHEAS</th>
<th>KARYOTYPE</th>
<th>OLFACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional delay in growth and adolescence</td>
<td>Short for chronologic age, usually appropriate for bone age</td>
<td>Prepubertal, later pubertal</td>
<td>Prepubertal, later pubertal</td>
<td>Prepubertal, later normal</td>
<td>Low for chronologic age, appropriate for bone age</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**HYPOGONADOTROPIC HYPOGONADISM**

<table>
<thead>
<tr>
<th>Isolated gonadotropin deficiency</th>
<th>Normal, absent pubertal growth spurt</th>
<th>Low</th>
<th>Prepubertal or no response</th>
<th>Low</th>
<th>Appropriate for chronologic age</th>
<th>Normal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kallmann syndrome</td>
<td>Normal, absent pubertal growth spurt</td>
<td>Low</td>
<td>Prepubertal or no response</td>
<td>Low</td>
<td>Appropriate for chronologic age</td>
<td>Normal</td>
<td>Anosmia or hyposmia</td>
</tr>
<tr>
<td>Idiopathic multiple pituitary hormone deficiencies</td>
<td>Short stature and poor growth since early childhood</td>
<td>Low</td>
<td>Prepubertal or no response</td>
<td>Low</td>
<td>Usually low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hypothalamic-pituitary tumors</td>
<td>Decrease in growth velocity of late onset</td>
<td>Low</td>
<td>Prepubertal or no response</td>
<td>Low</td>
<td>Normal or low for chronologic age</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**PRIMARY GONADAL FAILURE**

<table>
<thead>
<tr>
<th>Syndrome of gonadal dysgenesis and variants</th>
<th>Short stature since early childhood</th>
<th>High</th>
<th>Hyperresponsive for age</th>
<th>Low</th>
<th>Normal for chronologic age</th>
<th>XO or variant</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klinefelter syndrome and variants</td>
<td>Normal to tall</td>
<td>High</td>
<td>Hyperresponsive at puberty</td>
<td>Low or normal</td>
<td>Normal for chronologic age</td>
<td>XXY or variant</td>
<td>Normal</td>
</tr>
<tr>
<td>Familial XX or XY gonadal dysgenesis</td>
<td>Normal</td>
<td>High</td>
<td>Hyperresponsive for age</td>
<td>Low</td>
<td>Normal for chronologic age</td>
<td>XX or XY</td>
<td>Normal</td>
</tr>
</tbody>
</table>

- DHEAS, Dehydroepiandrosterone sulfate; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

### Hypergonadotropic Hypogonadism

Hypergonadotropic hypogonadism is characterized by elevated gonadotropins and low sex steroid levels resulting from primary gonadal failure. This permanent condition is almost always diagnosed following the lack of entry into gonadarche and is not suspected throughout childhood. Gonadotropins do not increase to greater than normal until shortly before or around the normal time of puberty.

**Pubertal Delay Gynecomastia**

- Decision-Making Algorithms Available @ StudentConsult.com
X chromosome or mosaicism are possible. The incidence of Turner syndrome is 1 in 2000 to 1 in 3000 births. The features of a girl with Turner syndrome need not be evident on physical examination or by history. The diagnosis must be considered in any girl who is short without a contributory history. Patients with other types of gonadal dysgenesis and galactosemia as well as patients treated undergoing radiation therapy or chemotherapy for malignancy may develop ovarian failure.

Klinefelter syndrome (seminiferous tubular dysgenesis) is the most common cause of testicular failure. The karyotype is 47,XXY, but variants with more X chromosomes are possible. The incidence is approximately 1 in 500 to 1 in 1000 in males. Testosterone levels may be close to normal, at least until mid-puberty, because Leydig cell function may be spared; however seminiferous tubular function characteristically is lost, causing infertility. Commonly LH levels may be normal to elevated, whereas testosterone levels are usually more unequivocally elevated. The age of onset of puberty is usually normal, but secondary sexual changes may not progress because of inadequate Leydig cell function.

**Primary Amenorrhea**

In addition to other diagnoses mentioned, other conditions need to be considered when evaluating girls with lack of menses. The Mayer-Rokitansky-Kuster-Hauser syndrome of congenital absence of the uterus occurs in 1 in 4000 to 5000 female births. Anatomic obstruction by imperforate hymen or vaginal septum also presents with normal secondary sexual development without menstruation. The complete syndrome of androgen insensitivity includes normal feminization, absence of pubic or axillary hair, and primary amenorrhea. In this syndrome, all müllerian structures, including ovaries, uterus, fallopian tubes, and upper third of the vagina, are lacking; the karyotype is 46,XY, and subjects have intra-abdominal testes.

**Evaluation**

When no secondary sexual development is present after the upper age limits of normal pubertal development, serum gonadotropin levels should be obtained to determine whether the patient has a hypogonadotropic or hypergonadotropic hypogonadism (see Table 174-2). Based on gonadotropin measurements only, the differentiation between constitutional delay in growth and hypogonadotropic hypogonadism is difficult; the gonadotropin levels are low in both conditions. Sometimes observation for months or years is necessary before the diagnosis is confirmed. Ultrasound of the pelvic structures in females would be helpful in the workup of delayed puberty.

**Treatment**

If a permanent condition is apparent, replacement with sex steroids is indicated. Females are given transdermal estradiol, low-dose ethinyl estradiol (5 to 10 μg) or conjugated estrogens (starting at 0.3 mg daily, increasing to 0.625 mg or 0.9 mg by 6 to 12 months later) in low daily doses until breakthrough bleeding occurs, at which time cycling is started with a dose for 25 days; on days 20 to 25, a gestational agent, such as medroxyprogesterone acetate (5 mg), is added to mimic the normal increases in gonadal hormones and to induce a normal menstrual period. Alternatively combined estrogen and progesterone agents (oral contraceptives) may be used after breakthrough bleeding occurs. In males testosterone enanthate or cypionate (50 to 100 mg monthly with a progressive increase to 100 to 200 mg) is given intramuscularly once every 4 weeks. This starting regimen is appropriate for patients with hypogonadotropic or hypergonadotropic hypogonadism, and doses are increased gradually to adult levels. Oral agents are not used for fear of hepatotoxicity. Patients with apparent constitutional delay in puberty who have, by definition, passed the upper limits of normal onset of puberty may be given a 3- to 6-month course of low-dose, sex-appropriate gonadal steroids to see whether spontaneous puberty occurs. This course of therapy might be repeated once without undue advancement of bone age. All patients with any form of delayed puberty are at risk for decreased bone density; adequate calcium intake is essential. Patients with hypogonadotropic hypogonadism may be able to achieve fertility by the administration of gonadotropin therapy or pulsatile hypothalamic-releasing hormone therapy administered by a programmable pump on an appropriate schedule. Subjects with hypergonadotropic hypogonadism have, by definition, a primary gonadal problem and are unlikely to achieve spontaneous fertility.

In subjects with Turner syndrome, the goals of therapy include promoting growth with exogenous human GH supplementation and induction of the secondary sexual characteristics and of menses with low-dose cyclic estrogen/progesterone replacement therapy. Patients with Turner syndrome have had successful pregnancies after in vitro fertilization with a donor ovum and endocrine support.

**SEXUAL PREOCITY**

Sexual precocity (precocious puberty) is classically defined as secondary sexual development occurring before the age of 9 years in boys or 8 years in girls (Tables 174-3 and 174-4). During the past 15 to 20 years, studies from the United States and Europe reported earlier breast development in girls, as compared to historical data. Studies clearly suggest an earlier age at puberty onset in American girls in the 1980s to 1990s compared to the 1930s and 1940s. However age at menarche occurred at the same time or slightly earlier. Thus the time span from breast development to menarche seemed to have increased. The findings could reflect that exogenous or lifestyle factors may influence the typical sequence of pubertal events.

**Central precocious puberty**, resulting in gonadarche, emanates from premature activation of the hypothalamic-pituitary-gonadal axis (GnRH-dependent). **Peripheral precocious
### Classification of Sexual Precocity

<table>
<thead>
<tr>
<th>TRUE PREOCIOUS PUBERTY OR COMPLETE ISOSEXUAL PREOCITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic true precocious puberty</td>
</tr>
<tr>
<td>CNS tumors</td>
</tr>
<tr>
<td>Hamartomas (ectopic GnRH pulse generator)</td>
</tr>
<tr>
<td>Other tumors</td>
</tr>
<tr>
<td>Other CNS disorders</td>
</tr>
<tr>
<td>True precocious puberty after late treatment of congenital virilizing adrenal hyperplasia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INCOMPLETE ISOSEXUAL PREOCITY (GnRH-INDEPENDENT SEXUAL PREOCITY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
</tr>
<tr>
<td>Chorionic gonadotropin-secreting tumors (hCG-dependent sexual precocity)</td>
</tr>
<tr>
<td>CNS tumors (e.g., germinoma, chorioepithelioma, teratoma)</td>
</tr>
<tr>
<td>Tumors in locations outside of the CNS (hepatoblastoma)</td>
</tr>
<tr>
<td>LH-secreting pituitary adenoma</td>
</tr>
<tr>
<td>Increased androgen secretion by adrenal or testis</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia (21-hydroxylase deficiency, 11-hydroxylase deficiency)</td>
</tr>
<tr>
<td>Virilizing adrenal neoplasm</td>
</tr>
<tr>
<td>Leydig cell adenoma</td>
</tr>
<tr>
<td>Familial testotoxicosis (familial premature gonadotropin-independent Leydig cell and germ cell maturation)</td>
</tr>
<tr>
<td>Females</td>
</tr>
<tr>
<td>Estrogen-secreting ovarian or adrenal neoplasms</td>
</tr>
<tr>
<td>Ovarian cysts</td>
</tr>
<tr>
<td>Males and females</td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
</tr>
<tr>
<td>Primary hypothyroidism</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
</tr>
<tr>
<td>Iatrogenic sexual precocity</td>
</tr>
</tbody>
</table>

### VARIATIONS OF PUBERTAL DEVELOPMENT

<table>
<thead>
<tr>
<th>Males (feminization)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal neoplasm</td>
</tr>
<tr>
<td>Increased extraglandular conversion of circulating steroids to estrogen</td>
</tr>
<tr>
<td>Females (virilization)</td>
</tr>
<tr>
<td>(Congenital adrenal hyperplasia, P-450,c21 deficiency, P-450,c11 deficiency, 11-Hydroxysteroid dehydrogenase deficiency)</td>
</tr>
<tr>
<td>Virilizing adrenal neoplasms</td>
</tr>
<tr>
<td>Virilizing ovarian neoplasms (e.g., arrhenoblastomas)</td>
</tr>
</tbody>
</table>


### GnRH-Independent Precocious Puberty

The most common cause of GnRH-independent precocious puberty, **McCune-Albright syndrome**, is more frequent in girls than boys and includes precocious gonadarche, a bone disorder with polyostotic fibrous dysplasia, and hyperpigmented cutaneous macules (café au lait spots). The precocious gonadarche results from ovarian hyperfunction and sometimes cyst formation, leading to episodic estrogen secretion. This disorder results from a post-conception somatic
**Table 174-4** Differential Diagnosis of Sexual Precocity

<table>
<thead>
<tr>
<th>CAUSATIVE DISORDER</th>
<th>SERUM GONADOTROPIN CONCENTRATION*</th>
<th>LH RESPONSE TO GNRH</th>
<th>SERUM SEX STEROID CONCENTRATIONS</th>
<th>GONADAL SIZE</th>
<th>MISCELLANEOUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True precocious puberty</strong></td>
<td>Pubertal values</td>
<td>Pubertal</td>
<td>Pubertal values of testosterone or estradiol</td>
<td>Normal pubertal testicular enlargement or ovarian and uterine enlargement (by sonography)</td>
<td>MRI scan of brain to rule out CNS tumor or other abnormality; bone scan for McCune-Albright syndrome</td>
</tr>
<tr>
<td><strong>Incomplete sexual precocity (pituitary gonadotropin-independent)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorionic gonadotropin-secreting tumor in males</td>
<td>High hCG (low LH)</td>
<td>Prepubertal (suppressed)</td>
<td>Prepubertal values of testosterone</td>
<td>Slight to moderate uniform enlargement of testes</td>
<td>Hepatomegaly suggests hepatoblastoma; MRI scan of brain if chorionic gonadotropin-secreting CNS tumor suspected</td>
</tr>
<tr>
<td>Leydig cell tumor in males</td>
<td>Suppressed</td>
<td>Suppressed</td>
<td>Very high testosterone</td>
<td>Irregular asymmetric enlargement of testes</td>
<td></td>
</tr>
<tr>
<td>Familial testotoxicosis</td>
<td>Suppressed</td>
<td>Suppressed</td>
<td>Pubertal values of testosterone</td>
<td>Testes symmetric and &gt;2.5 cm but smaller than expected for pubertal development; spermatogenesis may occur</td>
<td>Familial; probably sex-linked, autosomal dominant trait</td>
</tr>
<tr>
<td>Premature adrenarche</td>
<td>Prepubertal</td>
<td>Prepubertal</td>
<td>Prepubertal testosterone; DHEAS values appropriate for pubic hair stage 2</td>
<td>Testes prepubertal</td>
<td>Onset usually after 6 yr of age; more frequent in brain-injured children</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulosa cell tumor (presentation may be similar to that with follicular cysts)</td>
<td>Suppressed</td>
<td>Suppressed</td>
<td>Very high estradiol</td>
<td>Ovarian enlargement on physical examination, MRI, CT, or sonography</td>
<td>Tumor often palpable on abdominal examination</td>
</tr>
<tr>
<td>Follicular cyst</td>
<td>Suppressed</td>
<td>Suppressed</td>
<td>Prepubertal to very high estradiol values</td>
<td>Ovarian enlargement on physical examination, MRI, CT, or sonography</td>
<td>Single or repetitive episodes; exclude McCune-Albright syndrome (e.g., perform skeletal survey and inspect skin)</td>
</tr>
<tr>
<td>Feminizing adrenal tumor</td>
<td>Suppressed</td>
<td>Suppressed</td>
<td>High estradiol and DHEAS values</td>
<td>Ovaries prepubertal</td>
<td>Unilateral adrenal mass</td>
</tr>
<tr>
<td>Premature thelarche</td>
<td>Prepubertal</td>
<td>Prepubertal</td>
<td>Prepubertal or early pubertal estradiol</td>
<td>Ovaries prepubertal</td>
<td>Onset usually before 3 yr of age</td>
</tr>
<tr>
<td>Premature adrenarche</td>
<td>Prepubertal</td>
<td>Prepubertal</td>
<td>Prepubertal estradiol; DHEAS values appropriate for pubic hair Tanner stage 2</td>
<td>Ovaries prepubertal</td>
<td>Onset usually after 6 yr of age; more frequent in brain-injured children</td>
</tr>
</tbody>
</table>

*Modified from Grumbach MM, Styne DM: Puberty. In Wilson JD, Foster DW, editors: Williams Textbook of Endocrinology, ed 9, Philadelphia, 1997, WB Saunders. CNS, Central nervous system; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging.

*In supersensitive assays.
mutation in the G protein intracellular signaling system (specifically G_sss, which leads to unregulated constitutive activation of adenylate cyclase, and of cAMP in the absence of trophic hormone stimulation), in the affected cells in ovary, bone, and skin; other endocrine organs may also autonomously hyperfunction for the same reason. Hyperthyroidism, hyperadrenalinism, or acromegaly may occur. Adrenal carcinomas usually secrete adrenal androgens, such as DHEA; adrenal adenomas may virilize a child as a result of the production of androgen may feminize a child as a result of the production of estrogen.

Boys may have precocious gonadarche on the basis of a rare entity called familial GnRH-independent sexual precocity with premature Leydig cell maturation. This condition, with germ cell maturation caused by an X-limited dominant defect, produces constitutive activation of the LH receptor that leads to continuous production and secretion of testosterone without requiring LH or hCG.

The hCG-secreting tumors stimulate LH receptors and increase testosterone secretion. These tumors may be found in various places, including the pineal gland (dysgerminomas) or the liver (hepatoblastoma).

Ovarian cysts may occur once or may be recurrent. High serum estrogen values may mimic ovarian tumors. Congenital adrenal hyperplasia (CAH) is a cause of virilization in girls (see Chapter 178).

Evaluation of Sexual Precocity
The first step in evaluating sexual precocity is to determine which characteristics of normal puberty are apparent (see Chapter 67) and whether estrogen effects, androgen effects, or both are present (see Table 174-4). In girls the estrogen effect manifests as breast development, uterine increase, and, eventually, menarche. Both boys and girls manifest the androgen effect as adult body odor, pubic and axillary hair, and facial skin oiliness and acne. In boys it is also important to note whether the testes are enlarged more than 2.5 cm in length (4 mL volume), which implies gonadarche. If the testes are not enlarged but virilization is progressing, the source of the androgens may be the adrenal glands or exogenous sources.

Laboratory evaluation includes determination of sex steroid levels (testosterone, estradiol, DHEAS [dehydroepiandrosterone sulfate], or androstenedione) and baseline gonadotropin concentrations. The inherent nature of gonadotropin secretion is characterized by low secretory rates throughout childhood and pulsatile secretion in adolescents and adults. If baseline gonadotropin values are elevated into the normal pubertal range, central precocious puberty is likely. If baseline gonadotropins are low, however, no immediate conclusion may be drawn as to GnRH-dependent versus GnRH-independent precocious puberty. This distinction often requires the assessment of gonadotropin responsiveness to GnRH stimulation. A prepubertal GnRH response is FSH predominant, whereas a pubertal response is more LH predominant. Thyroid hormone determination also is useful because severe primary hypothyroidism can cause incomplete precocious puberty. If there is a suggestion of a CNS anomaly or a tumor (CNS, hepatic, adrenal, ovarian, or testicular), MRI of the appropriate location is indicated. The diagnosis of central precocious puberty mandates that an MRI of the CNS be performed.

Treatment
Long-acting, superactive analogs of GnRH (leuprolide depot, histrelin depot) are the treatment of choice for central precocious puberty. They suppress gonadotropin secretion by downregulating GnRH receptors in the pituitary gonadotropes (Table 174-5), causing gonadal secretion to revert to the prepubertal state. Boys with GnRH-independent premature Leydig cell and germ cell maturation do not respond to GnRH analogs but require treatment with an inhibitor of testosterone synthesis (e.g., ketoconazole), an antiandrogen (e.g., spironolactone), or an aromatase inhibitor (e.g., testolactone or letrozole). Patients with precocious puberty from a hormone-secreting tumor require surgical removal, if possible. The precocious puberty of the McCune-Albright syndrome is GnRH independent and unresponsive to therapy with GnRH.

<p>| Table 174-5 Pharmacologic Therapy of Sexual Precocity |</p>
<table>
<thead>
<tr>
<th>DISORDER</th>
<th>TREATMENT</th>
<th>ACTION AND RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH-dependent true or central precocious puberty</td>
<td>GnRH agonists</td>
<td>Desensitization of gonadotropes; blocks action of endogenous GnRH</td>
</tr>
<tr>
<td>GnRH-independent incomplete sexual precocity Girls</td>
<td>Medroxyprogesterone acetate</td>
<td>Inhibition of ovarian steroidogenesis; regression of cyst (inhibition of FSH release)</td>
</tr>
<tr>
<td>Autonomous ovarian cysts</td>
<td>Medroxyprogesterone acetate</td>
<td>Inhibition of ovarian steroidogenesis; regression of cyst (inhibition of FSH release)</td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
<td>Testolactone*</td>
<td>Inhibition of P-450 aromatase; blocks estrogen synthesis</td>
</tr>
<tr>
<td>Boys</td>
<td>Ketoconazole*</td>
<td>Inhibition of P-450 (mainly 17,20-lyase activity)</td>
</tr>
<tr>
<td>Familial GnRH-independent sexual precocity with premature Leydig cell maturation</td>
<td>Spironolactone* or flutamide and testosterone or fadrozole</td>
<td>Antiandrogen inhibition of aromatase; blocks estrogen synthesis</td>
</tr>
</tbody>
</table>

*If true precocious puberty develops, a GnRH agonist can be added.
analog. Therapy is provided with testolactone and antiandro gens or antiestrogen, such as tamoxifen.

**VARIATIONS IN PUBERTAL DEVELOPMENT**

**Isolated Premature Thelarche (Premature Breast Development)**

Benign premature thelarche is the isolated appearance of uni lateral or bilateral breast tissue in girls, usually at ages 6 months to 3 years. There are no other signs of puberty and no evidence of excessive estrogen effect (vaginal bleeding, thickening of the vaginal secretions, increased height velocity, or bone age acceleration). Ingestion or dermal application of estrogen-containing compounds must be excluded. Laboratory investigations are not usually necessary, but a pelvic ultrasound study rarely may be indicated to exclude ovarian disease. Girls with this condition should be re-evaluated at intervals of 6 to 12 months to ensure that apparent premature thelarche is not the beginning of progression into precocious puberty. The prognosis is excellent; if no progression occurs, no treatment other than reassurance is necessary.

**Gynecomastia**

In males breast tissue is termed **gynecomastia**, and it may occur to some degree in 45% to 75% of normal pubertal boys (see Chapter 67). Androgens normally are converted to estrogen by aromatization; in early puberty, only modest amounts of androgens are produced, and the estrogen effect can overwhelm the androgen effects at this stage. Later in pubertal development, the androgen production is so great that there is little effect from the estrogen produced by aromatization. Gynecomastia also can suggest the possibility of Klinefelter syndrome as puberty progresses. Prepubertal gynecomastia suggests an unusual source of estrogen either from exogenous sources (oral or dermal estrogen administration is possible from contamination of food or ointments) or from endogenous sources (from abnormal function of adrenal gland or ovary or from increased peripheral aromatization).

**Isolated Premature Adrenarche (Pubarche)**

The isolated appearance of pubic hair before age 6 to 7 years in girls or before age 9 years in boys is termed **premature pubarche**, usually resulting from adrenarche. It is relatively common. If the pubic hair is associated with any other feature of virilization (clitoral or penile enlargement or advanced bone age) or other signs (acne, rapid growth, or voice change), a detailed investigation for a pathologic cause of virilization is indicated. Measurements of serum testosterone, 17-hydroxyprogesterone, and DHEAS are indicated to investigate the possibility of CAH. Ultrasound studies may reveal a hyperplastic adrenal gland or a virilizing adrenal or ovarian tumor. Most patients with isolated pubic hair do not have progressive virilization and simply have premature adrenarche (**pubarche**) resulting from premature activation of DHEA secretion from the adrenal gland. The skeletal maturation, as assessed by bone age, may be slightly advanced and the height slightly increased, but testosterone concentrations are normal. DHEA levels usually are high for prepubertal age but are consistent with Tanner (sexuality maturity rating) stages II and III.

**THYROID DISEASE**

**THYROID PHYSIOLOGY AND DEVELOPMENT**

Thyrotropin-releasing hormone (TRH), a tripeptide synthesized in the hypothalamus, stimulates the release of pituitary thyroid-stimulating hormone (TSH). Pituitary TSH is a glycoprotein that stimulates the synthesis and release of thyroid hormones by the thyroid gland. Thyroid function develops in three stages. At the end of the first trimester, the gland descends from the floor of the primitive oral cavity to its definitive position in the anterior lower neck. The hypothalamic-pituitary-thyroid axis becomes functional in the second trimester. Peripheral metabolism of thyroid hormones matures in the third trimester.

Thyrooxine (T₄), triiodothyronine (T₃), and TSH do not cross the placenta in significant amounts. Concentrations in fetal serum reflect primarily fetal secretion and metabolism. Maternal thyroid antibodies, iodides (including radioactive iodides), and medications given to mothers to treat hyperthyroidism (methimazole and propylthiouracil) cross the placenta and affect fetal thyroid function. An infant born prematurely or with intrauterine growth restriction may have an interruption of the normal maturational process and appear to have hypothyroidism by standard tests.

The thyroid gland concentrates iodine and binds it to tyrosine molecules to produce either monoiodotyrosine or diiodotyrosine, with subsequent coupling of two tyrosines, T₄ or T₃. The major fraction of circulating T₃ (approximately two thirds) is derived from peripheral deiodination of T₄ to T₃, but some is produced by the thyroid gland itself. The conversion of T₄ to T₃ requires the removal of one iodine from the outer ring.
of tyrosine; removing an iodine from the inner ring results in reverse T3, which has little biologic effect. Preferential conversion of T4 to reverse T3 rather than T3 occurs in utero and in all forms of severe illness, including respiratory distress syndrome, fevers, anorexia, cachexia, and starvation. Conversion from T4 to T3 increases immediately after birth and throughout life. T4 and T3 are noncovalently bound to a specific serum carrier protein, thyroxine-binding globulin, and, to a lesser extent, albumin. Only small (<0.02%) fractions of T4 and T3 are not bound; free T4 (as it is converted to free T3) and free T3 are biologically active. Free T3 exerts metabolic effects and negative feedback on TSH release (Fig. 175-1).

Serum TSH increases just after birth but soon decreases to lower values considered normal for later life. T4 secretion increases after birth as a result of the peak in TSH and because of maturation of thyroid metabolism. It is important to refer to age-adjusted normative data to interpret thyroid function tests properly, whether relative to making diagnoses of hyperthyroidism or hypothyroidism or when adjusting therapy. Free T4 is the test of choice because it eliminates the effects of variation in protein binding, which can be substantial.

Table 175-1 summarizes laboratory test results in various types of thyroid abnormalities. In usual circumstances, plasma concentrations of TSH above the normal range indicate
primary hypothyroidism, and concentrations below the normal range most often indicate the presence of hyperthyroidism. Thyroid scans with 99m-pertechnetate or 123-I-iodine are occasionally indicated in the evaluation of pediatric thyroid disease. They can be useful in identifying thyroid agenesis or ectopic thyroid tissue.

**THYROID DISORDERS**

**Hypothyroidism**

Hypothyroidism is diagnosed by a decreased serum free T4 and may be the result of diseases of the thyroid gland (primary hypothyroidism), abnormalities of the pituitary gland (secondary), or abnormalities of the hypothalamus (tertiary).

Hypothyroidism is congenital or acquired and may be associated with a goiter (Table 175-2).

**Congenital Hypothyroidism**

Congenital hypothyroidism occurs in approximately 1 in 2000 to 4000 live births and is caused by dysgenesis (agenesis, aplasia, ectopia) or, less often, dyshormonogenesis (e.g., enzyme defects). Thyroid tissue usually is not palpable in these sporadic nongoitrous conditions. Dyshormonogenesis, disorders of intrathyroid metabolism, or goitrous congenital hypothyroidism occurs in about 1 in 30,000 live births. A goiter reflects an inborn error of metabolism in the pathway of iodide incorporation or thyroid hormone biosynthesis or reflects the transplacental passage of antithyroid drugs given to the mother. The free T4 concentration is low, and the TSH level is elevated. Routine neonatal screening programs to measure cord blood or, more often, heel-stick TSH values occur in every state in the United States. An immediate confirmatory serum sample should be obtained from any infant having a positive result on a screening test. A low free T4 and high TSH confirm the finding.

### Table 175-1

<table>
<thead>
<tr>
<th>ABNORMALITY</th>
<th>TOTAL T4</th>
<th>FREE T4</th>
<th>SERUM TSH</th>
<th>SERUM TBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hypothyroidism</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Hypothalamic (TRH) tertiary hypothyroidism</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>Pituitary (TSH) secondary hypothyroidism</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>TBG deficiency</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>TBG excess</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>↑</td>
</tr>
</tbody>
</table>

↓, decreased; ↑, increased; N, Normal; T4, thyroxine; TBG, thyroxine-binding globulin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

* TSH may be slightly elevated.

### Table 175-2

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>MANIFESTATION</th>
<th>CAUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>No goiter</td>
<td>Thyroid gland dysgenesis or ectopic location Exposure to iodides TSH deficiency TRH deficiency</td>
</tr>
<tr>
<td></td>
<td>+/- Goiter</td>
<td>Inborn defect in hormone synthesis’ or effect Maternal goitrogen ingestion, including propylthiouracil, methimazole, iodides Severe iodide deficiency (endemic)</td>
</tr>
<tr>
<td>Child</td>
<td>No goiter</td>
<td>Thyroid gland dysgenesis Cystinosis Hypothalamic-pituitary insufficiency Surgical after thyrotoxicosis or other thyroid surgery</td>
</tr>
<tr>
<td>Goiter</td>
<td></td>
<td>Hashimoto thyroiditis: chronic lymphocytic thyroiditis Inborn defect in hormone synthesis or effect Goitrogenic drugs infiltrative (sarcoid, lymphoma)</td>
</tr>
</tbody>
</table>

TRH, Thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

*Impaired iodide transport, defective thyroglobulin iodination, defective iodothyrosine dehalogenase, or defective thyroglobulin or its coupling to iodothyrosine.

Isolated secondary or tertiary hypothyroidism occurs in 1 in 100,000 live births; the free T4 is normal to low. When tertiary or secondary hypothyroidism is detected, assessment of other pituitary hormones and investigation of pituitary-hypothalamic anatomy via magnetic resonance imaging are indicated. Although not a hypothyroid condition, congenital thyroxine-binding globulin deficiency occurs in about 1 in 10,000 live births and is associated with low serum total T4 concentration, normal TSH, and normal serum free T4. This is a euthyroid condition and does not require treatment with thyroid hormone because it is merely a binding protein abnormality. It is commonly X-linked dominant.

**Clinical manifestations** of congenital hypothyroidism in the immediate newborn period usually are subtle but become
Acquired Hypothyroidism

The etiology of acquired hypothyroidism is presented in Table 175-2. The clinical manifestations may be subtle. Hypothyroidism should be suspected in any child who has a decline in growth velocity, especially if not associated with weight loss (see Table 175-3). The most common cause of acquired hypothyroidism in older children in the United States is lymphocytic autoimmune thyroiditis (Hashimoto thyroiditis). In many areas of the world, iodine deficiency is the etiology of endemic goiter (endemic cretinism). The failure of the thyroid gland may be heralded by an increase of TSH before T4 levels decrease. In contrast to untreated congenital hypothyroidism, acquired hypothyroidism is not a cause of permanent developmental delay.

Hashimoto thyroiditis. Also known as autoimmune or lymphocytic thyroiditis, Hashimoto thyroiditis is a common cause of goiter and acquired thyroid disease in older children and adolescents. A family history of thyroid disease is present in 25% to 35% of patients. The etiology is an autoimmune process targeted against the thyroid gland with lymphocytic infiltration and lymphoid follicle and germinal center formation preceding fibrosis and atrophy.

Clinical manifestations include a firm, nontender euthyroid, hypothyroid, or, rarely, hyperthyroid (hashitoxicosis) diffuse goiter with a pebble-like surface. See Table 175-3 for signs and symptoms, which can be diverse. Onset typically occurs after 6 years of age with a peak incidence in adolescence with a female predominance. Associated autoimmune diseases include diabetes mellitus type 1 (DM1), adrenal insufficiency, and hypoparathyroidism. Autoimmune polyglandular syndrome type I consists of hypoparathyroidism, Addison disease, mucocutaneous candidiasis and, often, hypothyroidism. Autoimmune polyglandular syndrome type II consists of Addison disease, DM1, and frequently autoimmune hypothyroidism. Trisomy 21 and Turner syndrome are predisposed to the development of autoimmune thyroiditis.

The diagnosis may be confirmed by serum antithyroid peroxidase (previously antimicrosomal) and antithyroglobulin antibodies. Neither biopsy nor thyroid scan is indicated in
Hashimoto thyroiditis, although the thyroid scan with reduced uptake may differentiate hashitoxicosis from Graves disease.

**Treatment** with thyroid hormone sufficient to normalize TSH and free T₄ is indicated for hypothyroidism in Hashimoto thyroiditis. Patients without manifestation of hypothyroidism require thyroid function testing (serum TSH and free T₄) every 6 to 12 months to detect the later development of hypothyroidism. Goiter with a normal TSH usually is not an indication for treatment.

**Hyperthyroidism**

**Graves Disease**

Most children with hyperthyroidism have Graves disease, the autonomous functioning of the thyroid caused by autoantibodies [thyroid stimulating immunoglobulins (TSIs)] stimulating the thyroid. The resulting excessive synthesis, release, and peripheral metabolism of thyroid hormones produce the clinical features. Hashimoto thyroiditis and thyrotoxicosis are on a continuum of autoimmune diseases; there is overlap in their immunologic findings. Antithyroid peroxidase and antithyrogbulin antibodies may be present in thyrotoxicosis, although the values are usually lower than in Hashimoto thyroiditis. Exceptionally high titers of antibodies may indicate the thyrotoxic phase of Hashimoto thyroiditis with the subsequent evolution toward permanent hypothyroidism. In Graves disease, serum free T₄ or T₃ or both levels are elevated, whereas TSH is suppressed. Rare causes of hyperthyroidism include McCune-Albright syndrome, thyroid nodule (often an adenoma), TSH hypersecretion, subacute thyroiditis, and iodine or thyroid hormone ingestion.

**Clinical manifestations.** Graves disease presents as hyperthyroidism (Table 175-4) and is about five times more common in girls than in boys, with a peak incidence in adolescence. Personality changes, mood instability, and poor school performance are common initial problems. Tremor, anxiety, inability to concentrate, and weight loss may be insidious and confused with a psychological disorder until thyroid function tests reveal the elevated serum free T₄ level. In rare cases, serum free T₄ may be near-normal whereas serum T₃ is selectively elevated (T₃ toxicosis). A firm homogeneous goiter is usually present. Many patients complain of neck fullness. Thyroid gland enlargement is best visualized with the neck only slightly extended and with the examiner lateral to the patient. Palpation of the thyroid gland is best performed with the examiner’s hands around the neck from the back. The patient swallows so that the examiner can feel and examine the size, consistency, nodularity and motion of the gland. The examiner should watch the patient swallow to note any discernible enlargement or asymmetry of the thyroid lobes. Auscultation may reveal a bruit over the gland that needs to be differentiated from a carotid bruit.

**Treatment.** Three treatment choices are available: pharmacologic, radioactive iodine, and surgical.

**Drugs.** Medical therapy to block thyroid hormone synthesis consists of methimazole (0.4 to 0.6 mg/kg/day once or twice daily) or propylthiouracil (5 to 7 mg/kg/day divided every 8 hours). Both medications are equally effective, however, propylthiouracil is no longer a first-line therapy secondary to concerns of severe liver injury and acute liver failure. A beta blocker, such as propranolol or atenolol, is started if symptoms are severe to control cardiac manifestations and is tapered as the methimazole takes effect. Antithyroid medication is usually continued for 1 to 2 years because the remission rate is approximately 25% per year. In patients complying with the treatment regimen, the 2-year course of treatment can be repeated. Medication should suppress thyroid function to normal, without the need to add thyroid hormone replacement to normalize serum free T₄. Complications of methimazole are muscle pain, rash, granulocytopenia, and jaundice. The granulocytopenia is an idiosyncratic complication of rapid onset, which is observed only in the early months after institution of antithyroid medication.

<table>
<thead>
<tr>
<th>Table 175-4</th>
<th>Clinical Manifestations of Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSOCIATED CHANGE</td>
<td>SIGN/SYMPTOM</td>
</tr>
<tr>
<td>Increased catecholamine effects</td>
<td>Nervousness, Palpitations, Tachycardia, Atrial arrhythmias, Systolic hypertension, Tremor, Brisk reflexes</td>
</tr>
<tr>
<td>Hypermetabolism</td>
<td>Increased sweating, Shiny, smooth skin, Heat intolerance, Fatigue, Weight loss—increased appetite, Increased bowel movement (hyperdefecation), Hyperkinesis</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Weakness, Periodic paralysis, Cardiac failure—dyspnea</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Proptosis, stare, exophthalmos, lid lag, ophthalmopathy, Hair loss, Inability to concentrate, Personality change (emotional lability), Goiter, Thyroid bruist, Onycholysis, Painful gland*</td>
</tr>
<tr>
<td>*Unusual except in subacute thyroiditis with hyperthyroid phase.</td>
<td></td>
</tr>
</tbody>
</table>

*Neck Masses*
and requires monitoring the complete blood count. If a suppressed white blood cell count is observed, antithyroid therapy must be discontinued. This potentially lethal rare complication affects 3 in 10,000 users a year. After resolution, the other of the two antithyroid medications can be started because there is usually less than a 50% chance of a similar reaction from the other medication. Iodine administration, which may suppress thyroid function but becomes ineffective in a few weeks, is sometimes used as a preparation for surgery but never for long-term therapy.

**Radioiodine.** Radioiodine ($^{131}$I) is slower in exerting therapeutic effects, may require repeated dosing, and is likely to cause permanent hypothyroidism. Hypothyroidism is the desired outcome because it is easier and safer to treat than continued hyperthyroidism. Although studies reveal no long-term consequences, concern remains about possible sequelae in children. This method of treatment is entering the mainstream for children and adolescents. Radioiodine given to a pregnant teenager renders the fetus hypothyroid and is contraindicated.

**Surgery.** Surgical treatment consists of partial or complete thyroidectomy. Risks associated with thyroidectomy include the use of anesthesia and the possibility that the thyroid removal will be excessive causing hypothyroidism or that it will be inadequate resulting in persistent hyperthyroidism. In addition, keloid formation, recurrent laryngeal nerve palsy, and hypoparathyroidism (transient postoperative or permanent) may occur. Thyroid storm caused by the release of large amounts of preformed hormone is a serious but rare complication. Even with optimal immediate postoperative results, patients may become hypothyroid within 10 years.

**Thyroid Storm**

Thyroid storm (see Table 175-4) is a rare medical emergency consisting of tachycardia, disorientation, elevated blood pressure, and hyperthermia. Treatment includes reducing the hyperthermia with a cooling blanket and administering a beta blocker to control the tachycardia, hypertension, and autonomic hyperfunction symptoms. Iodine may be given to block thyroid hormone release after an antithyroid medication is started. Hydrocortisone may be indicated for relative adrenal insufficiency, and therapy for heart failure includes diuretics and digoxin.

**Congenital Hyperthyroidism**

This disorder results from transplacental passage of maternal TSIs and may be masked for several days until the short-lived effects of transplacental maternal antithyroid medication wear off (assuming the mother was receiving such medication), at which time the effects of TSIs are observed. Irritability, tachycardia (often with signs of cardiac failure simulating cardiomyopathy), polythemia, craniosynostosis, bone age advancement, poor feeding, and failure to thrive are the clinical hallmarks. This condition may be anticipated if the mother is known to be thyrotoxic in pregnancy. Cure of hyperthyroidism before pregnancy (surgery or radioiodine treatment) limits or curtails T4 production but not the underlying immune disturbance producing TSIs; thus the infant still may be affected, at least transiently.

**Treatment** for a severely affected neonate includes methimazole and, as needed, a beta blocker to help decrease symptoms. Because the half-life of the immunoglobulin is several weeks, spontaneous resolution of neonatal thyrotoxicosis resulting from transplacental passage of TSIs usually occurs by 2 to 3 months of age. Observation without treatment is indicated in patients who are minimally affected.

**NODULES/TUMORS OF THE THYROID**

About 2% of children develop solitary thyroid nodules, most of which are benign. Evaluation of a nodule includes thyroid function tests, neck ultrasound, and, if needed, fine-needle aspiration (FNA). Ultrasound guidance may be needed for aspiration of small nodules or those not palpable. Nodules found to be benign on FNA may be monitored through clinical exam and ultrasound.

Carcinoma of the thyroid is rare in children (1% of all pediatric cancers in the 5- to 9-year-old age group and up to 7% of cancers in the 15- to 19-year-old age group). Papillary and follicular carcinomas represent 90% of childhood thyroid cancers. A history of therapeutic head or neck irradiation or radiation exposure from nuclear accidents predisposes a child to thyroid cancer. Carcinoma usually presents as a firm to hard, painless nonfunctional solitary nodule and may spread to adjacent lymph nodes. Rapid growth, hoarseness (recurrent laryngeal nerve involvement), and lung metastasis may be present. If the nodule is solid on ultrasound, is cold on radioiodine scanning, and feels hard, the likelihood of a carcinoma is high. Excisional biopsy usually is performed, but FNA biopsy also may be diagnostic.

**Treatment** includes total thyroidectomy, selective regional node dissection, and radioablation with $^{131}$I for residual or recurrent disease. The prognosis is usually good if the disease is diagnosed early.

**Medullary carcinoma of the thyroid** may be asymptomatic except for a mass. Diagnosis is based on the presence of elevated calcitonin levels, either in the basal state or after pentagastrin stimulation (difficult to obtain) and histologic examination. This tumor most often occurs with multiple endocrine neoplasia 2a or 2b (MEN), possibly in a familial pattern. In some families, the presence of mutations of the RET proto-oncogene is predictive of the development of medullary carcinoma of the thyroid. The location of the mutation can help determine when removal of the thyroid is warranted. Genetic screening of other members of the family is indicated after a proband is recognized. Prophylactic thyroidectomy is indicated for the family members with the same allele.
DISORDERS OF PARATHYROID BONE AND MINERAL ENDOCRINOLOGY

PARATHYROID HORMONE AND VITAMIN D

Calcium and phosphate are regulated mainly by diet and three hormones: parathyroid hormone (PTH), vitamin D, and calcitonin. PTH is secreted in response to a decrease in serum ionized calcium level. PTH attaches to its membrane receptor then acts via adenylate cyclase to mobilize calcium from bone into the serum and to enhance fractional reabsorption of calcium by the kidney while inducing phosphate excretion; all increase the serum calcium concentration and decrease serum phosphate. Lack of PTH effect is heralded by low serum calcium in the presence of elevated phosphate for age. PTH stimulates vitamin D secretion by increasing renal 1α-hydroxylase activity and acts indirectly to elevate serum calcium concentration by stimulating the production of 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D. Calcitonin increases the deposition of calcium into bone; in normal states the effect is subtle, but calcitonin may be used temporarily to suppress extremely elevated serum calcium values.

1,25-dihydroxyvitamin D enhances calcium absorption from the gastrointestinal tract, increasing serum calcium levels and bone mineralization. Vitamin D is derived from exposure of the skin to ultraviolet rays (usually via the sun) or from oral ingestion. It is modified first to 25-hydroxyvitamin D in the liver and then 1α-hydroxylated to the metabolically active form (1,25-dihydroxyvitamin D) in the kidney. The serum concentration of 25-hydroxyvitamin D is a better reflection of vitamin D sufficiency than the measurement of 1,25-hydroxyvitamin D (see Chapter 31).

HYPOCALCEMIA

The clinical manifestations of hypocalcemia result from increased neuromuscular irritability and include muscle cramps, carpopedal spasm (tetany), weakness, paresthesia, laryngospasm, and seizure-like activity. Tetany can be detected by the Chvostek sign (facial spasms produced by lightly tapping over the facial nerve just in front of the ear) or by the Trousseau sign (carpal spasms exhibited when arterial blood flow to the hand is occluded for 3 to 5 minutes with a blood pressure cuff inflated to 15 mm Hg above systolic blood pressure). Total serum calcium concentration is usually measured, although a determination of serum ionized calcium, the biologically active form, is preferable. Albumin is the major reservoir of protein-bound calcium. Disorders that alter plasma pH or serum albumin concentration must be considered when circulating calcium concentrations are being evaluated. The fraction of ionized calcium is inversely related to plasma pH; alkalosis can precipitate hypocalcemia by lowering ionized calcium without changing total serum calcium. Alkalosis may result from hyperpnea caused by anxiety or from hyperventilation related to physical exertion. Hypoproteinemia may lead to a false suggestion of hypocalcemia because the serum total calcium level is low even though the ionized Ca²⁺ remains normal. It is best to measure serum ionized calcium if hypocalcemia or hypercalcemia is suspected.

Primary hypoparathyroidism causes hypocalcemia but does not cause rickets. The etiology of primary hypoparathyroidism includes the following:

1. Congenital malformation (e.g., DiGeorge syndrome or other complex syndromes) resulting from developmental abnormalities of the third and fourth branchial arches (see Chapters 143 and 144)
2. Surgical procedures, such as thyroidectomy or parathyroidectomy, in which parathyroid tissue is removed either deliberately or as a complication of surgery for another goal
3. Autoimmunity, which may destroy the parathyroid gland

Pseudohypoparathyroidism (all with hypocalcemia and hyperphosphatemia) may occur in one of four forms as follows:

1. Type Ia: an abnormality of the G₃₉ protein linking the PTH receptor to adenylate cyclase; biologically active PTH is secreted in great quantities but does not stimulate its receptor
2. Type Ib: normal phenotype, normal G₃₉ with abnormalities in the production of adenylate cyclase
3. Type Ic: abnormal phenotype, normal production of adenylate cyclase, but a distal defect eliminates the effects of PTH
4. Type II: normal phenotype, normal production of adenylate cyclase, with a postreceptor defect, close to type Ib

Pseudohypoparathyroidism is an autosomal dominant condition that may present at birth or later. Pseudohypoparathyroidism is associated with Albright hereditary osteodystrophy whose clinical manifestations include short stature, stocky body habitus, round facies, short fourth and fifth metacarpals, calcification of the basal ganglia, subcutaneous calcification, and developmental delay. Albright hereditary osteodystrophy may be inherited separately so that a patient may have a normal appearance with hypocalcemia or may have the Albright hereditary osteodystrophy phenotype with normal serum calcium, phosphate, PTH, and response to PTH.

Transient neonatal hypocalcemia. During the first 3 days after birth, serum calcium concentrations normally decline in response to withdrawal of the maternal calcium supply via the placenta. Sluggish PTH response in a neonate may result in a transient hypocalcemia. Hypocalcemia caused by attenuated PTH release is found in infants of mothers with hyperparathyroidism and hypercalcemia; the latter suppresses fetal PTH release, causing transient hypoparathyroidism in the neonatal period.
Normal serum magnesium concentrations are required for normal parathyroid gland function and action. Hypomagnesemia may cause a secondary hypoparathyroidism, which responds poorly to therapies other than magnesium replacement.

The etiology of hypocalcemia usually can be discerned by combining features of the clinical presentation with determinations of serum ionized calcium, phosphate, alkaline phosphatase, PTH (preferably at a time when the calcium is low), magnesium, and albumin. If the PTH concentration is not appropriately elevated in relation to the low serum calcium, hypoparathyroidism (transient, primary, or caused by hypomagnesemia) is present. Vitamin D stores can be estimated by measuring serum 25-hydroxyvitamin D. Renal function is assessed by a serum creatinine measurement or determination of creatinine clearance (Table 176-1).

Treatment of severe tetany or seizures resulting from hypocalcemia consists of intravenous calcium gluconate (1 to 2 mL/kg of a 10% solution) given slowly over 10 minutes while cardiac status is monitored by electrocardiogram for bradycardia, which can be fatal. Long-term treatment of hypoparathyroidism involves administering vitamin D, preferably as 1,25-dihydroxyvitamin D and calcium. Therapy is adjusted to keep the serum calcium in the lower half of the normal range to avoid episodes of hypercalcemia that might produce nephrocalcinosis and to avoid pancreatitis.

RICKETS

Rickets is defined as decreased or defective bone mineralization in growing children; osteomalacia is the same condition in adults. The proportion of osteoid (the organic portion of bone) is excessive. As a result, the bone becomes soft and the metaphyses of the long bones widen. In older infants, poor linear growth, bowing of the legs on weight bearing (which can be painful), thickening at the wrists and knees, and prominence of the costochondral junctions (rachitic rosary) of the rib cage occur. At this stage, x-ray findings are diagnostic.

In nutritional vitamin D deficiency, calcium is not absorbed adequately from the intestine (see Chapter 31). Poor vitamin D intake or avoidance of sunlight in infants exclusively breastfed may contribute to the development of rickets. Fat malabsorption resulting from hepatobiliary disease (biliary atresia, neonatal hepatitis) or other causes (cystic fibrosis) also may produce vitamin D deficiency because vitamin D is a fat-soluble vitamin. Defects in vitamin D metabolism by the kidney (renal failure, autosomal recessive deficiency of 1α-hydroxylation, vitamin D–dependent rickets) or liver (defect in 25-hydroxylation) also can cause rickets.

In familial hypophosphatemic rickets, the major defect in mineral metabolism is failure of the kidney to adequately reabsorb filtered phosphate so that serum phosphate decreases and urinary phosphate is high. The diagnosis of this X-linked disease usually is made within the first few years of life and is typically more severe in males.

The etiology of rickets usually can be determined by an assessment of the mineral and vitamin D status (25-hydroxyvitamin D <8 ng/mL suggests nutritional vitamin D deficiency) (see Table 176-1). Further testing of mineral balance or measurement of other vitamin D metabolites may be required.

Several chemical forms of vitamin D can be used for treatment of the different rachitic conditions, but their potencies vary widely. Required dosages depend on the condition being treated (see Chapter 31). Rickets may also be treated with 1,25-hydroxyvitamin D and supplemental calcium. In hypophosphatemic rickets, phosphate supplementation (not calcium) must accompany vitamin D therapy, which is given to suppress secondary hyperparathyroidism. Adequate therapy restores normal skeletal growth and produces resolution of the radiographic signs of rickets. Nutritional rickets is treated with vitamin D given as one large dose, in weekly larger doses, or multiple smaller replacement doses. Surgery may be required to straighten legs in untreated patients with long-standing disease.
NORMAL SEXUAL DEVELOPMENT

The successive sequence of chromosomal sex, gonadal sex, and phenotypic sex leads to gender identity of the individual. Genes usually determine the morphology of internal organs and of gonads (gonadal sex); this directs the appearance of the external genitalia that form the secondary sex characteristics (phenotypic sex); self-perception of the individual (gender identity) and the perception of the individual by others (gender role) follow last. In most children, these features blend and conform, but, in some patients, one or more features may not follow this sequence, leading to the disorder of sexual development (DSD) (see Chapter 23).

The internal and external genitalia are formed between 6 and 13 weeks of gestation. Fetal gonad and external genitalia are bipotential and have the capacity to support development of a normal male or female phenotype (Fig. 177-1). In the presence of a gene called SRY for sex-determining region on the Y chromosome, the primitive fetal gonad differentiates into a testis (Fig. 177-2). The Leydig cells of the testis secrete testosterone, which has direct effects (stimulating development of the wolffian ducts) but also is locally converted to dihydrotestosterone (DHT) by the 5α-reductase enzyme. DHT causes enlargement, rugation, and fusion of the labioscrotal folds into a scrotum; fusion of the ventral surface of the penis to enclose a penile urethra; and enlargement of the

![Figure 177-1](image-url)

*Figure 177-1 Differentiation of male and female external genitalia as proceeding from a common embryonic anlage. Testosterone acts at 9 to 13 weeks of gestation to virilize the bipotential anlage. In the absence of testosterone action, the female phenotype develops. (From Grumbach MM, Conte FA: Disorders of sexual differentiation. In Wilson JD, Foster DW, editors: Textbook of Endocrinology, ed 8, Philadelphia, 1990, WB Saunders, p 873; adapted from Spaulding MH, Contrib Embryol Instit 13:69–88, 1921.)*
phallus with ultimate development of male external genitalia. Testicular production and secretion of müllerian-inhibitory substance by Sertoli cells cause the regression and disappearance of the müllerian ducts and their derivatives, such as the fallopian tubes and uterus. In the presence of testosterone, the wolffian ducts develop into the vas deferens, seminiferous tubules, and prostate.

The female phenotype develops unless specific male influences alter development. In the absence of SRY, an ovary spontaneously develops from the bipotential, primitive gonad. In the absence of fetal testicular secretion of müllerian-inhibitory substance, a normal uterus, fallopian tubes, and posterior third of the vagina develop out of the müllerian ducts, and the wolffian ducts degenerate. In the total absence of androgens, the external genitalia appear female.

Classification
The terms intersex, hermaphroditism, and pseudohermaphroditism are not useful. DSDs are categorized under three main subgroups according to karyotype (XX, XY, and sex chromosome for mosaic karyotypes).

Masculinization of the external genitalia of genotypic females (except for isolated enlargement of the clitoris, which can occur from later androgen exposure) is always caused by the presence of excessive androgens during the critical period of development (8 to 13 weeks of gestation) (Table 177-1). The degree of virilization can range from mild clitoral enlargement to the appearance of a male phallus with a penile urethra and fused scrotum with raphe. Congenital virilizing adrenal hyperplasia is the most common cause of female ambiguous genitalia; it is most commonly the result of an enzyme deficiency that impairs synthesis of glucocorticoids but does not affect androgen production. The impaired cortisol secretion leads to adrenocorticotropic hormone (ACTH) hypersecretion, which stimulates hyperplasia of the adrenal cortex and excessive adrenal production of androgens (see Chapter 178).

Underdevelopment of the male external genitalia occurs because of a relative deficiency of testosterone production or action (Table 177-2). The penis is small, with various degrees

**Table 177-1** Causes of Virilization in the Female

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>ADDITIONAL FEATURE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-450&lt;sub&gt;21&lt;/sub&gt; deficiency (21 hydroxylase)</td>
<td>Salt loss in some</td>
</tr>
<tr>
<td>3β-Hydroxysteroid dehydrogenase deficiency</td>
<td>Salt loss</td>
</tr>
<tr>
<td>P-450&lt;sub&gt;11&lt;/sub&gt; deficiency (11 hydroxylase)</td>
<td>Salt retention/hypertension</td>
</tr>
<tr>
<td>Androgenic drug exposure (e.g., progesterins)</td>
<td>Exposure between 9 and 12 weeks of gestation</td>
</tr>
<tr>
<td>Mixed gonadal dysgenesis or mosaic Turner syndrome</td>
<td>Karyotype = 46,XY/45,X</td>
</tr>
<tr>
<td>Ovotesticular DSD</td>
<td>Testicular and ovarian tissue present</td>
</tr>
<tr>
<td>Maternal virilizing adrenal or ovarian tumor</td>
<td>Rare, positive history</td>
</tr>
</tbody>
</table>
of hypospadias (penile or perineal) and associated chordee or ventral binding of the phallus; unilateral, but more often bilateral, cryptorchidism may be present. The testes should be sought carefully in the inguinal canal or labioscrotal folds by palpation or ultrasound. Rarely a palpable gonad in the inguinal canal or labioscrotal fold represents a herniated ovary or an ovotestis. The latter patients have ovarian and testicular tissue and usually ambiguous external genitalia. Production of testosterone by a gonad implies that testicular tissue is present and that at least some cells carry the SRY gene.

Testosterone production can be reduced by specific deficiencies of the enzymes needed for androgen biosynthesis or by dysplasia of the gonads. In the latter, if müllerian-inhibiting substance production also is reduced, a rudimentary uterus and fallopian tubes are present.

The complete form of androgen resistance or androgen insensitivity syndrome is the most dramatic example of resistance to hormone action by defects in the androgen receptor. Affected patients have a 46,XY karyotype, normally formed testes (usually located in the inguinal canal or labia majora), and female external genitalia with a short vagina and no internal müllerian structures. At the time of puberty, testosterone concentrations increase to normal or above normal male range. Because a portion of the testosterone is normally converted to estradiol in peripheral tissues and the estrogen cannot be opposed by the androgen, breast development ensues at the normal age of puberty without growth of pubic, facial, or axillary hair or the occurrence of menstruation.

5α-Reductase deficiency presents at birth with predominantly female phenotype or with ambiguous genitalia, including perineoscrotal hypospadias. The defect is in 5α reduction of testosterone to its metabolite DHT. At puberty spontaneous secondary male sexual development occurs. Gender identity and gender role are significant psychological issues with these patients if diagnosed at puberty.

### Table 177-2

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>ADDITIONAL FEATURE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3β-Hydroxysteroid dehydrogenase deficiency</td>
<td>Salt loss</td>
</tr>
<tr>
<td>P-450,17 deficiency</td>
<td>Salt retention/hypokalemia/hypertension</td>
</tr>
<tr>
<td>Isozymes P-450,17 deficiency with 17,20-desmolase deficiency</td>
<td>Adrenal function normal</td>
</tr>
<tr>
<td>17β-Hydroxysteroid oxidoreductase deficiency</td>
<td>Adrenal function normal</td>
</tr>
<tr>
<td>Dysgenetic testes</td>
<td>Possible abnormal karyotype; possible mutations in DAX1, SOX9, GATA4, WT1</td>
</tr>
<tr>
<td>Leydig cell hypoplasia</td>
<td>Rare</td>
</tr>
<tr>
<td>Complete androgen insensitivity</td>
<td>Female external genitalia, absence of müllerian structures</td>
</tr>
<tr>
<td>Partial androgen insensitivity</td>
<td>As previous with ambiguous external genitalia</td>
</tr>
<tr>
<td>5α-Reductase deficiency</td>
<td>Autosomal recessive, virilization at puberty</td>
</tr>
</tbody>
</table>

StAR, Steroid acute regulatory protein.

### Turner syndrome and Klinefelter syndrome

Turner syndrome and Klinefelter syndrome and their mosaic variants are classified as sex chromosome DSD. Mixed gonadal dysgenesis (45,X; 46,XY) often may present with genital ambiguity, asymmetric external genitalia, and inguinal hernias. There may be virilization on one side and none on the other. Similar findings may be seen with ovotesticular DSD, another classification of DSD.

### Approach to the infant with genital ambiguity

Ambiguous genitalia in a newborn must be attended to with as little delay as possible and with informed sensitivity to the psychosocial context as required. The laboratory evaluations required might take days or weeks to complete, delaying a sex assignment and naming of the infant, such that choice often precedes diagnosis. Beyond infancy and childhood, and to offset any gender uncertainty in the patient and confusion in the parents, health care providers must help families come to an appropriate closure and gender choice.

On physical examination, it is essential to note where the urethral opening lies and whether there is fusion of the anterior portion of the labioscrotal folds. Endogenous excessive production of androgen (as in congenital adrenal hyperplasia [CAH]) in a female fetus between 9 and 13 weeks of gestation leads to ambiguous genitalia. If the vaginal opening is normal, and there is no fusion, but the clitoris is enlarged without ventral fusion of the ventral urethra, the patient had later exposure to androgens. A patient with a fully formed scrotum, even if small, and a normally formed but small penis, termed a microphallus, must have had normal exposure to and action of androgen during 9 to 13 weeks of gestation.

The major goal is a rapid identification of any life-threatening disorders (salt loss and shock caused by the salt-losing form of CAH). Although the classic approach to sex assignment has been based on the feasibility of genital reconstruction and potential fertility rather than on karyotype or gonadal histology, the effects of prenatal androgen must be considered. Yet it may be inappropriate to raise a female infant who is severely virilized from virilizing CAH as a male; nonetheless in most reported cases, sex assignment and adult gender role remain female, and fertility can be retained because the internal organs are female. A 46,XY male with ambiguous genitalia and an extremely small phallus that does not increase in size with androgen therapy (partial androgen...
Diagnosis
The first step toward diagnosis is to determine whether the disorder represents virilization of a genetic female (androgen excess) or underdevelopment of a genetic male (androgen deficiency) (see Fig. 177-2). Inguinal gonads that are evident on palpation usually are testes and indicate that incomplete development of a male phenotype has occurred; this pattern is not consistent, and ovaries and ovotestes may feel similar. Similarly absence of female internal genitalia (detected by ultrasound) implies that müllerian-inhibiting substance was present and secreted by fetal testes. Karyotype determination is only one of many factors in deciding the sexual identity for purposes of rearing; the SRY gene may be found on chromosomes other than the Y chromosome, and, conversely, a Y chromosome may lack an SRY gene (it may have been translocated to an X chromosome, leading to the development of a 46,XX male–XX sex reversal, testicular DSD).

Statistically most virilized females have CAH; 90% of these females have 21-hydroxylase deficiency. The diagnosis is established by measuring the plasma concentration of 17-hydroxyprogesterone and androstenedione (see Chapter 178), which typically is hundreds of times above the normal range. Other enzymatic defects also may be diagnosed by quantifying circulating levels of the adrenal steroid precursor proximal to the defective enzyme block.

Establishing an accurate diagnosis is more difficult in underdeveloped males. When certain types of adrenal hyperplasia coexist with defects in androgen production of the testes, excessive ACTH secretion elevates substantially levels of specific adrenal steroid precursors, allowing a diagnosis. If the defect is restricted to testosterone biosynthesis, the measurement of testosterone and its precursors in the basal state and after stimulation by hCG may be required. Patients with normal levels of testosterone either have persistent androgen resistance or have had an interruption of normal morphogenesis of the genitalia. Abnormalities of the sex chromosomes may be associated with dysgenetic gonads, which may be associated with persistence of müllerian structures.

Treatment
Treatment consists of replacing deficient hormones (cortisol in adrenal hyperplasia or testosterone in a child with androgen biosynthetic defects who will be raised as male), surgical restoration to make the individual look more appropriate for the gender of rearing, and psychological support of the whole family. Gonads and internal organs discordant for the gender of rearing are often removed. Dysgenetic gonads with Y-genetic material always should be removed because gonadoblastomas or dysgerminomas may develop in the organ. Reconstructive surgery is usually performed by 2 years of age so that genital structure reflects gender of rearing. This recommendation for reconstructive surgery is controversial; some advocate that surgery not be performed in infancy or early childhood so that the child or young adolescent can be involved in the decision. A decision for gender of rearing is recommended from birth; however the knowledge that the person with a DSD may change gender later on is shared with parents from the outset.
Endocrinology

The clinical manifestations of inadequate adrenal function result from inadequate secretion or action of glucocorticoids, mineralocorticoids, or both (Table 178-1). In the case of enzyme defects that affect the gonad and the adrenal gland, overproduction or underproduction of potent androgens can occur, depending on the site of enzyme blockade (see Fig. 178-1). Progressive prenatal virilization of the external genitalia may occur in females; incomplete virilization may occur in males. Ambiguity of the external genitalia is a common manifestation of disordered fetal adrenal enzyme function. Precise diagnosis is essential for the prescription of appropriate therapy, long-term outlook, and genetic counseling. In patients with enzyme defects, an elevation in the precursor steroid is present proximal to the enzyme block and is metabolized through remaining alternate enzyme pathways, whereas a deficiency of steroids is present subsequent to the block.

The dominant clinical features of congenital adrenal mineralocorticoid deficiency are hyponatremia and hyperkalemia, usually developing by 5 to 7 days after birth but not immediately after birth. Vomiting, dehydration, and acidosis soon follow, as does hypotensive shock from glucocorticoid deficiency. Death may occur if the disorder remains undiagnosed and untreated. In females the ambiguity of the external genitalia is an obvious clue that salt-losing congenital adrenal hyperplasia (CAH) or simple virilizing CAH must be ruled out. Because these forms cannot be distinguished clinically, all presentations of ambiguous genitalia should involve evaluation for mineralocorticoid deficiency. In males the most common form of CAH, 21-hydroxylase deficiency, does not cause abnormal genitalia. There may be hyperpigmentation of the scrotal skin, but this is a subtle sign. In all infants, the diagnosis of adrenal insufficiency may be overlooked or confused with pyloric stenosis. In pyloric stenosis, in contrast to salt-losing CAH, vomiting of stomach contents results in hypochloremia, serum potassium is normal or low, and alkalosis is present. This distinction may be lifesaving in preventing unnecessary investigations or inappropriate therapy.

Not all forms of adrenal hyperplasia present at birth; the spectrum of disorder ranges from severe (classic) to mild (late-onset) or nonclassic. Milder forms may manifest in childhood, adolescence, or even young adulthood (not as
Deficient 21-hydroxylase activity (P-450c21 deficiency) impairs the conversion of 17α-hydroxyprogesterone (17-OHP) to 11-deoxycortisol and in the salt-losing form, of progesterone to deoxycorticosterone, a mineralocorticoid proximal in the pathway to the production of aldosterone. The decreased production of cortisol causes hypersecretion of ACTH, which stimulates the synthesis of steroids immediately proximal to the block and shunting of these to overproduction of androgens. The primary clinical manifestation is the virilization of the external genitalia of the affected female fetus; the development of the uterus, ovaries, and fallopian tubes remains unaffected by the androgens. The degree of virilization varies, ranging from mild clitororomegaly to complete fusion of labioscrotal folds, with severe clitororomegaly simulating a phallus (see Chapter 177). A male infant with this defect appears normal at birth, although penile enlargement may be apparent thereafter. The deficiency in aldosterone, found in about 75% of patients, causes salt wasting with shock and dehydration until the diagnosis is established and appropriate treatment is given.

The treatment of 21-hydroxylase deficiency requires hydrocortisone and fludrocortisone in the case of the salt-losing form. Therapy must be adjusted throughout childhood at regular intervals. Overtreatment will cause growth stunting and weight gain (cushingoid features), whereas undertreatment will cause excessive height gain, skeletal advance, and early appearance puberty, ultimately jeopardizing adult height potential.

Late-onset CAH is typically noted years after birth. Affected subjects have milder manifestations without ambiguous genitalia, but they may have acne, hirsutism, and in girls irregular menstrual cycles or amenorrhea. Late-onset CAH in girls may be confused with polycystic ovarian syndrome.

Biochemical diagnostic studies show elevated levels of serum 17-OHP, the substrate for the defective 21-hydroxylase enzyme activity. In newborns with CAH, the values are elevated a hundredfold to a thousandfold. In late-onset CAH, an ACTH stimulation test is necessary to show an abnormally high response of 17-OHP. Serum cortisol and aldosterone levels (in salt losers) are low, renin levels are high, whereas the testosterone level is elevated because it is derived from 17-OHP.

The goals of treatment are to achieve normal linear growth and bone age advancement. Long-term therapy consists of providing glucocorticoids at a dose of approximately 10 to 15 mg/m2/24 hours in three divided doses of oral hydrocortisone or its equivalent. Mineralocorticoid therapy for salt losers consists of fludrocortisone at a dose of 0.1 to 0.2 mg/24 hours, often with sodium chloride supplementation in infancy and early childhood. Surgical correction of ambiguous external genitalia may be considered. The adequacy of glucocorticoid replacement therapy is monitored by determining serum concentrations of adrenal precursors, including androstenedione and 17-OHP for 21-hydroxylase deficiency. In addition, the assessment of linear growth and skeletal age, by bone age determination, is required as a reflection of appropriate therapy. To avoid adrenal insufficiency, threefold higher doses of glucocorticoids are given during stressful states such as febrile illnesses and surgery. Intramuscular hydrocortisone is used in severe emergencies or with illnesses involving emesis. Mineralocorticoid therapy is monitored with serum sodium, potassium, and plasma renin activity levels. Prenatal treatment with dexamethasone to suppress fetal ACTH-induced glucocorticoid or mineralocorticoid deficiencies, but as androgen excess).

In patients with congenital adrenal hypoplasia or adrenal hemorrhage, the secretion of all adrenal steroids is low. In contrast CAH leads to a diagnostic steroid pattern in blood and urine (see Fig. 178-1). Deficiency of 21-hydroxylase is the most common form (95%) and serves as a paradigm for these disorders.

21-HYDROXYLASE DEFICIENCY

<table>
<thead>
<tr>
<th>Decision-Making Algorithms</th>
<th>Available @ StudentConsult.com</th>
</tr>
</thead>
</table>

- Hypertension
- Precocious Puberty in the Male
- Precocious Puberty in the Female
- Ambiguous Genitalia
- Hirsutism

The incidence of classic 21-hydroxylase deficiency is about 1 in 15,000 among various white populations. Nonclassic CAH may occur with an incidence of 1 in 50 in certain populations. The gene for 21-hydroxylase lies on the short arm of chromosome 6; the genotype may be determined in a proband, permitting prenatal diagnosis in a subsequent pregnancy.
<table>
<thead>
<tr>
<th>FEATURE</th>
<th>ELECTROLYTE DISTURBANCE*</th>
<th>VIRILIZED FEMALE</th>
<th>UNDER-VIRILIZED MALE</th>
<th>SERUM CORTISOL</th>
<th>URINE 11-DEOXYCORTISOL</th>
<th>17-OHCP</th>
<th>DHEA</th>
<th>ALDOSTERONE</th>
<th>17-OHCS</th>
<th>17-KS</th>
<th>PRE-GNANETRIOL</th>
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<td>D</td>
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<td>Hemorrhage</td>
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<td>No</td>
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<tr>
<td>Pseudohypoaldosteronism</td>
<td>Severe</td>
<td>No</td>
<td>No</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>NL</td>
<td>I</td>
<td>NL</td>
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</tr>
<tr>
<td>P-450,11 deficiency</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>D</td>
<td>I</td>
<td>NI</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>I</td>
<td>NI-sl I</td>
</tr>
<tr>
<td>P-450,17 deficiency</td>
<td>†</td>
<td>No</td>
<td>Yes</td>
<td>D</td>
<td>NI-D</td>
<td>D</td>
<td>D</td>
<td>NI-D</td>
<td>D</td>
<td>D</td>
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<tr>
<td>Unresponsiveness to ACTH</td>
<td>†</td>
<td>No</td>
<td>No</td>
<td>D</td>
<td>NI-D</td>
<td>NI-D</td>
<td>NI-D</td>
<td>NI-D</td>
<td>D</td>
<td>D</td>
<td>NI-D</td>
</tr>
</tbody>
</table>

17-KS, 17-Ketosteroid; 17-OHCS, 17-hydroxycorticosteroid; ACTH, adrenocorticotropic hormone; D, decrease; HSD, hydroxysteroid dehydrogenase; I, increase; NL, normal; StAR, steroid acute regulatory protein.

*Usually manifested after 5 days of age.

†High normal Na+ and low normal to low K+. 
androgen production can reduce or eliminate the ambiguity of the external genitalia in affected female fetuses, if begun at approximately 7 weeks of gestation; this remains controversial.

OTHER ENZYME DEFECTS
Other enzyme defects are rare in contrast to 21-hydroxylase deficiency. In 11-hydroxylase deficiency, the next most common cause of CAH, virilization occurs with salt retention and hypokalemia, as a result of the buildup of deoxycorticosterone (see Fig. 178-1), a potent mineralocorticoid. Hypertension develops as a result of excessive mineralocorticoid production. Table 178-2 summarizes the clinical and biochemical features of adrenal insufficiency in infancy.

ADDISON DISEASE
Addison disease is a rare acquired disorder of childhood, usually associated with autoimmune destruction of the adrenal cortex. It is a form of primary adrenal insufficiency with absence of glucocorticoid and mineralocorticoid.

Clinical manifestations are hyperpigmentation, salt craving, postural hypotension, fasting hypoglycemia, anorexia, weakness, and episodes of shock during severe illness. Baseline and ACTH-stimulated cortisol values are subnormal, confirming the diagnosis; hyponatremia, hyperkalemia, and elevated plasma renin activity indicate mineralocorticoid deficiency. Addison disease may occur within the context of autoimmune polyglandular syndromes (APS I and APS II). Other rare causes of adrenal insufficiency include adrenal leukodystrophy and conditions that affect the hypothalamus-pituitary whether acquired, such as in craniopharyngioma, or iatrogenic, such as in irradiation for treatment of malignancy.

Replacement treatment with 10 to 15 mg/m²/24 hours of hydrocortisone is indicated, with supplementation during stress at three times the maintenance dosage or the use of intramuscular hydrocortisone. The dose is titrated to allow a normal growth rate. Mineralocorticoid replacement with fludrocortisone is monitored by plasma renin activity and serum sodium and potassium determinations.

CUSHING SYNDROME
Classic clinical manifestations of Cushing syndrome in children include progressive central or generalized obesity, marked failure of longitudinal growth, hirsutism, weakness, a nuchal fat pad, acne, striae, hypertension, and often hyperpigmentation when ACTH is elevated. The most frequent cause is exogenous administration in the context of numerous conditions requiring long-term pharmacologic doses of glucocorticoids. Endogenous causes include adrenal adenoma, carcinoma, nodular adrenal hyperplasia, an ACTH-secreting pituitary microadenoma resulting in bilateral adrenal hyperplasia (Cushing disease), or an extremely rare ACTH-secreting tumor. Diagnostic tests include 24-hour urinary cortisol excretion, low-dose dexamethasone suppression test, high-dose dexamethasone suppression test (helps distinguish Cushing syndrome from Cushing disease), and late evening salivary cortisol sampling.

Treatment of Cushing syndrome is directed to the etiology and may include excision of autonomous adrenal, pituitary, or ectopic ACTH-secreting tumors. Rarely adrenalectomy is needed to control the symptoms. Parenteral glucocorticoid therapy is necessary during and immediately after surgical treatment to avoid acute adrenal insufficiency.

Suggested Reading
NEUROLOGY ASSESSMENT

A neurologic evaluation, including history, physical examination, and judicious use of ancillary studies, allows the localization and diagnosis of nervous system pathology. The process and interpretation of the neurologic examination varies with age; the newborn is unique with many transient and primitive reflex patterns, whereas the examination of adolescents and adults is similar. Careful evaluation of social, cognitive, language, fine motor and gross motor skills, and their age appropriateness is key.

HISTORY
Gathering neurologic history follows the traditional medical model with two additions: the pace of the process and the localization of the problem. The symptom evolution provides clues to the underlying process as symptoms may evolve in a progressive, static, or episodic fashion. Progressive symptoms may evolve suddenly (seizures, stroke); acutely over minutes or hours (epidural hemorrhage); subacutely over days or weeks (brain tumor); or slowly over years (hereditary neuropathies). Static neurologic abnormalities are observed early in life and do not change in character over time (cerebral palsy). Static lesions are often caused by congenital brain abnormalities or prenatal/perinatal brain injury. Intermittent attacks of recurrent, stereotyped episodes suggest epilepsy or migraine syndromes, among others. Episodic disorders are characterized by periods of symptoms, followed by partial or complete recovery (demyelinating, autoimmune, vascular diseases).

PHYSICAL EXAMINATION
Observation of the child's appearance, movement, and behavior begins at the start of the encounter. For example, the child may display an unusual posture, abnormal gait, or lack of awareness of the environment. Because the brain and skin have the same embryonic origin (ectoderm), abnormalities of hair, skin, teeth, and nails are associated with congenital brain disorders (neurocutaneous disorders) such as neurofibromatosis (NF type 1) in which café au lait macules (flat, light brown macules) are characteristic. Adenoma sebaceum, fibrovascular lesions that look like acne on the nose and malar regions, nail fibromas, ash-leaf spots (hypopigmented macules), and Shagreen patches (flesh-colored soft plaques with prominent follicular openings) are commonly seen in older children and adults with tuberous sclerosis.

The head circumference is measured in its largest occipitofrontal circumference and plotted against standard growth curves (Chapter 5). Microcephaly and macrocephaly represent an occipitofrontal circumference 2 standard deviations (SDs) below or above the mean, respectively. Measurements plotted over time may show an accelerating pattern (hydrocephalus) or decelerating pattern (brain injury, degenerative neurologic disorder). The anterior fontanelle is slightly depressed and pulsatile when a calm infant is placed upright. A tense or bulging fontanelle may indicate increased intracranial pressure (ICP) but may also be seen in a crying or febrile infant. Premature closure of one or more sutures (craniostenosis) results in an unusual shape of the head. Abnormal shape, location, and condition of the face, eyes, nares, philtrum, lips, or ears are found in many genetic syndromes.

A careful ocular examination is essential and should include a search for epicanthal folds, coloboma, conjunctival telangiectasias, and cataracts. Direct ophthalmoscopy assesses the optic disks and macula for abnormalities such as papilledema or a cherry-red spot. A complete examination of the retina involves dilating the pupil and use of indirect ophthalmoscopy, typically requiring ophthalmologic consultation. Examination of the hands and feet may reveal abnormal creases or digits (Chapters 50, 201). The neck and spine should be examined for obvious (myelomeningocele) or subtle (cutaneous dimples, sinus tracts, hair tufts, subcutaneous lipomas) midline defects. Nervous system abnormalities may result in kyphosis or scoliosis (Chapter 202).

NEUROLOGIC EXAMINATION OF A NEONATE
Because of the developmental immaturity of infants, the neonatal neurologic examination primarily assesses the function of the basal ganglia, brainstem, and more caudal structures. The plasticity of the developing nervous system means that examination results should be used cautiously in predicting developmental outcomes.

Mental Status
A healthy newborn infant should have periods of quiet, sustained wakefulness interspersed with active and quiet sleep.
Posture is the position that a calm infant naturally assumes when placed supine. An infant at 28 weeks of gestation shows an extended posture. By 32 weeks, there is a slight trend toward increase in tone and flexion of the lower extremities. At 34 weeks, the lower extremities are flexed; the upper extremities are extended. The term infant flexes lower and upper extremities.

Reflexes
Examination of the primitive reflexes provides assessment of the functional integrity of the brainstem and basal ganglia (Table 179-1). Many of these stereotyped motor responses are present at birth. They are symmetrical and disappear at 4 to 6 months of age, indicating the normal maturation of descending inhibitory cerebral influences. The grasp and rooting reflexes are inhibited by maturation of frontal lobes but may reappear later in life with acquired frontal lobe lesions. Asymmetry or persistence of the primitive reflexes may indicate focal brain or peripheral nerve lesions.

Movement and Tone
Spontaneous movements of premature infants are slow and writhing; those of term infants are more rapid.

Irritability, lethargy, or more severely depressed consciousness are nonspecific signs of abnormal brain function.

Reflexes
Examination of the primitive reflexes provides assessment of the functional integrity of the brainstem and basal ganglia (Table 179-1). Many of these stereotyped motor responses are present at birth. They are symmetrical and disappear at 4 to 6 months of age, indicating the normal maturation of descending inhibitory cerebral influences. The grasp and rooting reflexes are inhibited by maturation of frontal lobes but may reappear later in life with acquired frontal lobe lesions. Asymmetry or persistence of the primitive reflexes may indicate focal brain or peripheral nerve lesions.

Mental Status Evaluation
Alertness is assessed in infants by observing spontaneous activities, feeding behavior, and visual ability to fix and follow objects. Response to tactile, visual, and auditory stimuli is noted. If consciousness is altered, the response to painful stimuli is noted. Observation of toddlers at play allows a nonthreatening assessment of developmentally appropriate skills. In addition to language function, older children can be tested for reading, writing, numerical skills, fund of knowledge, abstract reasoning, judgment, humor, and memory.

The simplest way to assess intellectual abilities is through language skills. Language function is receptive (understanding speech or gestures) and expressive (speech and use of gestures). Abnormalities of language resulting from cerebral hemisphere disorders are referred to as aphasia. Anterior, expressive, or Broca aphasia is characterized by sparse, nonfluent language. Posterior, receptive, or Wernicke aphasia is characterized by an inability to understand language, with speech that is fluent but nonsensical. Global aphasia refers to impaired expressive and receptive language.

CRANIAL NERVE EVALUATION
The cranial nerve evaluation assesses brainstem integrity but depends on the stage of brain maturation and the ability to cooperate. A colorful toy may capture a young child’s attention and permit observation of coordination, movement, and cranial nerve function.

<table>
<thead>
<tr>
<th>REFLEX</th>
<th>DESCRIPTION</th>
<th>AGE AT APPEARANCE</th>
<th>AGE AT DISAPPEARANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moro</td>
<td>Light drop of head produces sudden extension followed by flexion of the arms and legs</td>
<td>Birth</td>
<td>6 mo</td>
</tr>
<tr>
<td>Grasp</td>
<td>Placing finger in infant’s palm results in flexing of infant’s fingers</td>
<td>Birth</td>
<td>6 mo</td>
</tr>
<tr>
<td>Rooting</td>
<td>Tactile stimulus about infant’s mouth results in the mouth pursuing the stimulus</td>
<td>Birth</td>
<td>4–6 mo</td>
</tr>
<tr>
<td>Trunk incursion</td>
<td>Stroking the skin along the edge of vertebrae produces curvature of the spine with concavity on the side of the stroke</td>
<td>Birth</td>
<td>4 mo</td>
</tr>
<tr>
<td>Placing</td>
<td>When dorsum of foot is brought into contact with the edge of a surface, infant places foot on the surface</td>
<td>Birth</td>
<td>4–6 mo</td>
</tr>
<tr>
<td>Asymmetrical tonic neck</td>
<td>With infant supine, turning of the head results in ipsilateral extension of the arm and leg with flexion of opposite extremities in a “fencing” posture</td>
<td>Birth</td>
<td>3 mo</td>
</tr>
<tr>
<td>Parachute</td>
<td>Infant is suspended face down by the chest. When infant is moved toward a table, the arms extend as if to protect self</td>
<td>8–10 mo</td>
<td>Never</td>
</tr>
<tr>
<td>Babinski</td>
<td>Stroking lateral aspect of sole from heel up results in dorsiflexion of the great toe and fanning of the remaining toes</td>
<td>Birth</td>
<td>12–18 mo</td>
</tr>
</tbody>
</table>
Cranial Nerve I
Smell can be assessed in verbal, cooperative children older than 2 years of age. Aromatic substances (perfumes, vanilla) should be used instead of volatile substances (ammonia), which irritate the nasal mucosa and stimulate the trigeminal nerve.

Cranial Nerve II
Full-term newborns in a quiet awake state follow human faces, lights in a dark room, or large, optokinetic strips. Visual acuity has been estimated to be 20/200 in newborns and 20/20 in 6-month-old infants. Standard visual charts displaying pictures instead of letters can be used to assess visual acuity in toddlers. Periperal vision is tested by surreptitiously bringing objects into the visual field from behind. A reduced pupillary reaction to light suggests anterior visual pathway lesions, including the retina, optic nerves, and chiasm. Unilateral optic nerve lesions are identified by the swinging flashlight test. With an optic nerve abnormality, both pupils constrict when light is directed into the normal eye. When light is swung over to the abnormal eye, both pupils dilate inappropriately; this is called an afferent pupillary defect or Marcus Gunn pupil. Interruption of the sympathetic innervation to the pupil produces Horner’s syndrome (ptosis, miosis, and unilateral facial anhidrosis). In this instance, anisocoria (unequal pupils) is more pronounced in a dark room, because the affected pupil is unable to dilate appropriately. Lesions of the posterior visual pathway, including the lateral geniculate, optic radiations, and occipital cortex, have normal pupillary light reactions but are expressed by loss of visual fields.

Cranial Nerves III, IV, and VI
These three cranial nerves control eye movement and are most easily examined with the use of a colorful toy to capture the child’s attention. For infants too young to fix and follow, rotating the infant’s head assesses oculocephalic vestibular reflexes (doll’s eye maneuver). If the brainstem is intact, rotating a newborn or comatose patient’s head to the right causes the eyes to move to the left, and vice versa. In awake, older patients, voluntary eye movements mask the reflex. Abnormalities of these cranial nerves may cause diplopia (double vision). With unilateral third cranial nerve (oculomotor nerve) palsy, the involved eye deviates down and out (infraducted, abducted), with associated ptosis and a dilated, mydriatic pupil. Injury to cranial nerve IV (trochlear nerve) causes weakness of downward eye movement with consequent vertical diplopia. Cranial nerve VI (abducens nerve) palsy results in the inability to move the eye outward. Because cranial nerve VI has a long intracranial route within the subarachnoid space, failure of abduction of one or both eyes is a frequent, but nonspecific, sign of increased ICP.

Cranial Nerve V
The muscles of mastication can be observed as an infant sucks and swallows. The corneal reflex can test cranial nerves V ophthalmic division and VII at any age. Facial sensation of light touch and pain can be determined with cotton gauze and pinprick. Facial sensation can be functionally assessed in an infant by gently brushing the cheek, which will produce the rooting reflex (turns head and neck with mouthing movement, as if seeking to nurse).

Cranial Nerve VII
Facial muscles are assessed by observing the face during rest, crying, and blinking. At older, cooperative ages, children can be asked to smile, blow out their cheeks, blink forcibly, and furrow their foreheads. Weakness of all unilateral muscles of the face, including the forehead, eye, and mouth, indicates a lesion of the ipsilateral peripheral facial nerve (Bell palsy). Because the upper third of the face receives bilateral cortical innervation, if the weakness affects only the lower face and mouth, a contralateral lesion of upper motor neuron in the brain (tumor, stroke, abscess) must be considered.

Cranial Nerve VIII
Lesions of cranial nerve VIII cause deafness, tinnitus, and vertigo. Normally, alert neonates blink in response to a bell or other abrupt, loud sound. Four-month-old infants turn their head and eyes to localize a sound. Hearing can be tested in a verbal child by whispering a word in one ear while covering the opposite ear. If there are any concerns about hearing, formal audiologic assessment is indicated. Lesions of the vestibular component of cranial nerve VIII produce symptoms of vertigo, nausea, vomiting, diaphoresis, and nystagmus. Nystagmus is an involuntary beating eye movement with a rapid phase in one direction and a slow phase in the opposite direction. By convention, the direction of the nystagmus is defined by the fast phase and may be horizontal, vertical, or rotatory.

Cranial Nerves IX and X
The gag reflex is brisk at all ages except the very immature neonate. An absent gag reflex suggests a lower motor neuron lesion of the brainstem, cranial nerves IX or X, neuromuscular junction, or pharyngeal muscles. Weak, breathy, or nasal speech; weak sucking; drooling and inability to handle secretions; gagging and nasal regurgitation of food are additional symptoms of cranial nerve X dysfunction.

Cranial Nerve XI
Observing the infant’s posture and spontaneous activity assesses the functions of the trapezius and sternocleidomastoid muscles. Head tilt and drooping of the shoulder suggest lesions involving cranial nerve XI. In later childhood, strength in these muscles can be tested directly and individually.

Cranial Nerve XII
Atrophy and fasciculation of the tongue, usually indicating a lesion of the anterior horn cells (spinal muscular atrophy [SMA]), can be observed at any age and are assessed most reliably when the infant is asleep. The tongue deviates toward the weak side in unilateral lesions.

MOTOR EXAMINATION
Power
In infants, power is assessed by observation of spontaneous movements and movements against gravity. Arm and leg movements should be symmetrical, seen best when the infant is held supine with one hand supporting the buttocks and
Tone
Tone represents the dynamic resistance of muscles to passive stretch. Lower motor and cerebellar lesions produce decreased tone (hypotonia). Upper motor lesions produce increased tone (spasticity). In extrapyramidal disease, an increase in resistance is present throughout passive movement of a joint (rigidity).

Bulk
Muscle bulk represents the volume of muscle tissue. In many lower motor neuron conditions (neuropathies, SMA), muscle bulk is diminished or atrophic. Excessive muscle bulk is seen in rare conditions, such as myotonia congenita; boys with Duchenne muscular dystrophy have pseudohypertrophy of their calves.

Coordination
Ataxia is the lack of coordination of movement, which is typically due to a dysfunction of the cerebellar pathways. Observation and functional analysis help assess coordination in infants and toddlers. Watching the child sit or walk assesses truncal stability. Exchanging toys or objects with the child permits assessment of intention tremor and dysmetria (errors in judging distance), signs of cerebellar dysfunction. Cooperative children can do repetitive finger or foot tapping to test rapid alternating movements. Cerebellar and corticospinal tract dysfunction produce slowing and irregularity during tests of rapid alternating movements.

Gait
Watching a child creep, crawl, cruise, or walk is the best global assessment for the motor and coordination systems (Chapter 197). Subtle deficits and asymmetries in power, tone, or balance may be observed. The toddler gait is normally wide-based and unsteady. The base of the gait narrows with age. By 6 years, a child is able to walk on toes, walk on heels, and tandem walk (heel to toe). Cerebellar dysfunction results in a broad-based, unsteady gait accompanied by difficulty in executing turns. Corticospinal tract dysfunction produces a stiff, scissoring gait and toe walking. Arm swing is decreased, and the affected arm is flexed across the body. Extrapyramidal dysfunction produces a slow, stiff, shuffling gait with dystonic postures. A waddling gait occurs with hip weakness due to lower motor neuron or neuromuscular disorders. A steppe gait results from weakness of ankle dorsiflexors (common peroneal palsy).

Reflexes
Deep tendon reflexes can be elicited at any age and are reported on a 5-point scale:
0 Absent
1 Trace
2 Normal
3 Exaggerated reflex, with spread to contiguous areas (tapping a patellar reflex and observing a bilaterally brisk quadriceps response)
4 Clonus (self-limited or sustained)
These reflexes are decreased in lower motor neuron diseases and increased in upper motor neuron disease. Babinski response, or extensor planter reflex, is an upward movement of the great toe and flaring of the toes on stimulation of the lateral foot and is a sign of corticospinal tract dysfunction. This reflex is unreliable in neonates except when asymmetrical because the "normal" response at this age varies. By 12 to 18 months of age, the plantar response should consistently be flexor (toes flexing down).

SENSORY EXAMINATION
The sensory examination of newborns and infants is limited to observing the behavioral response to light touch or gentle sterile pinprick. Stimulation of the limb should produce a facial grimace. A spinal reflex alone may produce withdrawal movement of the limb. In a cooperative child, the senses of pain, touch, temperature, vibration, and joint position can be tested individually. The cortical areas of sensation must be intact to identify an object placed in the hand (stereognosis) or a number written in the hand (graphesthesia) or to distinguish between two sharp objects applied simultaneously and closely on the skin (two-point discrimination).

SPECIAL DIAGNOSTIC PROCEDURES
Cerebrospinal Fluid Analysis
Analysis of cerebrospinal fluid (CSF) is essential when central nervous system (CNS) infection is suspected and provides important clues to other diagnoses (Table 179-2). Differentiating hemorrhagic CSF caused by a traumatic lumbar puncture (LP) from a true subarachnoid hemorrhage may be difficult. In most cases of traumatic LP, the fluid clears significantly as the sequence of tubes is collected. If there is clinical evidence of increased ICP (papilledema, depression of consciousness, focal neurologic deficits), caution must be exercised before performing an LP to limit risk of cerebral herniation. A computed tomography (CT) scan should be performed and confirmed to be normal before the LP if increased ICP is suspected. If increased ICP is present, it must be treated before an LP is performed.
Increased ICP, metabolic encephalopathy) must be suspected tumor, abscess, stroke). Bilateral disturbances of brain activity rhythms suggest an underlying structural abnormality (brain frequencies (focal slowing). Fixed slow wave foci (1 to 3 Hz) delta without any localized area of higher amplitude or slower fre-
synchrony between the background of the two hemispheres varies with age, but there should be general symmetry and
discrimination of epileptiform patterns. The background
patterns, behavioral state modulation, and pres-
assess for abnormalities of the neuromuscular apparatus,
including anterior horn cells, peripheral nerves, neuromuscu-
lar junctions, and muscles. Normal muscle is electrically silent at rest. Spontaneous discharge of motor fibers (fibrillations) or groups of muscle fibers (fasciculation) indicates denerva-
ting, revealing dysfunction of anterior horn cells or peripheral nerves. Abnormal muscle responses to repetitive nerve stim-
ulation are seen with neuromuscular junction disorders, such as myasthenia gravis and botulism. The amplitude and dura-
tion of the muscle compound action potentials are decreased in primary diseases of muscle. NCVs assess the action potential transmission along peripheral nerves. NCVs are slowed in demyelinating neuropathies (Guillain-Barré syndrome). The amplitude of the signal is diminished in axonal neuropathies.

### Electromyography and Nerve Conduction Studies

Electromyography and nerve conduction velocities (NCVs) assess for abnormalities of the neuromuscular apparatus, including anterior horn cells, peripheral nerves, neuromuscular junctions, and muscles. Normal muscle is electrically silent at rest. Spontaneous discharge of motor fibers (fibrillations) or groups of muscle fibers (fasciculation) indicates denervation, revealing dysfunction of anterior horn cells or peripheral nerves. Abnormal muscle responses to repetitive nerve stimulation are seen with neuromuscular junction disorders, such as myasthenia gravis and botulism. The amplitude and duration of the muscle compound action potentials are decreased in primary diseases of muscle. NCVs assess the action potential transmission along peripheral nerves. NCVs are slowed in demyelinating neuropathies (Guillain-Barré syndrome). The amplitude of the signal is diminished in axonal neuropathies.

### Neuroimaging

Imaging the brain and spinal cord is accomplished using CT or magnetic resonance imaging (MRI). CT is quick and access-
for emergency purposes. MRI provides fine detail and, with different sequences, permits detection of posterior fossa lesions, subtle cerebral abnormalities, vascular anomalies, low-grade tumors, and ischemic changes. For a child with a head injury or sudden headache, cranial CT is the study of choice because it can rapidly reveal intracranial hemorrhage or other large lesions. For a child with new-onset complex partial seizures, MRI is the study of choice, because an area of focal cortical dysplasia or other subtle lesions might not be apparent on CT. MRI also provides excellent views of the spinal cord. Cranial ultrasonography is a noninvasive bedside procedure used to visualize the brain and ventricles of infants and young children with open fontanelles.

### Electroencephalography

The electroencephalogram (EEG) records electrical activity generated by the cerebral cortex. EEG rhythms mature throughout childhood. There are three key features present: background patterns, behavioral state modulation, and presence or absence of epileptiform patterns. The background varies with age, but there should be general symmetry and synchrony between the background of the two hemispheres without any localized area of higher amplitude or slower frequencies (focal slowing). Fixed slow wave foci (1 to 3 Hz) delta rhythms suggest an underlying structural abnormality (brain tumor, abcess, stroke). Bilateral disturbances of brain activity (increased ICP, metabolic encephalopathy) must be suspected when there is diffuse slow wave activity (delta frequency). Spikes, polyspikes, and spike-and-wave abnormalities, either in a localized region (focal) or distributed bihemispherically (generalized), indicate an underlying seizure tendency.

### Headache and Migraine

#### Etiology and Epidemiology

Headache is a common symptom among children and adolescents. Headaches can be a primary problem (migraines, tension-type headaches) or secondary to another condition. Secondary headaches are most often associated with minor illnesses such as viral upper respiratory infections or sinusitis, but may be the first symptom of serious conditions (meningitis, brain tumors), so a systematic approach is necessary.
CLINICAL MANIFESTATIONS

Headaches

The temporal pattern of the headache must be clarified. Each pattern (acute, recurrent-episodic, chronic-progressive, chronic-nonprogressive) has its own differential diagnosis (Table 180-1).

Tension-type headaches are the most common recurrent pattern of primary headaches in children and adolescents. They are generally mild and lack associated symptoms, so are not typically disruptive to patients’ lifestyle or activities. The pain is global and squeezing or pressing in character, but can last for hours or days. There is no associated nausea, vomiting, phonophobia, or photophobia. Headaches can be related to environmental stresses or symptomatic of underlying psychiatric illnesses, such as anxiety or depression.

Migraine headaches are another common type of recurrent headaches and frequently begin in childhood. Headaches are stereotyped attacks of frontal, bitemporal, or unilateral, moderate to severe, pounding or throbbing pain that are aggravated by activity and last 1 to 72 hours. Associated symptoms include nausea, vomiting, pallor, photophobia, phonophobia, and an intense desire to seek a quiet dark room for rest. Toddlers may be unable to verbalize the source of their discomfort and exhibit episodes of irritability, sleepiness, pallor, and vomiting. Migraines can be associated with auras that may be typical (visual, sensory, dysphagic) or atypical. Aura can precede or coincide with the headache and typically persists for 15 to 30 minutes. Visual auras consist of spots, flashes, or lines of light that flicker in one or both visual fields. Atypical auras may also consist of brief episodes of unilateral or perioral numbness, unilateral weakness, or vertigo that persist for hours, then resolve completely. Complex, atypical symptoms (e.g., hemiparesis, monocular blindness, ophthalmoplegia, or confusion), accompanied by a headache, warrant careful diagnostic investigation, including a combination of neuroimaging, electroencephalogram, and appropriate metabolic studies.

Common causes of secondary headaches include head trauma, intercurrent viral illness, and sinusitis. Medication overuse headaches may complicate primary and secondary headaches. Serious causes of secondary headache include increased intracranial pressure (ICP) caused by a mass (tumor, vascular malformation) or intrinsic increase in pressure (pseudotumor cerebri). Increased ICP should be suspected if the headache and associated vomiting are worse when lying down or on first awakening; awaken the child from sleep; remit on arising; or are exacerbated by coughing, Valsalva maneuver, or bending over. Papilledema (Figure 180-1) or focal neurological deficits such as cranial nerve VI palsy may be seen on examination.

DIAGNOSTIC STUDIES

For most children, a thorough history and physical examination provide an accurate diagnosis and obviate the need for further testing. Neuroimaging is usually not necessary. Imaging is warranted, however, when the neurologic examination is abnormal, there are unusual neurologic features during the headache, or the child has signs or symptoms of increased ICP. P focal neurological deficits, alteration of consciousness, or a chronic progressive headache pattern may warrant imaging. In these cases, brain magnetic resonance imaging, with and without gadolinium contrast, is the study of choice, providing the highest sensitivity for detecting posterior fossa lesions and other, more subtle abnormalities. When the headache has a sudden, severe onset, emergent computed tomography (CT) can quickly evaluate for intracranial bleeding. If the CT

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**Table 180-1 Four Temporal Patterns of Childhood Headache**

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Single episode of pain without a history of such episodes. The “first and worst” headache, which raises concerns for aneurysmal subarachnoid hemorrhage in adults, is commonly due to febrile illness related to upper respiratory tract infection in children. Regardless, more ominous causes of acute headache (hemorrhage, meningitis, tumor) must be considered.</td>
</tr>
<tr>
<td>Acute recurrent</td>
<td>Pattern of attacks of pain separated by symptom-free intervals. Primary headache syndromes, such as migraine or tension-type headache, usually cause this pattern. Infrequently recurrent headaches can sometimes also be attributed to certain epilepsy syndromes (benign occipital epilepsy), substance abuse, or recurrent trauma.</td>
</tr>
<tr>
<td>Chronic progressive</td>
<td>Most ominous of the temporal patterns—implies a gradually increasing frequency and severity of headache. The pathologic correlate is increasing ICP. Causes of this pattern include pseudotumor cerebri, brain tumor, hydrocephalus, chronic meningitis, brain abscess, and subdural collections.</td>
</tr>
<tr>
<td>Chronic nonprogressive or chronic daily</td>
<td>Pattern of frequent or constant headache. Chronic daily headache generally is defined as &gt;4-month history of &gt;15 headaches/month, with headaches lasting &gt;4 hours. Affected patients have normal neurologic examinations; psychological factors and anxiety about possible underlying organic causes are common.</td>
</tr>
</tbody>
</table>

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*Figure 180-1* Papilledema with dilation of the vessels, obliteration of the optic cup, loss of disc margin, and hemorrhages around disc. (From Kliegman RE, Behrman, RM, Jenson HB, editors: Nelson Textbook of Pediatrics, ed 18, Philadelphia, 2007, Saunders, p 2107.)
Section 24 • Neurology

is negative, a lumbar puncture should be performed, with measurement of opening pressure and evaluation for red and white blood cells, protein, glucose, or xanthochromia.

TREATMENT

Treating migraines requires an individually tailored regimen to address the frequency, severity, and disability produced by the headache. Intermittent symptomatic, or abortive, analgesics are the mainstay for treatment of infrequent, intense episodes of migraine. Symptomatic therapy requires early administration of an analgesic, rest, and sleep in a quiet, dark room. Acetaminophen or a nonsteroidal anti-inflammatory drug such as ibuprofen or naproxen sodium is often effective. Hydration and antiemetics are also useful adjunctive therapies. If these first-line medications are insufficient, triptan agents may be considered. Triptans, available in injectable, nasal spray, oral disintegrating, and tablet form, are serotonin receptor agonists that may alleviate migraine symptoms promptly. Triptans are contraindicated for patients with focal neurological deficits associated with their migraines or signs consistent with basilar migraine (syncope) because of the risk of stroke.

Many children suffer with severe and frequent migraines that disrupt their daily lives. Children with more than one disabling headache per week may require daily preventive agents to reduce both attack frequency and severity. Preventative medications include tricyclic antidepressants (amitriptyline, nortriptyline), anticonvulsants (topiramate, valproic acid), antihistamines (cyproheptadine), beta-blockers (propranolol), and calcium channel blockers (flunarizine, verapamil).

Before initiating daily medications, lifestyle modifications must be put into place to regulate sleep, daily routines, and exercise and identify any precipitating or aggravating influences, eliminating as many as possible (caffeine, certain foods, stress, missed meals, dehydration). Other adjunctive treatment options include psychological support, counseling, stress management, and biofeedback.

Table 181-1 Paroxysmal Disorders of Childhood

<table>
<thead>
<tr>
<th>Seizures/epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine and variants</td>
</tr>
<tr>
<td>Paroxysmal torticollis of infancy</td>
</tr>
<tr>
<td>Paroxysmal vertigo (benign)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Syncope</th>
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<tbody>
<tr>
<td>Vasovagal syncope</td>
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<tr>
<td>Breath-holding spells</td>
</tr>
<tr>
<td>Cardiac syncope (arrhythmias, long QT syndrome)</td>
</tr>
<tr>
<td>Apnea</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Transient ischemic attack</th>
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<tbody>
<tr>
<td>Metabolic disorders</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
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</table>

<table>
<thead>
<tr>
<th>Sleep disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy, cataplexy</td>
</tr>
<tr>
<td>Night terrors</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Paroxysmal dyskinesias and other movement disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tics</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Shudders attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandifer syndrome (gastroesophageal reflux causing paroxysmal stiffening and posturing)</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Conversion disorder</th>
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<table>
<thead>
<tr>
<th>Normal behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal jitteriness</td>
</tr>
<tr>
<td>Benign sleep myoclonus</td>
</tr>
</tbody>
</table>

| Self-stimulatory behavior                         |

The differential diagnosis of paroxysmal disorders includes seizures and nonepileptic events (Table 181-1). Nonepileptic paroxysmal events are often normal or benign phenomena, although some are clinically significant and consequential. A thorough medical history from the patient and primary witnesses is the most reliable tool for establishing the correct diagnosis.

Acute symptomatic seizures are secondary to an acute problem affecting brain excitability, such as electrolyte imbalance or infection (Table 181-2). Epilepsy is defined as recurrent, unprovoked seizures. Epileptic seizures are generally classified as focal (or partial), arising from one region of the cortex, or generalized seizures, which arise from both hemispheres, simultaneously (Table 181-3). Approximately 4% to 10% of children experience at least one seizure. The incidence of childhood epilepsy is 1% to 2%.

FOCAL SEIZURES

Simple focal (or partial) seizures arise from a specific anatomic focus and may or may not spread to surrounding brain regions. Clinical symptoms include motor (tonic, clonic, myoclonic), sensory, psychic, or autonomic abnormalities, but consciousness is preserved. The location and direction of spread of the seizure focus determine the clinical symptoms.

Complex partial seizures can have similar sensorimotor signs but also have associated alteration of consciousness. Although the child may not be completely unresponsive, subtle slowing or alteration of mental status (dyscognitive features) may occur. Along with altered responsiveness, patients may have staring...

Chapter 181

SEIZURES (PAROXYSMAL DISORDERS)

A seizure is a transient occurrence of signs or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain.

ETIOLOGY AND EPIDEMIOLOGY

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Seizures and Other Paroxysmal Disorders
Seizures (Paroxysmal Disorders)

and automatisms during complex partial seizures. Automatisms are automatic semipurposeful movements of the mouth (lip smacking, chewing) or extremities (rubbing of fingers, shuffling of feet). Focal seizures that manifest only with psychic or autonomic symptoms, such as a feeling of déjà vu during a temporal lobe seizure, can be difficult to recognize. When focal seizures spread to involve the whole brain and produce a generalized seizure, they are said to have secondarily generalized. Such spread is classically described as progression from face to arm to leg (Jacksonian march). It is often difficult to distinguish primary generalized tonic and clonic seizures from secondarily generalized focal seizures on purely clinical grounds. This distinction is important, however, because evaluation and treatment for focal or generalized epilepsy syndromes are quite different.

GENERALIZED SEIZURES

Tonic, clonic, and biphasic tonic-clonic seizures may occur alone or in association with other seizure types. Typically the seizure begins abruptly but occasionally is preceded by a series of myoclonic jerks. During a tonic-clonic seizure, consciousness and control of posture are lost, followed by tonic stiffening and upward deviation of the eyes. Pooling of secretions,
Table 181-4  Differentiating Absence Seizure and Complex Partial Seizure

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>ABSENCE SEIZURE</th>
<th>COMPLEX PARTIAL SEIZURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Seconds</td>
<td>Minutes</td>
</tr>
<tr>
<td>Provoking maneuver</td>
<td>Hyperventilation</td>
<td>Variable, but often none</td>
</tr>
<tr>
<td>Postictal phase</td>
<td>None</td>
<td>Confusion, sleepiness</td>
</tr>
<tr>
<td>Number of seizures</td>
<td>Many per day</td>
<td>Infrequent (rarely more than one per day)</td>
</tr>
<tr>
<td>EEG features</td>
<td>Intercital: normal</td>
<td>Intercital: focal slowing or sharp waves</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>Normal</td>
<td>Normal, or focal deficits</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Normal</td>
<td>Normal, or focal abnormalities (mesial temporal sclerosis, focal cortical dysplasia, neoplasm, encephalomalacia)</td>
</tr>
<tr>
<td>First-line treatment</td>
<td>Ethosuximide or valproic acid†</td>
<td>Oxcarbazepine</td>
</tr>
</tbody>
</table>

*In the proper clinical context, and with an appropriate EEG, a diagnosis of absence epilepsy should be made without neuroimaging.
†Oxcarbazepine and carbamazepine are relatively contraindicated for children with typical absence epilepsy, as their seizures can be exacerbated by these medications.

Febrile Seizures
Seizures in the setting of fever may be caused by infections of the nervous system (meningitis, encephalitis, brain abscess), unrecognized epilepsy triggered by fever, or febrile seizures. The latter represents the most common cause of seizures among children between 6 months and 6 years of age, occurring in about 4% of all children. By definition, a febrile seizure occurs in the presence of fever. Simple febrile seizures are generalized at onset, last less than 15 minutes, and occur only once in a 24-hour period in a neurologically and developmentally normal child. If there are focal features, the seizure lasts longer than 15 minutes or recurs within 24 hours, or if the child has preexisting neurologic challenges, the seizure is referred to as a complex or atypical febrile seizure.

The prognosis of children with simple febrile convulsions is excellent. Intellectual achievements are normal. Febrile seizures recur in 30% to 50% of children. The risk of subsequent epilepsy is not substantially greater than that for the general population (approximately 2%). Factors that increase the risk for the development of epilepsy include abnormal neurologic examination or development, family history of epilepsy, and complex febrile seizures. Because febrile seizures are brief and the outcome is benign, most children require no treatment. Rectal diazepam can be administered during a seizure to abort a prolonged event and is a reasonable option for children with a history of prolonged febrile seizures. Because of the potential for side effects, daily administration of anticonvulsant medication is not recommended. Administration of antipyretics during febrile illnesses does not prevent febrile seizures.

Psychogenic Nonepileptic Seizures (PNES)
PNES (previously termed pseudoseizures) may be the manifestation of conversion disorders or malingering. Additionally, children with genuine epilepsy may, consciously or subconsciously, exhibit concurrent nonepileptic spells. Although the clinical differentiation can be difficult, PNES often differ from epileptic seizures in that the patient's eyes are often closed (typically eyes are open during epileptic seizures) and the movement is tremulous or thrashing rather than true tonic-clonic activity. Verbalization and pelvic thrusting are seen more commonly in PNES, urinary and fecal continence is usually preserved, and injury does not occur. If the tongue is bitten, more often the tip of the tongue is injured (as opposed to the sides of the tongue in epileptic seizures). PNES can often be initiated or terminated by suggestion. An EEG performed

Atypical Absence, Myoclonic, and Atonic Seizures
Atypical absence seizures manifest as episodes of impaired consciousness with automatisms, autonomic phenomena, and motor manifestations, such as eye opening, eye deviation, and body stiffening. They are associated with slower EEG discharges (2 Hz) and other seizure types. Myoclonus is a sudden jerk of all or part of the body; not all myoclonus is epileptic in nature. Nonepileptic myoclonus may be benign, as in sleep myoclonus, or indicate serious disease. Myoclonic epilepsy usually is associated with multiple seizure types. The underlying disorder producing myoclonic epilepsy may be static (juvenile myoclonic epilepsy) or progressive and associated with neurologic deterioration (neuronal ceroid lipofuscinosis). Myoclonic absence refers to the body jerks that commonly accompany absence seizures and atypical absence seizures. Although atonic seizures are typically brief (lasting 1 to 2 seconds), they are quite disabling because of a sudden loss of postural tone, resulting in falls and injuries.

Absence Seizures
Seizures in which the primary clinical feature is staring can be either absence (generalized) or complex partial seizures. The clinical hallmark of absence seizures is a brief (less than 15 seconds) loss of environmental awareness accompanied by eye fluttering or simple automatisms, such as fumbling with the fingers and lip smacking. Absence seizures usually begin between 4 and 6 years of age. Neurologic examination and brain imaging are normal. The characteristic electroencephalographic (EEG) patterns consist of generalized 3-Hz spike-and-wave activity. A clinical seizure can be provoked by hyperventilation or strobe light stimulation. Differentiating absence from complex partial seizures can be difficult, but is essential for appropriate evaluation and treatment (Table 181-4).
Epilepsy Syndromes

The epilepsy syndromes represent clinical entities in which age, pattern of clinical events, EEG features, natural history, and prognosis are distinctive (see Table 181-3).

Benign childhood epilepsy with centrotemporal spikes, also known as benign Rolandic epilepsy, is among the most common epilepsy syndromes and usually begins between ages 5 and 10 years. The seizures typically occur only during sleep or on awakening in more than half of patients. Affected children usually have focal motor seizures involving the face and arm (abnormal movement or sensation around the face and mouth, drooling, rhythmic guttural sound). Speech and swallowing may be impaired. Seizures sometimes secondarily generalize. The interictal EEG demonstrates independent bilateral centrotemporal sharp waves but is otherwise normal. With a classic history and EEG, and a normal neurological examination, the diagnosis can be made with confidence and neuroimaging is not required. Seizures usually respond promptly to anticonvulsant therapy. Intellectual outcome is normal, and the epilepsy resolves after puberty. Comorbid learning difficulties and attention deficit/hyperactivity disorder (ADHD) are common.

Childhood absence epilepsy is another common syndrome. Absence seizures typically begin in the early school years and usually resolve by late childhood or adolescence. If absence does not remit, 44% will go on to develop juvenile myoclonic epilepsy (see later discussion). Ethosuximide is the first-choice therapy. A subset of patients also has generalized tonic-clonic seizures. For these children, valproic acid is the first choice as it can prevent both absence and convulsive seizures. Comorbid learning disabilities and ADHD are common. There is no contraindication to treating these children’s ADHD with stimulant medication.

Juvenile myoclonic epilepsy (of Janz) is the most common generalized epilepsy among adolescents and young adults. Onset is typically in early adolescence with myoclonic jerks (exacerbated in the morning, often causing the patient to drop objects), generalized tonic-clonic seizures, and absence seizures. Seizures usually resolve promptly with anticonvulsant medication (classically valproic acid, but several medications have been shown to be efficacious), but therapy must be maintained for life.

Infantile spasms are brief contractions of the neck, trunk, and arm muscles, followed by a phase of sustained muscle contraction lasting less than 2 seconds. Spasms occur most frequently when the child is awakening from or going to sleep. Each jerk is followed by a brief period of relaxation with repeated spasms in clusters of variable duration. Many clusters occur each day. West syndrome is the triad of infantile spasms, developmental regression, and a dramatically abnormal EEG pattern (hypsarrhythmia). Hypsarrhythmia consists of chaotic high-voltage slow waves, spikes, and polyspikes. The peak age at onset is 3 to 8 months. When flexion of the thighs and crying are prominent, the syndrome may be mistaken for colic or gastroesophageal reflux. The underlying etiology of the spasms dictates the prognosis. More than 200 different etiologies have been identified, including tuberous sclerosis, malformations of cortical development (lissencephaly), genetic syndromes (trisomy 21), acquired brain injury (stroke, perinatal hypoxic-ischemic encephalopathy), and metabolic disorders (phenylketonuria). Infants for whom an etiology is determined are classified as having symptomatic infantile spasms and are at very high risk for long-term neurodevelopmental difficulties. The etiology is not determined for a significant subset of children. These patients with cryptogenic spasms have a somewhat better long-term prognosis but remain at high risk for adverse outcomes. First-line treatment options for infantile spasms include adrenocorticotropic hormone, high-dose oral corticosteroids, and vigabatrin. For infants with underlying tuberous sclerosis, vigabatrin is considered the treatment of choice. For other patients, treatment determinations are made on a case-by-case basis.

Lennox-Gastaut syndrome is a severe epilepsy syndrome with variable age of onset. Most children present before age 5 years. Frequent, multiple seizure types, including atonic, focal, atypical absence, and generalized tonic, clonic, or tonic-clonic varieties, characterize the disorder. Many children have underlying brain injury or malformations. The seizures usually respond poorly to treatment, and most patients have significant intellectual disability.

Benign neonatal convulsions are an autosomal dominant genetic disorder linked to abnormal neuronal potassium channels. Otherwise well newborns present with focal seizures toward the end of the first week of life, leading to the colloquial term fifth-day fits. Response to treatment is generally excellent, and the long-term outcome is typically favorable.

Acquired epileptic aphasia (Landau-Kleffner syndrome) is characterized by the abrupt loss of previously acquired language in young children. The language disability is an acquired cortical auditory deficit (auditory agnosia). The EEG is highly epileptiform in sleep, the peak area of abnormality often being in the dominant perisylvian region (language areas). This diagnosis should be considered for young patients with clear autistic regression, as it is a potentially treatable entity.

Status Epilepticus

Status epilepticus is a neurologic emergency and is defined as ongoing seizure activity or repetitive seizures without return of consciousness for greater than 30 minutes. Status epilepticus carries an approximately 14% risk of new neurologic deficits, most secondary to the underlying pathology. Similarly, the mortality rate of status epilepticus (4% to 5%) is related to the underlying etiology. Etiologies include new-onset epilepsy of any type, drug intoxication, drug withdrawal (especially missed anticonvulsant doses among children with preexisting epilepsy), hypoglycemia, electrolyte imbalance, acute head trauma, infection, ischemic stroke, intracranial hemorrhage, metabolic disorders, and hypoxia.

The first priority of treatment is to ensure an adequate airway, breathing, and circulation (Chapter 38). Vital signs should be obtained and oxygen administered if needed. If respirations are inadequate, positive-pressure ventilation may be required. Intravenous (IV) access should be obtained. In patients with no history of seizures, laboratory evaluation should be undertaken (see below). Several pharmacologic options exist for management of status epilepticus (Table 181-5). Initial management is usually with a benzodiazepine. Lorazepam, diazepam, and midazolam all are effective agents. Diazepam distributes rapidly to...
the brain but has a short duration of action. If IV access is not available, liquid preparations may be administered per rectum. If the seizure does not resolve after two doses of benzodiazepine, a second-line agent must be administered. Either IV phenytoin or fosphenytoin is effective, but cardiac monitoring is required to evaluate for arrhythmia. If the seizures persist, a loading dose of phenobarbital or valproic acid is appropriate (see Table 181-5). Alternatively, continuous infusions, such as midazolam or pentobarbital, can be employed as third-line agents (with appropriate airway protection, blood pressure support, and strong consideration of continuous video-EEG monitoring to evaluate for ongoing subclinical seizures). If this approach is ineffective, preparations for general anesthesia are undertaken. When status epilepticus stops, maintenance therapy is initiated with the appropriate anticonvulsant.

LABORATORY AND DIAGNOSTIC EVALUATION

For an otherwise healthy child with an unprovoked seizure and a normal physical and neurological examination, no laboratory evaluation is required. Children with simple febrile seizures who have recovered completely require little or no laboratory evaluation other than studies necessary to evaluate the source of the fever. If the clinical presentation does not meet these criteria and acute symptomatic seizures are suspected, potentially life-threatening causes such as meningitis, sepsis, head trauma, and toxins should be pursued. A complete laboratory evaluation for new onset of seizures includes a complete blood count and measurement of glucose, calcium, sodium, potassium, chloride, bicarbonate, urea nitrogen, creatinine, magnesium, and phosphorus, as well as blood or urine toxicology screening. Children with clinical signs and symptoms of meningitis (neck stiffness, Kernig sign, Brudzinski sign), or history or physical examination suggestive of intracranial infection, should undergo a lumbar puncture. Cerebrospinal fluid (CSF) should be analyzed for cell counts, culture, protein, and glucose levels. In children less than 18 months old, particularly young infants, the clinical symptoms of meningitis may be subtle. Neonates also may require testing for inborn errors of metabolism; blood ammonia; CSF glucose and lactate, as well as herpes simplex polymerase chain reaction; urine and stool culture (cytomegalovirus and enterovirus); and a clinical trial of pyridoxine.

The EEG is the most useful neurodiagnostic test for distinguishing seizures from nonepileptic paroxysmal disorders and for classifying seizures as having focal or generalized onset. The EEG must be interpreted in the context of the clinical history, because some normal children have focal or epileptiform EEG patterns. Children with seizures may have normal interictal EEGs. When the diagnosis is unclear, more sophisticated EEGs with prolonged recordings and simultaneous video monitoring of the patient in an attempt to capture a typical event may be necessary.

Magnetic resonance imaging (MRI) is superior to computed tomography (CT) in showing most brain pathology, but in the emergency department setting, CT can be performed rapidly and often shows acute intracranial hemorrhage more clearly than MRI. MRI is unnecessary in patients with the primary generalized epilepsies, such as typical absence and juvenile myoclonic epilepsy. Lesions (tumors, arteriovenous malformations, cysts, strokes, gliosis, focal atrophy) may be identified in 25% of patients, even when the clinical examination and EEG do not suggest focal features. Identification of some lesions, such as focal cortical dysplasia, hamartoma, and mesial temporal sclerosis, can assist in consideration of surgical treatment of pharmacoresistant epilepsy.

LONG-TERM THERAPY

The decision to institute daily seizure medications for a first unprovoked seizure is based on the likelihood of recurrence balanced against the risk of long-term drug therapy. Determination of the recurrence risk is based on the clinical history and neurodiagnostic testing (Table 181-6). If the recurrence risk is 75% or greater, it is usually suggested that daily medication be prescribed. Absence seizures, infantile spasms, atypical absence seizures, and atonic seizures are universally recurrent at the time of diagnosis, indicating the need for therapy.

![Table 181-5](#) Management of Status Epilepticus

<table>
<thead>
<tr>
<th>STABILIZATION</th>
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<tbody>
<tr>
<td>ABCs (airway, breathing, circulation)</td>
</tr>
<tr>
<td>Cardiac monitoring</td>
</tr>
<tr>
<td>Oxygen and pulse oximetry</td>
</tr>
<tr>
<td>Intravenous access</td>
</tr>
<tr>
<td>Immediate laboratory tests</td>
</tr>
<tr>
<td>Glucose</td>
</tr>
<tr>
<td>Basic metabolic panel—sodium, calcium, magnesium</td>
</tr>
<tr>
<td>Anticonvulsant drug levels</td>
</tr>
<tr>
<td>Toxicology studies as appropriate</td>
</tr>
<tr>
<td>Complete blood counts, platelets, and differential</td>
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</tbody>
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<table>
<thead>
<tr>
<th>PHARMACOLOGIC MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepine (max rate of administration = 1 mg/min)</td>
</tr>
<tr>
<td>Lorazepam 0.05–0.1 mg/kg (maximum 2–4mg per dose)</td>
</tr>
<tr>
<td>Diazepam 0.2–0.5 mg/kg</td>
</tr>
<tr>
<td>Midazolam 0.1–0.2 mg/kg</td>
</tr>
<tr>
<td>Standard anticonvulsant medications</td>
</tr>
<tr>
<td>Phenytoin 10–20 mg/kg (phenytoin equivalents)</td>
</tr>
<tr>
<td>Phenobarbital 10–20 mg/kg</td>
</tr>
<tr>
<td>Valproic acid 20 mg/kg</td>
</tr>
<tr>
<td>Continuous infusions</td>
</tr>
<tr>
<td>Pentobarbital</td>
</tr>
<tr>
<td>Midazolam</td>
</tr>
<tr>
<td>General anesthesia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 181-6</th>
<th>Recurrence Risk after a First Unprovoked Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEIZURE TYPE</strong></td>
<td><strong>EEG NORMAL, EXAM NORMAL</strong></td>
</tr>
<tr>
<td>Generalized</td>
<td>25%</td>
</tr>
<tr>
<td>Focal</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Most recurrences occur within 2 years*
The goal of treatment is to maintain an optimal functional state. Medication toxicity should be weighed against the risk of seizure itself. Initial drug selection is based on the mechanism of the seizure (Fig. 181-1). A single agent limits toxicity, contains cost, and improves compliance. Approximately 60% of children obtain satisfactory seizure control and minimal side effects with the initial drug. If seizure control is not achieved, despite good compliance, addition of a second drug is considered. When available, measuring anticonvulsant blood levels can be helpful in adjusting dosing and monitoring compliance. Levels should be interpreted in light of the patient’s clinical state; a patient with a “low” drug level who is seizure free does not necessarily need a higher dose. Anticonvulsant drug levels should be drawn at trough, usually before the morning doses. When hepatic or renal disease is present, drug binding is likely to be altered. In this instance, free and bound anticonvulsant levels can be helpful.

The duration of anticonvulsant treatment varies according to seizure type and epilepsy syndrome. For most children, anticonvulsant medications can be weaned off after 2 years without seizures. There are some exceptions. For example, children with juvenile myoclonic epilepsy, progressive myoclonic epilepsy, atypical absence seizures, and Lennox-Gastaut syndrome usually require treatment for life. Children who have other neurological comorbidities, seizures that were initially difficult to control, or persistently epileptiform EEGs are at highest risk for recurrence when therapy is discontinued.

Although cognitively normal children with epilepsy have the same rates of injury as normal healthy children, there are important safety considerations for people with epilepsy. The risk of drowning is high, so swimming and bathing must only occur under direct adult supervision. Children should use appropriate helmets for sports such as bicycling or ice skating. There is no contraindication to participation in contact sports, but scuba diving, hang gliding, and free climbing are not safe for people with epilepsy. Each country and individual states have specific laws regarding driving for people with epilepsy. Most require a period of seizure freedom before issuing a driving permit.

Weakness and Hypotonia

Weakness is a decreased ability to voluntarily and actively move muscles. This may be generalized or localized to one aspect of the body. Hypotonia is a state of low muscle resistance to movement. Hypotonia can be associated with weakness, but in some cases is present with normal motor strength. The differential diagnosis for weakness is extensive (Table 182-1).

**Etiology**
Weakness and hypotonia may be due to disorders of upper motor neurons or lower motor neurons. Upper motor neurons originate in the cerebral motor cortex; their axons form the corticospinal tract ending in the spinal cord and control voluntary motor activity. The anterior horn cells, their motor roots, peripheral motor nerves, neuromuscular junctions, and muscles represent the lower motor neurons and muscle units. Maintenance of normal strength, tone, and coordination requires integrated communication throughout this complex system, including the cerebral cortex, cerebellum, brainstem, thalamus, basal ganglia, and spinal cord.

**Clinical Manifestations**
Weakness caused by upper motor neuron disease differs from weakness produced by lower motor neuron disease (Table 182-2). Dysfunction of the upper motor neuron causes loss of voluntary
control, but not total loss of movement because motor nuclei of the basal ganglia, thalamus, and brainstem have tracts that produce simple or complex stereotyped patterns of movement. The corticospinal tract permits fine motor activity and is best tested by rapid alternating movements of the distal extremities. Mild dysfunction produces slowed, stiff motions. More severe dysfunction produces stiff, abnormal involuntary postures (spasticity) consisting of forearm flexion at the elbow and wrist and adduction close to the chest, with leg extension and adduction.

Damage to the spinal cord leaves residual simple, stereotyped reflex movements coordinated by local spinal reflexes below the level of the lesion. Destruction of the lower motor neuron, the final common pathway producing muscle activity, leads to total absence of movement with hypotonia. Function is best tested by measuring the strength of individual muscle groups or, in a young child, by observing the ability to perform tasks requiring particular muscle groups (e.g., walk up or down stairs, arise from the ground, walk on toes or heels, raise the hands above the head, squeeze a ball).

**DISEASE OF THE UPPER MOTOR NEURON**

**Etiology and Epidemiology**

Tumors, trauma, infections, demyelinating syndromes, infarction, metabolic diseases, and degenerative diseases may injure the corticospinal tract, producing an upper motor neuron pattern of weakness coupled with increased deep tendon reflexes, spasticity, and extensor plantar responses (Babinski sign).

**Clinical Manifestations**

The distribution of weakness depends on the location of the lesion. A tumor in the left parietal region may produce a right hemiparesis. A brainstem glioma may produce a slowly progressive quadriparesis. A diffuse disorder of myelin synthesis, such as a leukodystrophy, would produce a progressive symmetrical quadriparesis.

**DISEASES OF THE SPINAL CORD**

Acute spinal cord lesions, such as infarction or compression, may produce a flaccid, areflexic paraparesis that mimics lower motor neuron disease. A child who exhibits an acute or subacute flaccid paraparesis is most likely to have either an acute cord syndrome or Guillain-Barré syndrome. The hallmarks of spinal cord disease are a sensory level, a motor level, disturbance of bowel and bladder function, and local spinal pain or tenderness. The acute cord syndrome may be the result of transverse myelitis, cord tumor, infarction, demyelination, or trauma. Transverse myelitis, an acute postinfectious demyelinating disorder of the spinal cord, is treated with high-dose steroids. Trauma and tumors (neuroblastoma, lymphoma, sarcoma) compressing the spinal cord necessitate immediate neurosurgical management to preserve vital function.

**DISEASES OF THE LOWER MOTOR NEURON**

Neuromuscular disease affects any component of the lower motor neuron unit. The distribution of muscle weakness can point toward specific diseases (Table 182-3).

**Spinal Muscular Atrophy**

**Etiology**

Progressive degeneration of anterior horn cells is the key manifestation of spinal muscular atrophy (SMA), a genetic disease that may begin in intrauterine life or any time thereafter. About
25% of patients have a severe infantile form (SMA type 1/Werdnig-Hoffmann disease), 50% have a late infantile and more slowly progressive form (SMA type 2/Kugelberg-Welander syndrome), and 25% have a more chronic, juvenile form (SMA type 3). SMA is one of the most frequent autosomal recessive diseases, with a carrier frequency of 1 in 50.

Clinical Manifestations

The earlier in life the process starts, the more severe the progression. Infants with SMA type 1 present in early infancy with severe hypotonia, generalized weakness, and facial involvement. Infants have normal cognitive, social, and language skills and sensation. Fasciculations (quivering of the lateral aspect of the tongue) are best identified by inspecting the mouth when the child is asleep. Deep tendon reflexes are absent. With progression, breathing becomes rapid, shallow, and predominantly abdominal. In an extremely weak child, respiratory compromise leads to atelectasis, pulmonary infection, and death. Most infants with SMA type 1 die within the first 2 years. Children with SMA type 2 may survive to adulthood. Children with SMA type 3 can appear normal, with slower progression of weakness and a normal life expectancy.

Laboratory and Diagnostic Studies

The diagnosis is made by genetic testing. Creatine phosphokinase (CK) may be normal or mildly elevated. The electromyogram (EMG) shows fasciculations, fibrillations, and other signs of denervation. Muscle biopsy specimens show grouped atrophy.

Treatment

No specific treatment delays progression of SMA, although a number of promising agents are being studied. Symptomatic therapy is directed toward minimizing contractures, preventing scoliosis, maximizing nutrition, and avoiding infections. Respiratory infections are managed early and aggressively with pulmonary hygiene, oxygen, and antibiotics. The use or nonuse of artificial ventilation and tube feedings must be individualized for each patient in each stage of the illness.

Peripheral Neuropathy

There are many peripheral nerve diseases in childhood, but the most classic presentations are: Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), hereditary motor sensory neuropathy (HMSN), and tick paralysis. Peripheral neuropathies produced by diabetes mellitus, alcoholism, chronic renal failure, exposure to toxins, vasculitis, and the effects of neoplasm are common in adults but are rare in children.

Guillain-Barré Syndrome

Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy) is a postinfectious autoimmune peripheral neuropathy that can occur about 10 days after a respiratory or gastrointestinal infection (classically Mycoplasma pneumoniae or Campylobacter jejuni). It occurs in people of all ages and is the most common cause of acute flaccid paralysis in children.

The characteristic symptoms are areflexia, flaccidity, and symmetrical ascending weakness. Progression can occur rapidly, in hours, or more indolently over weeks. Typically symptoms start with numbness or paresthesia in the hands and feet, then a heavy, weak feeling in the legs. Weakness ascends to involve the arms, trunk, and bulbar muscles (tongue, pharynx, larynx). Deep tendon reflexes are absent even when strength is relatively preserved. Objective signs of sensory loss are usually minor compared with the dramatic weakness. Bulbar and respiratory insufficiency may progress rapidly. Dysfunction of autonomic nerves can lead to blood pressure changes, tachycardia and other arrhythmias, urinary retention or incontinence, or stool retention. This polynuropathy can be difficult to distinguish from an acute spinal cord syndrome. Preservation of bowel and bladder function, loss of arm reflexes, absence of a sensory level, and lack of spinal tenderness point toward Guillain-Barré syndrome. A cranial nerve variant of Guillain-Barré syndrome called the Miller Fisher variant manifests with ataxia, partial ophthalmoplegia, and areflexia.
The cerebrospinal fluid in Guillain-Barré syndrome is sometimes normal early in the illness but classically shows elevated protein levels without significant pleocytosis. Magnetic resonance imaging (MRI) with gadolinium may reveal enhancement of the spinal nerve roots. Electrophysiology studies (EMG, nerve conduction velocity [NCV]) are not always required but can provide corroborative diagnostic evidence and prognostic indicators.

Children in early stages of the disease should be admitted to the hospital. Those with moderate, severe, or rapidly progressive weakness should be cared for in an intensive care unit. Pulmonary and cardiac functions are monitored continuously. Endotracheal intubation should be performed in patients with impending respiratory failure or an inability to clear secretions. Most patients are treated initially with intravenous immunoglobulin (IVIG). Plasma exchange and immunosuppressive drugs are alternatives when IVIG treatment is unsuccessful or in rapidly progressive disease. Physical, occupational, and speech therapies are mainstays of treatment.

The illness usually resolves spontaneously, albeit slowly; 80% of patients recover normal function within 1 to 12 months. Twenty percent of patients are left with mild to moderate residual weakness. Some children will suffer acute relapse or chronic symptoms.

Chronic Inflammatory Demyelinating Polyneuropathy

CIDP is an immune-mediated peripheral neuropathy and can affect patients of all ages. Patients present with both proximal and distal weakness (usually in an episodic, relapsing-remitting pattern) affecting the extremities. Patients may also experience sensation changes such as numbness, tingling, or pain. The diagnosis is clinical, although EMG or nerve biopsy may confirm the diagnosis. The mainstays of treatment for CIDP are IVIG, glucocorticoids, and plasmapheresis. Prognosis varies, with some patients undergoing complete remission, whereas others experience partial remission or severe disability.

Hereditary Motor Sensory Neuropathy

HMSN (also called Charcot-Marie-Tooth Disease [CMT]) is a group of progressive peripheral nerve diseases. Motor components generally dominate the clinical picture, with sensation and autonomic functions affected later. The most common HMSN is CMT type 1A. Other forms may have milder symptoms. Some subtypes present with severe symptoms starting in infancy.

The peroneal and tibial nerves are the earliest and most severely affected. Most often, complaints begin in the preschool to early adolescent years, with weakness of the ankles and frequent tripping. Examination shows pes cavus deformity of the feet (high-arched feet), bilateral weakness of foot dorsiflexors, and normal sensation despite occasional complaints of paresthesia. Peripheral nerves can become markedly enlarged and may be palpable on exam. Progression of HMSN is slow, extending over years and decades. Eventually, patients develop weakness and atrophy of the entire lower legs and hands and mild to moderate sensory loss in the hands and feet. Some patients never have more than a mild foot deformity, loss of ankle reflexes, and electrophysiologic abnormalities. Others in the same family may be confined to a wheelchair and have difficulties performing everyday tasks with their hands.

HMSN can be either demyelinating (CMT1, with severely decreased NCV and hypertrophic changes on sural nerve biopsy) or axonal (CMT2, with normal NCV but decreased action potential amplitudes and axonal degeneration on biopsy). Specific genetic testing is available for many subtypes of HMSN. Specific treatment for HMSN is not available, but braces that maintain the feet in dorsiflexion can improve function.

Tick Paralysis

Tick paralysis produces an acute lower motor neuron pattern of weakness, clinically similar to Guillain-Barré syndrome. An attached female tick releases a toxin, similar to botulism, blocking neuromuscular transmission. Affected patients present with a severe generalized flaccid weakness, including ocular, papillary, and bulbar paralysis. A methodical search for an affixed tick, particularly in hairy areas, must be made in any child with acute weakness. Removal of the tick results in a prompt return of motor function.

Myasthenia Gravis

Myasthenia gravis is an autoimmune condition. Most commonly, antibodies block the acetylcholine receptors (AChR) at the neuromuscular junction, decreasing the number of effective receptors, which results in rapid fatigability of striated muscle, though other types of auto-antibodies exist. The three childhood varieties are juvenile myasthenia gravis in late infancy and childhood, transient neonatal myasthenia, and congenital myasthenia.

Juvenile Myasthenia

Variable ptosis, diplopia, ophthalmoplegia, and facial weakness are the presenting symptoms. Dysphagia, poor head control, and extremity weakness may occur. Rapid fatigue of muscles distinguishes myasthenia from other neuromuscular disorders, with progressive worsening over the day or with repetitive activity. In some children, the disease never advances beyond ophthalmoplegia and ptosis (ocular myasthenia). Others have a progressive and potentially life-threatening illness that involves all musculature, including that of respiration and swallowing. Treatment includes pyridostigmine, an inhibitor of acetylcholinesterase, and, depending on severity, various forms of immunosuppression.
Transient Neonatal Myasthenia Gravis

A transient myasthenic syndrome develops in 10% to 20% of neonates born to mothers with myasthenia gravis, presenting in the first hours to days after birth. Almost all infants born to mothers with myasthenia have maternal anti-AChR antibodies. Signs include ptosis, ophthalmoparesis, facial diplegia, and respiratory distress. Neonates with transient myasthenia gravis require cholinesterase inhibitors and supportive care for a few days to weeks until the weakness remits.

Congenital Myasthenia Gravis

A variety of rare disorders of the neuromuscular junction have been reported that are not autoimmune mediated. The congenital myasthenic syndromes (CMS) are due to gene mutations in the components of the neuromuscular junction. They typically present in infancy with hypotonia, ophthalmoparesis, facial diplegia, and extremity weakness, although they can present throughout childhood. Respiratory function and feeding may be compromised. Children with CMS usually have lifelong disability. Some children will respond to pyridostigmine or other drugs that improve neuromuscular junction function.

Diagnostic Studies

Autoimmune myasthenia is most commonly diagnosed through the combination of clinical symptoms and antibody testing. The majority of individuals have antibodies to the AChR, although some have antibodies to other components of the neuromuscular junction. Neurophysiology may exhibit the classic feature of electrodecrement with 3-Hz repetitive stimulation during nerve conduction studies. Administration of a cholinesterase inhibitor (edrophonium chloride) can result in transient improvement in strength, particularly of ptosis, and thus can additionally be used for diagnostic verification.

Infant Botulism

Infant botulism results from intestinal infection by *Clostridium botulinum*, which produces a neurotoxin that blocks presynaptic cholinergic transmission. Young age and the absence of competitive bowel flora predispose infants to this disease. Infants may ingest dust, soil, or food (honey or poorly canned foods) contaminated with spores. The progressive neuromuscular blockade ranges from mild to severe. Infants often present with constipation and poor feeding. Hypotonia and weakness develop, along with cranial nerve dysfunction manifested by decreased gag reflex, diminished eye movements, decreased pupillary contraction, and ptosis. Heart rate and blood pressure may fluctuate. Affected infants may develop respiratory failure. The diagnosis is made by the presence of *C. botulinum* spores and toxin in stool samples. Therapy with botulism IVIG should be administered as soon as the diagnosis is suspected.

With prompt treatment and respiratory and supportive care, the prognosis is good.

Duchenne Muscular Dystrophy

Muscular dystrophies are a group of genetic muscle diseases characterized by progressive myofiber degeneration and the gradual replacement of muscle by fibrotic tissue. Duchenne muscular dystrophy is the most common muscular dystrophy and one of the most common genetic disorders of childhood.

Etiology

Duchenne *muscular dystrophy* is an X-linked disorder (Xp21) affecting approximately 1 in 3500 boys and resulting from a gene mutation of dystrophin. Becker *muscular dystrophy* is an allelic disorder associated with more mild symptoms; its mutations at least partially preserve the function of the resulting gene product.

Clinical Manifestations

Infant boys are only rarely symptomatic in early infancy. At about 2 to 3 years of age, boys develop an awkward gait and an inability to run properly. Some have an antecedent history of mild slowness in attaining motor milestones or poor head control during infancy. Examination shows firm calf hypertrophy and mild to moderate proximal leg weakness with a hyperlordotic, waddling gait. The child typically arises from a lying position on the floor by using his arms to *climb up* his legs and body (*Gower sign*). Arm weakness is evident by age 6 years, and most boys are wheelchair dependent by age 12 years. Other manifestations include cardiomyopathy, scoliosis, respiratory decline, and, in some boys, cognitive and behavioral dysfunction. Many boys with Duchenne live into adulthood. Most die in their 20s or early 30s, usually as a result of progressive respiratory decline or cardiac dysfunction.

Laboratory and Diagnostic Studies

Serum CK levels are always markedly elevated. Diagnosis is established by genetic testing for the dystrophin gene mutation. Prenatal diagnosis is possible. Approximately one third of cases represent new mutations. Occasionally, the diagnosis is not made until a muscle biopsy shows muscle fiber degeneration and regeneration accompanied by increased intrafascicular connective tissue.

Treatment

Steroid therapy is now instituted to slow the pace of the disease and delay motor disability. Supportive care includes physical therapy, bracing, proper wheelchairs, and treatment of cardiac dysfunction or pulmonary infections. A multidisciplinary approach is recommended. Through improvements in
management, patients are now living significantly longer than in the pre-steroid era.

**Myotonic Dystrophy**  
**Etiology and Epidemiology**
Myotonic dystrophy (DM) is the second most common muscular dystrophy and the most common form to present in adulthood. An autosomal dominant genetic disease, DM is caused by progressive expansion of a triplet repeat, CTG, in the myotonic dystrophy protein kinase gene. Presentation is roughly correlated with the number of CTG repeats, and the disease is characterized by genetic anticipation, where each generation presents with earlier and more severe symptoms.

**Clinical Manifestations**
Although DM most typically presents in adulthood, it can present at any age. Clinical features of childhood-onset “classic” DM include slowly progressive facial and distal extremity weakness as well as myotonia. Myotonia is a disorder of muscle relaxation after contraction. Patients grasp onto an object and have difficulty releasing their grasp, peeling their fingers away slowly. The facial appearance is characteristic, with hollowing of muscles around temples, jaw, and neck; ptosis; facial weakness; and drooping of the lower lip. The voice is nasal and mildly dysarthric. Not only is the striated muscle affected, but smooth muscle of the alimentary tract, uterus, and cardiac tissue are involved. Patients have variable arrhythmias, endocrinopathies, immunologic deficiencies, cataracts, and intellectual impairment.

A severe congenital form of DM can appear in infants of mothers with myotonic dystrophy because of rapid expansion of the CTG repeat length. Infants are immobile and hypotonic, with ptosis, absence of sucking and Moro reflexes, poor feeding, and respiratory difficulties. Often, weakness and atony of uterine smooth muscle during labor lead to associated hypoxic ischemic encephalopathy and its sequelae, which make the clinical diagnosis more difficult. The presence of congenital contractures, clubfoot, or a history of poor fetal movements indicates intranatal neuromuscular disease. Those requiring prolonged ventilation have an infant mortality of 25%. Individuals with congenital DM often make significant gains in terms of motor skills, and nearly all children eventually ambulate independently. However, approximately 50% of DM patients have mental retardation. In addition, children with congenital DM experience a second progressive phase of the disease in the teen years, including potentially fatal cardiac arrhythmias.

**Diagnosis**
Diagnosis is established by genetic testing.

**Other Forms of Childhood Muscle Disease**
**Congenital muscular dystrophies (CMDs)** refer to a group of genetically determined conditions that present in infancy or early childhood. The most common subtypes include merosin-deficient congenital muscular dystrophy, Ullrich congenital muscular dystrophy, and the dystroglycanopathies. The characteristic clinical features include hypotonia, extremity weakness, delayed motor development, and congenital contractures. Diagnosis is established through the combination of elevated serum CK and dystrophic changes detected on muscle biopsy. In most individuals, the disease course is slow or nonprogressive, although many children with CMD are wheelchair dependent and require some type of respiratory support. Contractures and scoliosis are often progressive and severely worsen; respiratory status diminishes with age.

**Emery-Dreifuss muscular dystrophy** (EDMD), also known as humeroperoneal muscular dystrophy, can be inherited as an X-linked recessive, autosomal dominant, or autosomal recessive disorder. Symptoms typically begin in childhood, although adult onset has been noted. Patients may experience early contractures, slowly progressive humeroperoneal muscle weakness or wasting, and cardiac disease with conduction defects and arrhythmias. EDMD is associated with mild elevations of serum CK levels, abnormal electrocardiograms (ECG), characteristic changes on muscle imaging, and abnormal but nonspecific muscle biopsies. There are no disease-specific modifying therapies for EDMD, although early placement of defibrillators in patients with abnormal ECGs reduces the incidence of sudden death.

Several forms of **limb-girdle muscular dystrophy** (LGMD) have been described, which are usually inherited in an autosomal recessive pattern. Depending on the subtype of LGMD, presentation can be throughout childhood. A subset of children will have a Duchenne-like presentation. LGMD primarily affects muscles of the hip and shoulder girdles. Distal muscles may later become weak and atrophic. Many children with LGMD will lose the ability to ambulate. Some may also have progressive cardiac and respiratory failure.

**Facioscapulohumeral dystrophy** is an autosomal dominant myopathy. Weakness first appears in the facial and shoulder girdle muscles. Shoulder weakness results in the characteristic observation of scapular winging, which can often be asymmetric. Patients have mild ptosis, a decrease in facial expression, inability to pucker the lips or close eyes during sleep, neck weakness, difficulty in fully elevating the arms, and thinness of upper arm musculature. Progression is slow, although children often have a more severe presentation and can have significant disability related to upper extremity weakness and dysfunction.

**Congenital myopathies** (CM) are a relatively common group (prevalence approximately 1:20,000) of nondystrophic muscle disorders that, like congenital muscular dystrophies, most typically present in infancy with hypotonia and weakness. Additional signs and symptoms include congenital contractures, hip subluxation/dislocation, small/atrophic muscles, thin body habitus, and characteristic facial appearance (the “myopathic facies”). Symptoms are often nonprogressive or only slowly progressive, although children often have severe lifelong disabilities including wheelchair dependence, severe scoliosis, and respiratory failure. Clinical finding may distinguish CMDs and other dystrophies (e.g., involvement of the facial musculature in congenital myopathies). Diagnosis is ultimately established based on laboratory studies, biopsy findings, and genetic test results. Histopathologic subtypes are distinguished by characteristic features on muscle biopsy, the most common being nemaline myopathy, centronuclear myopathy, and core myopathy. More than 15 different genetic causes have been established for CMs. However, nearly 50% of cases are genetically unresolved. Although no specific therapies currently exist for any CM subtype, several promising therapies have shown efficacy in preclinical models of disease.
**Metabolic Myopathies**
Glycogen storage disease type II (Pompe disease) and muscle carnitine deficiency are discussed in Chapters 52 and 55. Several mitochondrial myopathies may present with hypotonia, ophthalmoplegia, and progressive weakness, but the phenotype of these disorders is broad (Chapter 57). Endocrine myopathies, including hyperthyroidism, hypothyroidism, hyperparathyroidism, and Cushing syndrome, are associated with proximal muscle weakness. Periodic paralysis due to familial forms of hypokalemia or hyperkalemia produces episodic weakness.

**Laboratory and Diagnostic Studies**
The diagnostic evaluation should be guided by the clinical history and physical examination (Chapter 179).

**Malignant Hyperthermia**
Malignant hyperthermia is a life-threatening syndrome manifested by a rapid increase of body temperature, muscle rigidity, metabolic and respiratory acidosis, hypotension, arrhythmias, and convulsions. Acute episodes are precipitated by exposure to anesthetic agents in patients with a genetic predisposition. Patients with Duchenne muscular dystrophy, central core myopathy, and other myopathies are susceptible, although malignant hyperpyrexia can also occur in children without muscle disease as an autosomal dominant genetic disorder. A family history of unexplained death during anesthesia is often noted. Serum CK levels rise and myoglobinuria can result in tubular necrosis and acute renal failure. Diagnosis of idiopathic malignant hyperthermia is possible with genetic testing or an in vitro muscle contraction test that reveals excessive tonic contracture on exposure to halothane and caffeine. Treatment consists of IV dantrolene, sodium bicarbonate, and cooling.

**Neonatal and Infantile Hypotonia**
The clinical distinction between upper and lower motor neuron disorders in infants is blurred because incomplete myelination of the developing nervous system limits expression of many of the cardinal signs, such as spasticity. The two critical clinical points are whether the child is weak and the presence or absence of deep tendon reflexes. Hypotonia and weakness coupled with depressed or absent deep tendon reflexes suggest a neuromuscular disorder. A stronger child with brisk reflexes suggests an upper motor neuron source for the hypotonia. Causes of neonatal weakness are outlined earlier. A diagnostic algorithm for infants with hypotonia or weakness is presented in Figure 182-1.

**Hypotonia without Significant Weakness (Central Hypotonia)**

![Decision-Making Algorithm](Available @ StudentConsult.com)

Hypotonia and Weakness

Some infants who appear to move well when supine in their cribs are *floppy* when handled or moved. When lifted, their heads flop, they *slip through* at the shoulders, do not support weight on their legs, and form an *inverted* U in prone suspension (Landau posture). When placed prone as neonates, they may lie flat instead of keeping their arms and legs flexed. Passive tone is decreased, but reflexes are normal. Hypotonia may be associated with significant cerebral disease or may be a benign phenomenon that is outgrown (Table 182-4). The most common cause of hypotonia is hypoxic-ischemic encephalopathy.

**Prader-Willi syndrome** (PWS) presents with severe neonatal hypotonia; severe feeding problems leading to failure to thrive; small hands and feet; and, in boys, a small penis, small testicles, and cryptorchidism. Severe hyperphagia and obesity develop in early childhood. Approximately 60% to 70% of affected individuals have an interstitial deletion of paternal chromosome 15q11q13. PWS and trisomy 21 are the most common genetic causes of neonatal hypotonia.

Infants who have a connective tissue disorder, such as Ehlers-Danlos syndrome, Marfan syndrome, or familial laxity of the ligaments, may exhibit marked passive hypotonia, *ligamentous laxity*, and increased skin elasticity. They have normal strength and cognition and achieve motor and mental milestones normally. They may have peculiar postures of their feet or unusual gaits.

Infants with benign congenital hypotonia typically exhibit the condition at 6 to 12 months old with delayed gross motor skills. They are unable to sit, creep, or crawl, but have good verbal, social, and manipulative skills. Strength appears normal, and the infants can kick arms and legs briskly and bring their toes to their mouths. The children often display head lag, slip-through in ventral suspension, and floppiness of passive tone. The infant seems floppy from birth. The differential diagnosis includes upper and motor neuron disorders and connective tissue diseases. Extensive laboratory investigation is often unrevealing. Most of these children catch up to peers and
Table 182-4  Approach to Differential Diagnosis in the Floppy Infant

<table>
<thead>
<tr>
<th>HYPOTONIA WITH WEAKNESS</th>
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<tr>
<td><strong>Awareness Intact</strong></td>
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<tr>
<td>Neuromuscular disease</td>
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<tr>
<td>Spinal muscular atrophy*</td>
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<tr>
<td>Myasthenic syndromes</td>
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<tr>
<td>Congenital neuropathy or myopathy</td>
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<tr>
<td>Spinal cord disease (cervical cord trauma or compression)</td>
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<tr>
<td>Tumor</td>
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<tr>
<td>Spinal cord infarct</td>
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<td>Malformation</td>
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<td>Spina bifida</td>
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<tr>
<td>Syringomyelia</td>
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<tr>
<td><strong>Consciousness Depressed</strong></td>
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<tr>
<td>Severe brain illness*</td>
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<tr>
<td>Structural (hydrocephalus)</td>
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<tr>
<td>Infectious</td>
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<tr>
<td>Metabolic (e.g., anoxia or hypoglycemia)</td>
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<tr>
<td>Intoxication through mother</td>
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<tr>
<td>Magnesium sulfate</td>
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<td>Barbiturates</td>
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<td>Narcotics</td>
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<td>Benzodiazepines</td>
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<td>General anesthesia</td>
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<tr>
<td>Metabolic abnormality</td>
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<tr>
<td>Hypoglycemia</td>
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<tr>
<td>Kernicterus</td>
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**HYPOTONIA WITHOUT WEAKNESS**

| Acute systemic illness* |   |
| Specific syndromes     |   |
| Down syndrome*         |   |
| Cerebrohepatorenal (Zellweger peroxisomal disorder) |   |
| Oculocerebrorenal (Lowe syndrome) |   |
| Kinky hair disease (Menkes syndrome—copper metabolism disorder) |   |
| Neonatal adrenal leukodystrophy |   |
| Prader-Willi syndrome  |   |
| Connective tissue disorder |   |
| Ehlers-Danlos syndrome |   |
| Marfan syndrome        |   |
| Congenital laxity of ligaments |   |
| Nutritional-metabolic disease |   |
| Rickets                |   |
| Renal tubular acidosis |   |
| Celiac disease         |   |
| Biliary atresia        |   |
| Congenital heart disease |   |
| Benign congenital hypotonia* |   |

*Common.

Table 182-5  Causes of Stroke in Childhood

<table>
<thead>
<tr>
<th><strong>ARTERIAL ISCHEMIC STROKE</strong></th>
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<tr>
<td>Arteriopathic</td>
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<tr>
<td>Idiopathic arterial stenosis</td>
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<tr>
<td>Vasculitis (autoimmune or infectious)</td>
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<tr>
<td>Arterial dissection (traumatic or spontaneous)</td>
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<td>Moyamoya disease</td>
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<tr>
<td><strong>Cardiac</strong></td>
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<tr>
<td>Cyanotic congenital heart disease</td>
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<td>Valvular disease</td>
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<td>Patent foramen ovale</td>
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<tr>
<td>Arrhythmias</td>
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<tr>
<td>Cardiomyopathy</td>
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<tr>
<td>Infective endocarditis</td>
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<tr>
<td><strong>Hematologic</strong></td>
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<tr>
<td>Sickle cell anemia</td>
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<tr>
<td>Iron deficiency anemia</td>
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<tr>
<td>Hypercoagulable state</td>
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<tr>
<td>Hereditary prothrombotic states (factor V Leiden)</td>
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<tr>
<td>Acquired prothrombotic states (antiphospholipid antibodies)</td>
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<tr>
<td>Prothrombotic medications (oral contraception)</td>
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<tr>
<td><strong>CEREBRAL SINOVENOUS THROMBOSIS</strong></td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Hypercoagulable state (see above)</td>
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<tr>
<td>Iron deficiency anemia</td>
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<tr>
<td>Severe dehydration</td>
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<td>Infections</td>
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<td>Meningitis</td>
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<td>Otitis media</td>
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<td>Mastoiditis</td>
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<td>Systemic disease</td>
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<td>Leukemia</td>
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<td>Inflammatory bowel disease</td>
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<td>Nephrotic syndrome</td>
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<tr>
<td>Trauma</td>
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<td><strong>HEMA RRHAGIC STROKE</strong></td>
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<tr>
<td>Head trauma (accidental or abusive)</td>
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<tr>
<td>Vascular malformations</td>
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<tr>
<td>Arteriovenous malformations</td>
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<td>Cerebral aneurysms</td>
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<td>Brain tumor</td>
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<td>Vasculitis</td>
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<td>Moyamoya disease</td>
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The incidence of pediatric stroke is 2.5 to 10 per 100,000 children and is higher among neonates, approaching that of elderly patients. A wide spectrum of conditions can produce stroke in childhood (Table 182-5). Pediatric strokes may be due to ischemia (arterial ischemic stroke, cerebral sinovenous thrombosis) or hemorrhage. **Arterial ischemic stroke** (AIS) is focal brain infarction that results from occlusion of the arteries in the brain. The most common causes are vasculitis resulting in abnormal cerebral arteries (either autoimmune or infectious, such as vasculitis associated with meningitis) and cardioembolic infarcts due to congenital heart disease, sickle cell anemia, or coagulation disorders. Coagulation disorders also increase the risk of cerebral sinovenous thrombosis (CSVT), the occlusion of venous structures in the brain, which can result in ischemia as the cerebral venous pressure rises.
CSVT can also be caused by infections or dehydration. **Hemorrhagic strokes (HS)** may be intraparenchymal (primary, or secondary bleeding after AIS) or associated with intraventricular, subarachnoid, subdural, or epidural bleeds. The most common causes of HS are vascular malformations, head trauma, and vasculitis.

**Clinical Manifestations**

The acute onset of focal neurologic deficits in a child is stroke until proven otherwise. Symptoms may be subtle and nonspecific, which can lead to a delay in diagnosis. AIS typically presents with acute, focal neurologic deficits. Hemiparesis is most common, but visual, speech, sensory, or balance deficits may be present. Unlike AIS in adults, focal seizures are quite common in childhood presentation of AIS. Similarly, neonatal AIS most often presents with acute symptomatic focal seizures (typically in the first day of life) or with encephalopathy.

Symptoms of CSVT may progress more gradually and be more variable and nonspecific than AIS. In CSVT, acute focal deficits may be present, or the child may have progressive signs of elevated intracranial pressure, including headache, papilledema, diplopia (most often from cranial nerve VI palsy), seizures, lethargy, or confusion.

HS tends to present acutely, with a sudden “thunderclap” headache. HS may also present with loss of consciousness, nuchal rigidity, focal deficits, or seizures and can be rapidly fatal.

Congenital hemiplegia becomes apparent as infants develop, with decreased use of one side of the body, early handedness, or ignoring one side. Neuroimaging reveals an area of encephalomalacia in the contralateral cerebral hemisphere. The details of the child’s intratumerine, labor, delivery, and postnatal history often are unremarkable. The area of encephalomalacia may predispose the child to epilepsy.

**Differential Diagnosis**

There are many conditions that mimic pediatric stroke, most of which are more common than AIS, HS, or CSVT. Some of these mimics are benign (migraine, psychogenic weakness, musculoskeletal abnormalities), but others require specific, prompt diagnosis and/or treatment (e.g., transient postictal weakness, intracranial infection, inflammatory disease of the central nervous system, tumor, or posterior reversible leukoencephalopathy).

**Diagnostic Tests and Imaging**

On initial presentation, acute neuroimaging is necessary. A noncontrast head computed tomography (CT) scan is highly sensitive to acute HS and can reveal larger, mature AIS; acute, nonhemorrhagic stroke may not be seen on routine CT. Therefore, MRI with diffusion-weighted imaging is required for most presentations. Angiography by magnetic resonance angiography (MRA) or CT angiography is used to confirm arterial occlusion in AIS and can identify underlying arteriopathy, vascular malformations, and aneurysms. Diagnosis of CSVT requires a high clinical suspicion and purposeful imaging of the cerebral venous system with venography by MRI or CT. If clinical assessment does not reveal the cause of the stroke, a complete laboratory investigation should be undertaken promptly based on suspected etiologies (see Table 182-5). Many children with AIS have more than one predisposing factor, so identifying one risk factor does not obviate the need for a complete evaluation.

**Treatment**

Treatment must focus on limiting secondary neuronal injury and prevention of future strokes. Neuroprotection by maintaining control of temperature, blood pressure, glucose, and seizures is essential. Emergency thrombolysis with medications or catheterization is not yet established for children, but this is an area of active clinical research. Anticoagulants (IV heparin, subcutaneous low-molecular-weight heparin, oral warfarin) and platelet antiaggregants (aspirin) are used for secondary stroke prevention in some instances. For those with progressive CSVT, anticoagulation is the mainstay of therapy. Long-term rehabilitation programs are required for most survivors.

**ATAXIA AND MOVEMENT DISORDERS**

**ATAXIA**

Ataxia is the inability to make accurate, smooth and coordinated movements, usually due to a dysfunction of the cerebellar pathways. If either the afferent (joint position senses) or efferent cerebellar connections (cerebellum through thalamus to cerebral cortex) are disturbed, the patient has ataxia. **Truncal ataxia** reflects disturbances of the midline cerebellar vermis (e.g., medulloblastoma, acute postinfectious cerebellar ataxia, or ethanol intoxication). **Appendicular ataxia** reflects disturbances of the ipsilateral cerebellar hemisphere (e.g., cystic cerebellar astrocytoma). The most common causes of acute ataxia in childhood are postinfectious acute cerebellar ataxia and drug intoxications. Discrete lesions within the posterior fossa, tumors (e.g., medulloblastoma, ependymoma, cerebellar astrocytoma), multiple sclerosis, strokes, and hemorrhages may cause ataxia. Other causes include benign paroxysmal vertigo, head trauma, seizures, postictal states, migraine, paraneoplastic opsoclonus-myoclonus syndrome associated with neuroblastoma, and inborn errors of metabolism. Congenital disorders also may produce chronic, nonprogressive ataxia. There are a number of inherited ataxia syndromes (Table 183-1).

**Clinical Manifestations**
Table 183-1 Causes of Ataxia

<table>
<thead>
<tr>
<th>Causes of Ataxia</th>
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</thead>
<tbody>
<tr>
<td>Brain tumors</td>
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<tr>
<td>Medulloblastoma*</td>
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<tr>
<td>Ependymoma</td>
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<tr>
<td>Cerebellar astrocytoma*</td>
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<tr>
<td>Brainstem glioma</td>
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<td>Paraneoplastic disease</td>
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<tr>
<td>Neuroblastoma (opsoclonus-myoclonus-ataxia)</td>
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<tr>
<td>Infectious disorders</td>
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<tr>
<td>Encephalitis*</td>
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<tr>
<td>Brainstem encephalitis</td>
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<td>Meningitis</td>
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<tr>
<td>Labrynthitis*</td>
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<tr>
<td>Cerebellar abscess</td>
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<tr>
<td>Postinfectious disorders</td>
<td></td>
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<tr>
<td>Acute cerebellar ataxia (acute postinfectious cerebellitis)*</td>
<td></td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
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<tr>
<td>Migrainous disorders</td>
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<tr>
<td>Basilar migraine*</td>
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<tr>
<td>Benign paroxysmal vertigo</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Cerebellar hemorrhage</td>
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<tr>
<td>Cerebellar contusion</td>
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<tr>
<td>Concussion</td>
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<tr>
<td>Postconcussive syndrome*</td>
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<tr>
<td>Vertebrobasilar occlusion</td>
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<tr>
<td>Toxic ingestions*</td>
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<tr>
<td>Ethanol</td>
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<td>Anticonvulsants</td>
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<td>Antihistamines</td>
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<td>Benzodiazepines</td>
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<td>Carbon monoxide</td>
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<td>Inhalants</td>
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<tr>
<td>Drugs of abuse</td>
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<tr>
<td>Vascular disorders</td>
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<tr>
<td>Cerebellar hemorrhage or infarction</td>
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<tr>
<td>Vertebral artery dissection</td>
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<tr>
<td>Demyelinating disorders</td>
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<td>Multiple sclerosis</td>
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<tr>
<td>Acute disseminated encephalomyelitis</td>
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<tr>
<td>Structural or congenital disorders</td>
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<tr>
<td>Cerebellar hypoplasia</td>
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<td>Vermal aplasia</td>
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<tr>
<td>Dandy-Walker malformation</td>
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<td>Arnold-Chiari malformation</td>
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<td>Hydrocephalus</td>
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<tr>
<td>Hereditary ataxic disorders</td>
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<tr>
<td>Episodic ataxia</td>
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<tr>
<td>Friedreich ataxia</td>
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<tr>
<td>Ramsay Hunt syndrome</td>
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<tr>
<td>Spinocerebellar ataxia 1 and 2</td>
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<tr>
<td>Ataxia-telangiectasia</td>
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<tr>
<td>Marinesco-Sjögren syndrome</td>
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<tr>
<td>Genetic and metabolic disorders</td>
<td></td>
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<tr>
<td>Metachromatic leukodystrophy</td>
<td></td>
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<tr>
<td>Adrenoleukodystrophy</td>
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<tr>
<td>Maple syrup urine disease</td>
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<tr>
<td>Hartnup disease</td>
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<tr>
<td>GM2 gangliosidosis (juvenile)</td>
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<td>Refsum disease</td>
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<td>Vitamin E deficiency</td>
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<tr>
<td>Leigh disease</td>
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<tr>
<td>Wilson disease</td>
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<tr>
<td>Abetalipoproteinemia</td>
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</tbody>
</table>

*Common.

The usual symptoms of ataxia are a broad-based, unsteady gait (truncal ataxia) and intention tremor or dysmetria (over-or undershooting of the target due to abnormal distance perception). An intention tremor worsens as the arm/hand approaches the target. Classically, these symptoms stem from disorders of the cerebellar pathways, but peripheral nerve lesions causing loss of proprioceptive inputs to the cerebellum (Guillain-Barré syndrome) may present with similar symptoms. In addition, weakness may intensify or mimic ataxia, so strength must be assessed, along with coordination.

**Drug intoxication** is the most common cause of acute ataxia among children. Overdosage with any sedative-hypnotic agent can produce acute ataxia and lethargy, but ataxia without lethargy usually results from intoxication with ethanol or anticonvulsant drugs. It is important to ask about any medications or drugs of abuse the patient may have access to. Treatment is supportive.

**Postinfectious acute cerebellar ataxia** may occur 1 to 3 weeks following varicella, infectious mononucleosis, mild respiratory or gastrointestinal viral illnesses, or other infections. The pathogenesis is uncertain and may represent either a direct viral infection of the cerebellum or, more likely, an autoimmune response precipitated by the viral infection and directed at the cerebellar white matter. Symptoms begin abruptly, causing truncal ataxia, staggering, and frequent falling. Dysmetria of the arms, dysarthria, nystagmus, vomiting, irritability, and lethargy may be present. Symptoms, which may be severe enough to prevent standing or sitting, usually peak within 2 days, then stabilize and resolve over...
several weeks. Cerebrospinal fluid (CSF) examination sometimes shows a mild lymphocytic pleocytosis or mild elevation of protein content. Brain magnetic resonance imaging may reveal cerebellar enhancement. No specific therapy is available except to prevent injury during the ataxic phase.

Brain tumors are the second most common neoplasm in children. About 50% arise from within the posterior fossa. Tumors that arise in the posterior fossa or brainstem produce progressive ataxia with headache that may be acute or gradual in onset. There is a progressive worsening over days, weeks, or months, typically with associated signs and symptoms of elevated intracranial pressure. The ataxia and dysmetria may result from primary cerebellar invasion or from obstruction of the CSF pathways (aqueduct of Sylvius or fourth ventricle) with resultant hydrocephalus. The most common tumors in this region include medulloblastoma, ependymoma, cerebellar astrocytoma, and brainstem glioma.

Rarely, a neuroblastoma located in the adrenal medulla or anywhere along the paraspinal sympathetic chain in the thorax or abdomen is associated with degeneration of Purkinje cells and the development of severe ataxia, dysmetria, irritability, myoclonus, and opsoclonus. An immunologic reaction directed toward the tumor may be misdirected to attack Purkinje cells and other neuronal elements. The myoclonic movements are irregular, lightning-like movements of a limb or the head. Opsoclonus is a rapid, multidirectional, conjugate movement of the eyes, which suddenly dart in random directions. The presence of opsoclonus-myoclonus in a child should prompt a vigorous search for an occult neuroblastoma.

Several rare inborn errors of metabolism can present with intermittent episodes of ataxia and somnolence. These include Hartnup disorder, maple syrup urine disease, mitochondrial disorders, abetalipoproteinemia, and vitamin E deficiency.

Difficulty walking with a severe staggering gait is one manifestation of acute labyrinthitis, but the diagnosis usually is clarified by the associated symptoms of a severe sense of spinning dizziness (vertigo), nausea and vomiting, and associated signs of pallor, sweating, and nystagmus.

Ataxia-telangiectasia, an autosomal recessive genetic disorder, is the most common of the degenerative ataxias. Affected patients present with ataxia around age 2 years, progressing to loss of ambulation by adolescence. In mid-childhood, telangiectasia is evident over the sclerae, nose, ears, and extremities. Abnormalities in immune function and greatly increased risk of lymphoreticular tumors result in early death.

Friedreich ataxia is a relentlessly progressive, autosomal recessive disorder. Children present in the late elementary years with ataxia, dysmetria, dysarthria, diminished proprioception and vibration, absent deep tendon reflexes, and nystagmus, and many develop hypertrophic cardiomyopathy and skeletal abnormalities (high-arched feet, hammer toes, kyphoscoliosis).

### MOVEMENT DISORDERS

**Decision-Making Algorithm**

Involuntary Movements

Movement disorders or dyskinesias are a diverse group of entities associated with abnormal excessive, exaggerated, chaotic, or explosive movements of voluntary muscles. They are generally the result of abnormalities of the extrapyramidal system or the basal ganglia. Movement disorders in children are typically hyperkinetic (increased movement) patterns. The abnormal movements are activated by stress and fatigue and often disappear in sleep. They are typically diffuse and migratory (chorea) but may be isolated to specific muscle groups (segmental myoclonus, palatal myoclonus) and may not disappear in sleep.

Chorea is a hyperkinetic, rapid, unsustained, irregular, purposeless movement that seems to flow from one body part to another. Affected patients demonstrate difficulty keeping the tongue protruded or maintaining grip (milkmaid grip). Patients often attempt to incorporate the involuntary movements into more purposeful movements, making them appear fidgety. Choreiform movement abnormalities may be autoimmune/parainfectious, infectious, genetic, structural, metabolic or toxic in origin (Table 183-2). The movements may occur

<table>
<thead>
<tr>
<th>Table 183-2 Causes of Movement Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHOREA</strong></td>
</tr>
<tr>
<td>Autoimmune/parainfectious (acute rheumatic fever, systemic lupus erythematosus)</td>
</tr>
<tr>
<td>Infectious (human immunodeficiency virus, neurosyphilis, scarlet fever, encephalitis)</td>
</tr>
<tr>
<td>Genetic (Huntington disease, ataxia-telangiectasia)</td>
</tr>
<tr>
<td>Structural (stroke, neoplasm)</td>
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<tr>
<td>Metabolic/toxic (hepatic/renal failure, hyperthyroidism)</td>
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<tr>
<td>Drug induced</td>
</tr>
<tr>
<td><strong>ATHETOSIS</strong></td>
</tr>
<tr>
<td>Cerebral palsy’</td>
</tr>
<tr>
<td>Kernicterus</td>
</tr>
<tr>
<td>Hypoxic-ischemic encephalopathy</td>
</tr>
<tr>
<td>Drug induced</td>
</tr>
<tr>
<td>Pantothenate kinase-associated neurodegeneration</td>
</tr>
<tr>
<td>Pelizaeus-Merzbacher disease</td>
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<tr>
<td><strong>DYSTONIA</strong></td>
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<tr>
<td>Inherited primary dystonias</td>
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<tr>
<td>Acute dystonic reaction</td>
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<tr>
<td>Tardive dyskinesia</td>
</tr>
<tr>
<td>Cerebral palsy’</td>
</tr>
<tr>
<td>Metabolic disorders (Wilson disease)</td>
</tr>
<tr>
<td><strong>TREMOR</strong></td>
</tr>
<tr>
<td>Physiologic’</td>
</tr>
<tr>
<td>Essential tremor’</td>
</tr>
<tr>
<td>Hereditary, degenerative (Huntington disease, Wilson disease)</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Metabolic (hyperthyroidism, hepatic encephalopathy, electrolyte disturbances)</td>
</tr>
<tr>
<td>Drugs/toxins’ (caffeine, bronchodilators, amphetamines, tricyclic antidepressants)</td>
</tr>
<tr>
<td>Psychogenic tremor</td>
</tr>
<tr>
<td><strong>MYOCOLONUS</strong></td>
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<tr>
<td>Epilepsy</td>
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<tr>
<td>Benign</td>
</tr>
<tr>
<td>Infection</td>
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<tr>
<td>Toxin</td>
</tr>
<tr>
<td>Metabolic encephalopathies</td>
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<tr>
<td><strong>TICS</strong></td>
</tr>
<tr>
<td>Transient</td>
</tr>
<tr>
<td>Chronic motor tic disorder</td>
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<tr>
<td>Tourette syndrome</td>
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</tbody>
</table>

*Common
Altered Mental Status

Disorders of Consciousness

Consciousness represents awareness of self and environment (place and time). Arousal represents the system that initiates and maintains consciousness. Consciousness is mediated by the cerebral cortex; arousal is mediated by the reticular activating system extending from the midbrain to the hypothalamus to the thalamus.

Lethargic patients have difficulty maintaining an aroused state. Patients who are obtunded have decreased arousal but are responsive to stimuli. Stupor is a state of responsiveness to pain but not to other stimuli. Coma is a state of unresponsive unconsciousness and is caused by dysfunction of the cerebral hemispheres (bilaterally), the brainstem, or both simultaneously.

Acute Disorders of Consciousness

Acute changes in consciousness vary in degree from mild lethargy and confusion to deep coma. In childhood, the most common causes of coma are toxins, infections, head trauma, hypoxia-ischemia (cardiac arrest, near-drowning), and seizure (postictal state, subclinical status epilepticus) (Table 184-1).

Assessment

The most common cause of long-term morbidity in a patient with depressed consciousness is hypoxia; therefore, airway, breathing and circulation are addressed first. Vital signs, including pulse oximetry, must be assessed. A glucose level should also be checked immediately because hypoglycemia is a rapidly treatable cause of altered mental status. Physical examination searches for clues as to the cause of altered consciousness, such as unusual odors, needle tracts, trauma, or signs of dehydration or organ system failure.

Breathing patterns may provide important clues to the depth, neurologic localization, and etiology of the depressed consciousness. In Cheyne-Stokes respiration, a period of...
### Table 184-1 Causes of Coma and Diagnostic Approach

<table>
<thead>
<tr>
<th>CAUSES</th>
<th>Diagnostic Approach</th>
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<tbody>
<tr>
<td>Infection</td>
<td>Increased intracranial pressure</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Brain tumor</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Cerebral edema</td>
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<tr>
<td>Brain abscess</td>
<td>Hydrocephalus</td>
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<tr>
<td>Herpes simplex virus meningoencephalitis</td>
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<tr>
<td>Human immunodeficiency virus</td>
<td></td>
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<tr>
<td>Tubercular meningitis</td>
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<tr>
<td>Toxic shock syndrome</td>
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<tr>
<td>Postinfectious (acute disseminated encephalomyelitis)</td>
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<tr>
<td>Trauma</td>
<td>Migraine</td>
</tr>
<tr>
<td>Shaken baby syndrome</td>
<td>Systemic disorders</td>
</tr>
<tr>
<td>Epidural hemorrhage</td>
<td>Gastrointestinal (intussusception)</td>
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<tr>
<td>Subdural hemorrhage</td>
<td>Vasculitis (systemic lupus erythematosus)</td>
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<tr>
<td>Subarachnoid hemorrhage</td>
<td>Hepatic failure</td>
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<tr>
<td>Concussion</td>
<td>Hypertensive encephalopathy</td>
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<tr>
<td>Toxins (intoxication or withdrawal)</td>
<td>Eye syndrome</td>
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<tr>
<td>Ethanol</td>
<td>Endocrine disorders (adrenal insufficiency, thyroid disorders)</td>
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<tr>
<td>Narcotics</td>
<td>Renal disorders (uremia)</td>
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<tr>
<td>Barbiturates</td>
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<tr>
<td>Antihistamines</td>
<td>Metabolic derangements</td>
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<tr>
<td>Anticonvulsants</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Iron</td>
<td>Hypernatremia or its correction</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Hyperkalemia or its correction</td>
</tr>
<tr>
<td>Aspirin (Reye syndrome)</td>
<td>Hyperosmolality or its correction</td>
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<tr>
<td>Illicit drugs</td>
<td>Hypercapnia</td>
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<tr>
<td>Lead poisoning</td>
<td>Hyperammonemia</td>
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<tr>
<td>Thiamine deficiency (Wernicke encephalopathy)</td>
<td>Inborn errors of metabolism</td>
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<tr>
<td>Hypoxia-ischemia</td>
<td>Diabetes mellitus—ketoacidosis or hypoglycemia</td>
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<tr>
<td>Near-drowning</td>
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<tr>
<td>Post–cardiopulmonary arrest</td>
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<td>Cardiac arrhythmia</td>
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<td>Obstructive cardiomyopathy</td>
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<td>Carbon monoxide intoxication</td>
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<td>Perinatal asphyxia</td>
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<tr>
<td>Strangulation</td>
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<td>Epilepsy</td>
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<tr>
<td>Subclinical (or nonconvulsive) status epilepticus</td>
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<tr>
<td>Postictal states</td>
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<tr>
<td>Stroke</td>
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<tr>
<td>Arterial ischemic stroke</td>
<td></td>
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<td>Cerebral sinovenous thrombosis</td>
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<td>Hemorrhage</td>
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ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; MRI/MRA/MRV, magnetic resonance imaging/angiography/venography; PCR, polymerase chain reaction; PT, prothrombin time; PTT, partial thromboplastin time.

Hyperventilation with a crescendo-decrescendo pattern alternates with a shorter period of apnea and is due to the loss of cerebral, thalamic, or hypothalamic modulation of respiration. This pattern also can be seen in patients with metabolic disorders, heart failure, or primary respiratory disease. A mid-brain lesion yields central neurogenic hyperventilation, which consists of sustained rapid deep breathing. Gasping respirations are irregularly irregular and indicate dysfunction of the lower brainstem (medulla). Gasping is omenous and usually is followed by terminal apnea.

The Glasgow Coma Scale (see Table 42-2) can be used to assess unresponsive patients regarding their best verbal and motor responses and eye opening to stimulation with a score of 3 to 15 points.

The detailed neurologic examination of a comatose patient focuses on the integrity of the brainstem which is the location of the reticular activating system, mediating arousal. Pupillary responses assess the midbrain function. Eye movements are observed or elicited with the doll’s eye maneuver (oculocerephalic response) (Chapter 179) or cold caloric stimulation (oculovestibular response). If the oculocephalic responses are not elicited or unclear, cold water is flushed into the external ear canal. In a conscious person, this maneuver elicits nystagmus to the opposite side and extreme vertigo with vomiting. In a comatose patient, cold water irrigation into the ear canal elicits a tonic eye deviation toward the ear irrigated if the brainstem is functioning and the patient is not brain dead. With complete loss of oculomotor function, the eyes remain in
the center of the orbit regardless of any stimulation, indicating brainstem failure.

Body posture at rest and after noxious stimulation can indicate the anatomic level responsible for the alteration of consciousness. Mildly altered mental status may be manifested by a comfortable sleeping posture. Frequent spontaneous readjustments of position, yawns, and sighs are observed. Patients who lie in a flat, extended, unvarying position with eyes half-open exhibit a deeper coma. An asymmetrical posture suggests motor dysfunction of one side. Asymmetry may be subtle, such as mild external rotation of the affected leg.

Posturing in response to noxious stimulation indicates more serious neurologic conditions. Decorticate posturing consists of rigid extension of the legs and feet, flexion and supination of the arms, and fisting of the hands. It indicates bilateral cortical or subcortical abnormalities or herniation, with preserved brainstem function. Decerebrate posturing (rigid extension and internal rotation of legs and arms) indicates a midbrain abnormality and is classically associated with herniation or toxic–metabolic abnormalities. These postures may be exhibited unilaterally or bilaterally. A structural cause is likely when posturing is asymmetric, whereas symmetric posturing may be more likely with underlying toxic–metabolic etiologies.

**Etiology**

The evolution of change in consciousness is an important clue to the etiology. A detailed history and physical examination usually provide sufficient clues to differentiate among the three major diagnostic categories producing coma: **metabolic/toxic, infectious, and structural**. In most clinical situations, the cause of coma is readily identified.

Metabolic derangements are common causes of altered mental status. Disturbances of blood chemistries (glucose, sodium, calcium, bicarbonate, blood urea nitrogen, ammonia) may produce depressed mental status. Metabolic causes of acute coma are suggested by spontaneous fluctuations in the level of consciousness, tremors, myoclonus, asterixis, visual and tactile hallucinations, and deep coma with preservation of pupillary light reflexes. Acute metabolic or toxic disorders usually produce a hypotonic, limp state, but hypertonia, rigidity, and decorticate and decerebrate posturing are sometimes observed in coma caused by hypoglycemia, hepatic encephalopathy, and short-acting barbiturates. A subacute course of somnolence progressing to difficulty arousing from a deep sleep (stupor) over hours suggests drug intoxication or organ system failure (kidney, liver) producing a metabolic encephalopathy. Care must be taken to investigate background medical conditions that may produce a decline in consciousness (e.g., diabetes mellitus, leukemia, kidney failure, liver disease). Intoxication and ingestion are common causes of acute alteration of consciousness, and a thorough history must be taken to search for the offending agent (Chapter 45). A history of social and emotional difficulties, drug abuse, or depression raises concern for self-inflicted injury or toxic ingestion.

Central nervous system infection, such as meningitis or encephalitis, usually causes abrupt alteration of mental status, although viral meningoencephalitis (particularly herpes simplex virus) can present with subacute alterations in mental status. The presence of fever, petechiae, chills, and sweats suggests infection. Prodromal photophobia and pain on movement of the head or eyes are symptoms of meningeal irritation. Premonitory symptoms, such as abdominal pain, diarrhea, sore throat, conjunctivitis, cough, or rash, point toward viral encephalitis or a postinfectious syndrome as the cause of the altered consciousness.

Structural processes, such as hemorrhage, infarction, or acute hydrocephalus, can cause sudden depressed consciousness in children. An evolution of headache and morning vomiting suggests increased intracranial pressure (ICP). A gradual fading of alertness or declining school performance over preceding weeks suggests an expanding intracranial mass, subdural hematoma, or chronic infection (e.g., tuberculous meningitis, human immunodeficiency virus). Deprivation of oxygen to the brain, caused by either deficient oxygen in the blood (hypoxemia) or deficient delivery of blood to the brain (ischemia), impairs consciousness.

**Clinical Manifestations**

Papilledema or paralysis of cranial nerves III or VI in a patient with depressed consciousness is strong evidence of elevated ICP, a medical and neurosurgical emergency. **Herniations** occur under the falx, through the tentorial notch, or into the foramen magnum (Table 184-2). Recognition of the signs associated with the major herniation syndromes can be life-saving, if emergent neuroimaging and treatment are initiated. **Uncal herniation** implies displacement of the mesial temporal lobe over the tentorial edge, producing a unilateral third

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**Table 184-2** Herniation Syndromes

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>ETIOLOGY</th>
<th>DESCRIPTION</th>
<th>CLINICAL FINDING(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transtentorial</td>
<td>Unilateral (uncal) or bilateral</td>
<td>Supratentorial mass lesions, diffuse brain swelling, focal edema, or acute hydrocephalus</td>
<td>Headache, Altered consciousness, Dilated ipsilateral pupil, Cranial nerve III palsy, Hemiparesis, Decerebrate posturing, Cushing triad, Respiratory arrest</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Downward displacement of supratentorial brain tissue into infratentorial compartment (below tentorium), compressing the cerebral peduncles, midbrain, third cranial nerve, and posterior circulation</td>
<td>Weakness, bladder incontinence, coma</td>
</tr>
<tr>
<td>Subfalcian</td>
<td>Increased pressure in one hemisphere (mass, focal edema)</td>
<td>Brain tissue displaced under the falx cerebri, compressing the anterior cerebral artery</td>
<td>Bradycardia, bradypnea, hypertension, death</td>
</tr>
<tr>
<td>Foremen magnum</td>
<td>Cerebellar mass or edema</td>
<td>Downward displacement of cerebellar tonsils, compressing the medulla oblongata and upper spinal cord</td>
<td>Bradycardia, bradypnea, hypertension, death</td>
</tr>
</tbody>
</table>
nerve palsy ("blown pupil") and hemiparesis (which can be ipsilateral, because of compression of the contralateral cerebral peduncle, or contralateral if the uncus compresses the ipsilateral peduncle). **Transtentorial (or central) herniation** occurs with gradual downward pressure from the diencephalon through the tentorium, resulting in compression of the brainstem (first midbrain, then progressing to pons and medulla). A progressive loss of consciousness accompanied by a characteristic progression of motor, oculomotor, pupillary, and respiratory signs indicates incipient transtentorial herniation.

**Laboratory and Diagnostic Imaging**

Evaluation is guided by the history and physical examination (see Table 184-1). Computed tomography (CT) remains the preferred imaging technique in emergency situations because it can be performed rapidly and accurately identifies acute hemorrhages, large space-occupying lesions, edema, and shifts of the midline. The initial head CT scan is done without contrast to identify blood and calcifications. Contrast can be administered to identify inflammatory and neoplastic lesions, but is not usually required for identification of major lesions. Several metabolic derangements (hepatic encephalopathy, Reye syndrome, hyponatremia, lead encephalopathy, diabetic ketoacidosis, and hypoxic-ischemic injury) may give rise to severe elevations of ICP without producing obvious CT abnormalities. Lumbar puncture (LP) in a patient with elevated ICP can result in transtentorial herniation, so imaging should be performed before LP if elevated ICP is suspected, especially if there are any focal neurologic deficits on exam. If trauma or immersion injuries are suspected, neck manipulation should be avoided until cervical spine imaging excludes vertebral fracture or subluxation. Examination of the cerebrospinal fluid (CSF) may establish the cause of the alteration of consciousness. Appropriate neuroimaging should be performed to ensure that no added injury is likely to be inflicted with LP. The presence of red blood cells in the CSF may suggest primary subarachnoid hemorrhage, parenchymal hemorrhage, or hemorrhagic infection (herpes simplex virus), or it may be due to a traumatic procedure. White blood cells in the CSF usually denote infectious meningitis or meningoencephalitis but may also be associated with vasculitis or parainfectious syndrome. Elevated CSF protein is seen in patients with meningeal inflammation or tumors, and abnormal CSF glucose levels are also markers of infection and inflammation.

**Treatment**

The etiology of altered mental status determines the treatment. Ingestions may necessitate gastric lavage, charcoal administration, forced diuresis, dialysis, or specific antidotes (Chapter 45). Infections are treated with appropriate antibiotics or antiviral agents (Chapter 95). If mental status changes are due to increased ICP, acute medical interventions (osmotic agents, steroids, hyperventilation) must be instituted, emergent neuroimaging performed, and urgent neurosurgical consultation obtained. Structural brain lesions may necessitate medical treatment of increased ICP or surgical excision.

**Prognosis**

The outcome of altered mental status relates to many variables, including etiology. Intoxication typically carries a good prognosis, whereas hypoxia carries a poor prognosis. Other prognostic factors include the duration of coma and the age of the patient; children have better outcomes than adults. Complete recovery from traumatic coma of several days’ duration is possible in children; however, many survivors of prolonged coma are left in a persistent vegetative state or with severe neuropsychiatric disability.

**Transient, Recurrent Depression of Consciousness**

Episodic alteration or depression of consciousness with full recovery is usually due to seizure, migraine, syncope, or metabolic abnormality (hypoglycemia). Consciousness can be impaired during seizures or in the postictal state. Nonconvulsive (subclinical) status epilepticus (generalized or focal) can directly impair consciousness and is a common complicating factor for patients with acute neurological disorders (head trauma, meningitis, following convulsive status epilepticus). Some patients may have a prolonged postictal state after an unrecognized seizure.

Basilar artery or **confusional migraines** can last hours and be accompanied by agitation, ataxia, cortical blindness, vertigo, or cranial nerve palsies. Headache may precede or follow the neurologic signs.

**Syncope** is one of the most common causes of abrupt, episodic loss of consciousness. Neurocardiogenic syncope, cardiac arrhythmia, or an obstructive cardiomyopathy can cause recurrent episodes of loss of consciousness. Two thirds of children with syncope have irregular, myoclonic movements as they lose consciousness (anoxic seizures), which must be distinguished from epilepsy (unprovoked seizures). Children with unexplained syncope require a complete cardiac examination (Chapter 140).

Metabolic derangements, particularly **hypoglycemia**, give rise to episodes of lethargy, confusion, seizures, or coma. Several other metabolic disorders cause recurrent bouts of **hyperammonemia** (Chapter 53). Symptoms include nausea, vomiting, lethargy, confusion, ataxia, hyperventilation, and coma.

**TRAUMATIC BRAIN INJURY**

Following head injury, children may have immediate depression of consciousness and neurologic deficits or may be completely alert without any immediate signs of neurologic injury. Most serious trauma results from motor vehicle crashes, sports, recreation-related injuries, and violence. Head trauma may result in concussion, posttraumatic intracranial hemorrhage, skull fractures, or cranial nerve or cervical spine injuries. Head injury, or other injuries, with associated retinal hemorrhages in infants and young children should raise the suspicion of abusive head trauma.

**Concussion**

Concussion is the process in which traumatic forces on the brain result in the rapid onset of short-lived neurologic impairment that typically resolves spontaneously. Patients may have signs or symptoms in one or more domain: somatic (headache), cognitive (slowed reaction times, feeling like they are in a fog, poor attention), emotional (lability, irritability), sleep
disturbance (drowsiness), or physical signs (loss of consciousness, amnesia). Acute symptoms usually reflect a functional disturbance rather than structural injury, and no abnormalities are seen on standard imaging. The majority of concussions resolve within 10 days, although the recovery may be slower in children, and in a small percentage of cases, the symptoms are prolonged.

Repeated concussions, especially within a short time frame (days or weeks) carry a significant risk of permanent brain injury (second impact syndrome). Children must not be permitted to resume physical activities until well after the symptoms resolve (Table 184-3).

**Traumatic Intracranial Hemorrhage**

Head trauma can result in epidural, subdural, parenchymal, and subarachnoid intracranial hemorrhages, as well as brain contusions (Table 184-4). Symptoms include headache, vomiting, lethargy, decreased consciousness and seizures. The classic presentation of epidural hematomas involves a lucid interval, where, following primary brain injury, a child has a decreased level of consciousness, then returns to normal for several hours before developing rapidly progressive neurologic symptoms. Subdural hematomas may result from direct trauma or rotational forces from vigorous shaking (shaken baby syndrome). In neonates and infants with open fontanelles, signs and symptoms may be absent or nonspecific. Occasionally, epidural, subdural, or intracranial hemorrhage or a rapid, life-threatening increase in ICP develops unexpectedly in children due to cerebral edema.

**Skull Fractures**

**Skull fractures** may be linear, diastatic (spreading the suture), depressed (an edge displaced inferiorly), or compound (bone fragments breaking the skin surface). Linear and diastatic fractures necessitate no treatment, but indicate trauma capable of producing an underlying hematoma. Small, depressed fractures have the same significance as linear fractures, but if the depression is more than 0.5 to 1 cm, surgical elevation of bone fragments and repair of associated dural tears are generally recommended. Compound fractures or penetrating injuries necessitate emergent surgical debridement and tetanus prophylaxis. The risk of associated brain contusion and early seizures is high in compound fractures.

Skull fractures may present with localized swelling and pain; subcutaneous bleeding over the mastoid process (Battle sign) or around the orbit (raccoon eyes); blood behind the tympanic membrane (hemotympanum); or CSF leak from the nose (rhinorrhea) or ear (otorrhea). Rarely, a few weeks to months after linear skull fractures, a soft, pulsatile scalp mass develops, usually over the mastoid process. Imaging is indicated when any of these symptoms are present, as imaging is often normal early in the course of the fracture. Although small skull fractures are transitory, larger fractures may produce persistent symptoms, which may indicate subperiosteal hemorrhage, dural tears, meningeal cysts, or a skull fracture with a vascular injury. Skull fractures may lead to hemorrhage or CSF leak, and they may produce pain, neurologic symptoms, and abnormalities on imaging studies.

**Table 184-3** Protocol for Return to Sport after Concussion

<table>
<thead>
<tr>
<th>Step</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>No activity, complete physical and mental rest.</td>
</tr>
<tr>
<td>2.</td>
<td>Light aerobic exercise such as walking or stationary cycling; no resistance training.</td>
</tr>
<tr>
<td>4.</td>
<td>Noncontact, more progressive training drills; resistance training.</td>
</tr>
<tr>
<td>5.</td>
<td>Full-contact practice after medical clearance.</td>
</tr>
<tr>
<td>6.</td>
<td>Game play.</td>
</tr>
</tbody>
</table>


**Table 184-4** Syndromes of Posttraumatic Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>CLINICAL AND RADIOLOGIC CHARACTERISTICS</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural</td>
<td>Onset over minutes to hours Lucid interval followed by progressive neurologic deficits Lens-shaped extracerebral hemorrhage compressing brain</td>
<td>Surgical evacuation or observation Prognosis good with prompt treatment, otherwise poor</td>
</tr>
<tr>
<td>Acute subdural</td>
<td>Onset over hours Focal neurologic deficits Crescent extracranial hemorrhage compressing brain</td>
<td>Surgical evacuation Prognosis guarded</td>
</tr>
<tr>
<td>Chronic subdural</td>
<td>Onset over weeks to months Anemia, macrocephaly Seizures, vomiting Crescentic, low-density mass on CT</td>
<td>Subdural taps or subdural shunt as necessary Prognosis can be good</td>
</tr>
<tr>
<td>Intraparenchymal</td>
<td>Depressed consciousness Focal neurologic deficits ± Additional multiple contusions</td>
<td>Supportive care Prognosis guarded</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>Stiff neck Worst headache of life Late hydrocephalus</td>
<td>Supportive care Prognosis variable</td>
</tr>
<tr>
<td>Contusion</td>
<td>Focal neurologic deficits Brain swelling with transtentorial herniation CT findings: multifocal low-density areas with punctate hemorrhages</td>
<td>Medical treatment of elevated intracranial pressure* Prognosis guarded</td>
</tr>
</tbody>
</table>

CT, Computed tomography.

*Mannitol, elevation of head of bed, diuresis, hyperventilation, steroids.
within the subdural, subarachnoid, or ventricular space also indicates a dural tear and open communication between the nose or paranasal sinuses and brain. In most cases, the dura heals spontaneously when the patient's head is kept elevated. Patients with CSF leaks are at risk for the development of meningitis or extradural abscesses. If the leak persists or recurs or if meningitis develops, the dura is surgically repaired. Cranial nerve pales, secondary to a laceration or contusion of the cranial nerves, may result from a skull fracture and may be transitory or permanent. Longitudinal fracture of the petrous bone produces a conductive hearing loss and facial palsy, which begin hours after the injury and usually resolve spontaneously. Transverse petrous fractures produce sensorineural hearing loss and immediate facial palsy with a poor prognosis for spontaneous recovery. Disruption of the ossicular chain can cause hearing loss and may necessitate surgery. Vestibular disturbances, producing prolonged posttraumatic vertigo, are extremely common. Permanent loss of olfaction after a head injury is the result of a rupture of the thin olfactory nerves within the cribiform plate. Disruption of cranial nerves III, IV, and VI produces ophthalmoplegia, diploia, and head tilt. Even seemingly minor head injuries can produce sixth nerve palsy with medial deviation (or incomplete abduction) of one or both eye(s).

Other Complications of Head Trauma

Cervical spine injuries must be suspected in any unconscious child, especially if bruises are present on the head, neck, or back. In conscious children, findings of neck or back pain, burning or stabbing pains radiating to the arms, paraplegia, quadriparesis, or asymmetrical motor or sensory responses of arms or legs suggest spinal cord injury. Cervical spine injury (displaced or fractured vertebra) may result in complete transection of the cord with spinal shock, loss of sensation, and flaccid paralysis. A contused cord (without vertebral abnormality) may present in a similar manner. Any patient with a clinical or radiologic abnormality of the spine requires immediate spine and cardiopulmonary stabilization and neurosurgical consultation.

Posttraumatic seizures are divided into one of three patterns: impact seizures, early posttraumatic seizures, and late posttraumatic seizures. Impact seizures occur within seconds of the injury and are presumed to reflect a direct mechanical stimulation to the cortex. The prognosis is excellent, and likelihood of later epilepsy is negligible. Early posttraumatic seizures occurring within the first week of the head injury are likely the result of a localized area of cerebral contusion or edema. The long-term prognosis for these seizures is quite favorable. Late posttraumatic seizures arise more than a week after the trauma and most likely indicate an area of cortical gliosis or scarring that will be a source for long-term epilepsy. These patients often require long-term antiepileptic drug therapy.

Transient neurologic disturbances may develop a few minutes after head trauma and last for minutes to hours before clearing. The most common symptoms are cortical blindness and confusional states, but hemiparesis, ataxia, or any other neurologic deficit may appear. These symptoms may represent a trauma-triggered migraine in susceptible children, but care must be exercised to exclude intracranial pathology.

Drowsiness, headache, and vomiting are common after head trauma. They are not, by themselves, of concern if consciousness is preserved, the clinical trend is one of improvement, and results of the neurologic examination are normal. Children are especially susceptible to somnolence after head trauma but should be easily arousable. If symptoms worsen or persist for more than 1 to 2 days, neuroimaging may be indicated to look for subdural hematoma or cerebral edema.

Evaluation and Treatment

Children who have been unconscious or have amnesia following a head injury should be evaluated in an emergency department. High-risk patients include those with persistent depressed or decreasing level of consciousness, focal neurologic signs, penetrating skull injury, depressed skull fractures, or worsening symptoms. Because patients with intracranial hemorrhage may progressively deteriorate and require immediate neurosurgical care, these patients warrant care in a skilled trauma center.

The Glasgow Coma Scale is a valuable tool for monitoring the course of patients after trauma for signs of deterioration (Chapter 42). Management includes ensuring an appropriate airway, breathing, and circulation. Neuroimaging with CT or magnetic resonance imaging (MRI), and skull and cervical spine radiographs are obtained emergently. Neuroimaging is not necessary for uncomplicated concussions but should be employed whenever suspicion of structural intracranial lesion exists.

The observation period varies with the severity of the injury and may include hospitalization even for children without neurologic deficits who have sustained a concussion. Any patient demonstrating any features of a concussion should be medically evaluated, and disposition (return to play) must be determined by a health care provider (see Table 184-3). The child should be monitored for deterioration over the initial few hours after injury and not left alone. If the child appears well after several hours and is discharged home, parents should be instructed to call their physician for any change in alertness, orientation, or neurologic functioning. An increase in somnolence, headache, or vomiting is cause for concern and neuroimaging.

Patients with intracranial hemorrhage may require emergent surgical intervention for decompression and drainage of the blood collection. Increased ICP may require monitoring, placement of a ventricular drain, and aggressive medical management, including intubation and ventilation, osmotic therapy, and sedation (see later discussion).

Prognosis

Children with concussion without subsequent neurologic deficits have a favorable long-term prognosis, and late sequelae are rare. Children with moderate contusions usually make good recoveries even when neurologic signs persist for weeks. Long-term sequelae may include poor memory, slowing of motor skills, generalized decrease in cognitive skills, behavioral alterations, or attention deficits. Language function, especially in a young child, frequently makes a good recovery. Rehabilitation programs with physical therapy, behavioral management, and appropriate education may be necessary. Poor prognostic signs include a Glasgow Coma Scale score of less than 4 on
admission without improvement in 24 hours, absent pupillary light reflexes, and persistent extensor plantar reflexes.

Children with cerebral contusion who survive acute cerebral swelling may improve gradually or may remain vegetative. Extracranial trauma also contributes to the morbidity of these patients (aspiration pneumonia, acute respiratory distress syndrome, sepsis, emboli). Maximal recovery may take weeks or months. Coma lasting for weeks after head trauma may be compatible with a good outcome, although the risk of late sequelae is significant. Patients who remain in a vegetative state for months after head injury are unlikely to improve.

### INCREASED INTRACRANIAL PRESSURE

**Etiology**

When the cranial sutures are fused, the skull becomes a rigid container enclosing a fixed volume, including the brain (80% to 85%), CSF (10% to 15%), and blood (5% to 10%). The exponential relationship between the volume within a closed container and pressure results in a massive increase in ICP as intracranial volume increases. The brain accommodates increased ICP initially by expelling CSF and blood from the intracranial compartment into the spinal subarachnoid space. When the limits of this accommodation are reached, the brain itself begins to shift in response to the continuing elevation of ICP. Brain shifts may cause herniations across the dural extensions or skull barriers (see Table 184-2).

The causes of increased ICP include mass lesion, hydrocephalus, cerebral edema due to trauma or infection and idiopathic intracranial hypertension (Tables 184-5, 184-6).

**Mass lesions** (brain tumor, abscess, hemorrhage) may produce increased ICP not only by virtue of large size, but by blockage of CSF pathways, blockage of venous outflow, or production of vasogenic cerebral edema. Brain abscesses usually present as mass lesions, producing focal neurologic signs and increased ICP. Symptoms of infection, including fever, malaise, anorexia, and stiff neck, may be subtle or absent. Brain edema around an abscess is usually severe and extends into the surrounding white matter. Children with chronic cardiac or pulmonary disease may exacerbate infected material to their brains, predisposing them to brain abscesses. Brain tumors in children are most often located in the posterior fossa and can result in elevated ICP due to obstruction of CSF flow through the cerebral aqueduct and fourth ventricle.

**Hydrocephalus** from congenital abnormalities or due to an intracranial mass is typically characterized by a slowly evolving syndrome of increased ICP extending over weeks or months. CSF is continuously produced by the choroid plexus within the lateral, third, and fourth ventricles. CSF flows from the lateral ventricles through the intraventricular foramen of Monro to the third ventricle, then passes through the cerebral aqueduct to the fourth ventricle. CSF exits the fourth ventricle from the foramen of Magendie and foramina of Luschka. Subarachnoid flow occurs superiorly to the cisterns of the brain and inferiorly to the spinal subarachnoid space. Absorption of CSF is accomplished predominantly by the arachnoid villi into the large dural sinuses. Hydrocephalus is due to the obstruction of CSF flow anywhere along its course (see Table 184-6). **Obstructive hydrocephalus** is caused by a block before the CSF flows to the subarachnoid space, usually within the fourth ventricle or at the level of the aqueduct. Impairment of CSF flow within the subarachnoid space or impairment of

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**Table 184-5** Causes of Increased Intracranial Pressure

<table>
<thead>
<tr>
<th>MASS EFFECT</th>
<th>ETIOLOGIC DISORDER/CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocephalus</td>
<td>Intraventricular foramina (Monro) obstruction</td>
</tr>
<tr>
<td>Infarction with edema</td>
<td>Parasellar mass (craniopharyngioma, germinoma, pituitary tumor)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Intraventricular tumor (ependymoma)</td>
</tr>
<tr>
<td>Tumor</td>
<td>Tuberous sclerosis with subependymal giant cell astrocytoma</td>
</tr>
<tr>
<td>Abscess</td>
<td>Aqueduct of Sylvius (cerebral aqueduct) obstruction</td>
</tr>
<tr>
<td>Cyst</td>
<td>Aqueductal stenosis</td>
</tr>
<tr>
<td>Inflammatory mass</td>
<td>Midbrain or pineal region tumor</td>
</tr>
<tr>
<td>Tumor</td>
<td>Postinfectious or postinflammatory</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Posthemorrhagic</td>
</tr>
<tr>
<td>Infarction with edema</td>
<td>Impaired flow from the fourth ventricle foramina of Luschka and Magendie</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Basilar impression</td>
</tr>
<tr>
<td>Idiopathic intracranial hypertension (pseudotumor cerebri)</td>
<td>Platybasia</td>
</tr>
<tr>
<td>Drugs</td>
<td>Dandy-Walker malformation</td>
</tr>
<tr>
<td>Withdrawal of long-term steroid administration</td>
<td>Arnold-Chiari malformation</td>
</tr>
<tr>
<td>Endocrinologic disturbance</td>
<td>Bone lesions of the cranial base (achondroplasia, rickets)</td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
</tbody>
</table>

**Table 184-6** Causes of Hydrocephalus

<table>
<thead>
<tr>
<th>PATHOGENIC MECHANISM</th>
<th>ETIOLOGIC DISORDER/CONDITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction of CSF pathways</td>
<td>Intraventricular foramina (Monro) obstruction</td>
</tr>
<tr>
<td></td>
<td>Parasellar mass (craniopharyngioma, germinoma, pituitary tumor)</td>
</tr>
<tr>
<td></td>
<td>Intraventricular tumor (ependymoma)</td>
</tr>
<tr>
<td></td>
<td>Tuberous sclerosis with subependymal giant cell astrocytoma</td>
</tr>
<tr>
<td></td>
<td>Aqueduct of Sylvius (cerebral aqueduct) obstruction</td>
</tr>
<tr>
<td></td>
<td>Aqueductal stenosis</td>
</tr>
<tr>
<td></td>
<td>Midbrain or pineal region tumor</td>
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<tr>
<td></td>
<td>Postinfectious or postinflammatory</td>
</tr>
<tr>
<td></td>
<td>Posthemorrhagic</td>
</tr>
<tr>
<td></td>
<td>Impaired flow from the fourth ventricle foramina of Luschka and Magendie</td>
</tr>
<tr>
<td>Overproduction of CSF</td>
<td>Basilar impression</td>
</tr>
<tr>
<td></td>
<td>Platybasia</td>
</tr>
<tr>
<td></td>
<td>Dandy-Walker malformation</td>
</tr>
<tr>
<td></td>
<td>Arnold-Chiari malformation</td>
</tr>
<tr>
<td></td>
<td>Bone lesions of the cranial base (achondroplasia, rickets)</td>
</tr>
<tr>
<td></td>
<td>Hydroplasia of the arachnoid villi</td>
</tr>
<tr>
<td></td>
<td>Postinfectious or posthemorrhagic</td>
</tr>
<tr>
<td></td>
<td>Destruction of arachnoid villi</td>
</tr>
<tr>
<td></td>
<td>Subarachnoid fibrosis</td>
</tr>
<tr>
<td></td>
<td>Extensive cerebral sinovenous thrombosis</td>
</tr>
</tbody>
</table>

CSF, Cerebrospinal fluid.
absorption is known by the misnomer communicating hydrocephalus, where there is actually extraventricular obstruction of CSF flow (external hydrocephalus). Hydrocephalus caused by overproduction of CSF without true obstruction is seen in choroid plexus papillomas, which account for 2% to 4% of childhood intracranial tumors.

Bacterial meningitis may produce increased ICP by blockage of CSF pathways, toxic cerebral edema, increase in cerebral blood flow, or multifocal cerebral infarctions (Chapter 100). Most children with bacterial meningitis can undergo LP safely because the brain swelling is diffuse and distributed evenly throughout the brain and spinal CSF compartments. A few patients with meningitis, however, develop transtentorial herniation within a few hours of LP. Focal neurologic signs, poorly reactive pupils, and a tense fontanelle are contraindications to LP in a patient with suspected bacterial meningitis.

Idiopathic intracranial hypertension (pseudotumor cerebri) is a cause of increased ICP with normal brain imaging. Patients exhibit a daily debilitating headache associated with diplopia, abducens palsy, transient visual obscurations, and papilledema. If untreated, permanent visual field loss may develop. The syndrome has been associated with ingestion of medications (tetracycline, vitamin A, oral contraceptive agents) and endocrine disturbances (thyroid disease, Addison disease). Most commonly, this condition is idiopathic and affects children who are otherwise well except for being overweight, with rapid weight gain being a predisposing factor. Treatment including acetazolamide or other diuretic, topiramate, or corticosteroids, is generally effective. Weight loss and cessation of triggering medications are also mainstays of treatment. Infrequently, chronic papilledema from persistent idiopathic intracranial hypertension produces visual impairment, and more aggressive management is required (optic nerve fenestration) to preserve visual function.

Clinical Manifestations

The symptoms and signs of increased ICP include headache, vomiting, lethargy, irritability, altered consciousness, sixth nerve palsy, strabismus, diplopia, and papilledema. Headaches suggestive of increased ICP are those associated with nocturnal wakening; worse in the morning; with cough, micturition, defecation, or Valsalva maneuver; or progressively worsening. Infants who have an open fontanelle usually do not develop papilledema or abducens palsy. Specific signs of increased ICP in infants consist of a bulging fontanelle, suture diastasis, distended scalp veins, a persistent downward deviation of the eyes (sunsetting), and rapid growth of head circumference. Specific signs of increased ICP in the infratentorial compartment (posterior fossa) include stiff neck and head tilt. Focal neurologic deficits reflect the site of the lesion that is producing the increased ICP and may include hemiparesis from supratentorial lesions, or ataxia and cranial nerve palsies from infratentorial lesions. Critically increased ICP may result in herniation syndromes, as discussed earlier. In addition, the Cushing triad of elevated blood pressure, bradycardia, and irregular respirations is a late sign of critically elevated ICP.

The clinical manifestations of hydrocephalus are caused by ventricular distention and increased ICP. Dilation of the lateral ventricles stretches the corticopontocerebellar and corticospinal pathways, resulting in ataxia and spasticity that initially are most marked in the lower extremities because the leg fibers are closest to the ventricles. Distention of the third ventricle may compress the hypothalamic regions and result in endocrine dysfunction. The optic nerves, chiasm, and tracts also are in proximity to the anterior third ventricle, and visual dysfunction results when these structures are compressed. Dilation of the cerebral aqueduct compresses the surrounding periaqueductal vertical gaze center, causing downward deviation of the eyes. Manifestations of increased ICP may evolve slowly when obstruction is not complete and there is time for transependymal absorption of CSF into the veins, or rapidly when obstruction is abrupt and complete (subarachnoid hemorrhage) and compensation cannot occur.

Laboratory and Diagnostic Studies

The cause of increased ICP is determined by brain imaging with either head CT or brain MRI. CT is rapid, readily available, and provides clear visualization of an acute hemorrhage or dilated ventricles. Mass lesions, hydrocephalus, and trauma are easily recognized. Diffuse brain swelling produced by hypoxic-ischemic injury, meningitis, encephalitis, metabolic abnormalities, or toxins may be better delineated by MRI. MRI is also superior to CT for visualizing the posterior fossa and cortical contusions. LP is the diagnostic test for infection and for documentation of elevated ICP (essential for patients with idiopathic intracranial hypertension). However, LP is contraindicated in the setting of an intracranial mass lesion or clear hydrocephalus, because withdrawal of CSF can change pressures between the intracranial compartments and promote brainstem shifts and herniation. Idiopathic intracranial hypertension is diagnosed when direct measurement of ICP with a manometer during LP reveals elevated ICP in the absence of other CSF or imaging abnormalities.

Treatment of Elevated ICP

The treatment of acute increased ICP should be carried out in an intensive care setting with continuous monitoring and vigilant attention to vital signs. The patient’s response to specific interventions must be carefully assessed. The head is placed at midline and the head of the bed elevated 30°. Immediate endotracheal intubation and hyperventilation (to a Paco₂ not lower than 35 mm Hg) produces rapid, but transient, reduction in ICP by cerebral vasoconstriction, leading to decreased cerebral blood volume. Mannitol or 3% saline may be used acutely to produce an osmotic shift of fluid from the brain to the plasma. A ventricular catheter may be used to remove CSF and to monitor the ICP continuously. Pentobarbital-induced coma reduces pressure by severely suppressing cerebral metabolism and cerebral blood flow. Acetazolamide and furosemide may transiently decrease CSF production. Because acute interventions such as hyperventilation, osmotic therapies, and barbiturates can have negative impacts on systemic and cerebral perfusion and have only transient effects on ICP, they must be used judiciously.
The treatment of hydrocephalus may be medical or surgical, depending on the etiology. After subarachnoid hemorrhage or meningitis, the flow or absorption of CSF may be transiently impaired. In this circumstance, the use of medication that decreases CSF production, such as acetazolamide, may be beneficial. Surgical management consists of removing the obstructive lesion, placing a shunt, or both. A shunt consists of polyethylene tubing extending usually from a lateral ventricle to the peritoneal cavity (ventriculoperitoneal shunt). Shunts carry the hazards of infection or sudden occlusion with signs and symptoms of acute hydrocephalus.

Vasopressor drugs may be necessary to maintain adequate arterial pressure and cerebral perfusion pressure. Serum electrolytes and osmolarity should be monitored because of risk of the syndrome of inappropriate antidiuretic hormone or cerebral salt wasting. Maintaining normoglycemia may have a positive impact on outcomes. Other supportive measures include controlling agitation, fever, and seizures.

All treatments for increased ICP are temporary measures intended to prevent herniation until the underlying disease process either is treated or resolves spontaneously. Timely intervention can reverse cerebral herniation. Complete neurologic recovery is possible, but rare, after signs of transtentorial or foramen magnum herniation have begun. When these signs are complete, however, with bilaterally dilated, unreactive pupils, absent eye movements, and flaccid quadriplegia, recovery is no longer possible.

Chapter 185

NEURODEGENERATIVE DISORDERS

Children typically acquire developmental milestones in a variable but predictable sequence (Chapter 7). Rarely, children present with stagnation of development or frank loss of previously acquired skills. These neurodegenerative disorders encompass a large heterogeneous group of diseases that result from specific genetic and biochemical defects and varied unknown causes. Neurodegenerative disorders can present at any age. Clinically, phenotypes also vary, but neurologic deterioration may be demonstrated as loss of speech, vision, hearing, and intellectual or motor abilities—sometimes in concert with seizures, feeding difficulties, and mental retardation. Progression may be slow over many years, or may lead to death in early childhood.

HEREDITARY AND METABOLIC DEGENERATIVE DISEASES

Degenerative diseases may affect gray matter (neuronal degenerative disorders), white matter (leukodystrophies), both gray and white matter, or specific, focal regions of the brain. Early seizures and intellectual impairment mark grey matter disorders, whereas upper motor neuron signs and progressive spasticity are the hallmarks of white matter disorders. Many neurodegenerative illnesses result from enzymatic disorders within subcellular organelles, including lysosomes, mitochondria, and peroxisomes (Table 185-1). Therefore, any

<table>
<thead>
<tr>
<th>Table 185-1 Selected Clinical Features of Neurodegenerative Disorders and Relevant Diagnostic Tests</th>
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<tbody>
<tr>
<td><strong>SPHINGOLIPIDOSES</strong></td>
</tr>
<tr>
<td>Niemann-Pick Disease</td>
</tr>
<tr>
<td>Cognitive regression, hepatosplenomegaly, jaundice, seizures</td>
</tr>
<tr>
<td>Test: acid sphingomyelinase (ASM) enzyme activity</td>
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<tr>
<td>Gaucher Disease</td>
</tr>
<tr>
<td>Hepatosplenomegaly, cytopenia, spasticity, hyperextension,</td>
</tr>
<tr>
<td>extracranial palsies, trismus, difficulty swallowing</td>
</tr>
<tr>
<td>Test: glucosylceramidase enzyme activity</td>
</tr>
<tr>
<td>GM1 Gangliosidoses</td>
</tr>
<tr>
<td>Infantile form—early feeding difficulties, global retardation,</td>
</tr>
<tr>
<td>seizures, coarse facial features, hepatosplenomegaly, cherry</td>
</tr>
<tr>
<td>red spot</td>
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<tr>
<td>Juvenile form—incoordination, weakness, language regression;</td>
</tr>
<tr>
<td>later, seizures, spasticity, blindness</td>
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<tr>
<td>Adult form</td>
</tr>
<tr>
<td>Test: GM1 ganglioside enzyme activity; GLB1 gene testing</td>
</tr>
<tr>
<td>GM2 Gangliosidoses</td>
</tr>
<tr>
<td>Tay-Sachs—progressive weakness, marked startle reaction,</td>
</tr>
<tr>
<td>blindness, convulsions, spasticity, and cherry red spots</td>
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<tr>
<td>Test: β-hexosaminidase A (HEX A) enzymatic activity</td>
</tr>
<tr>
<td>Sandhoff disease—phenotype similar to Tay-Sachs</td>
</tr>
<tr>
<td>Test: hexosaminidase A and B enzyme activity (both deficient)</td>
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<tr>
<td>Krabbe Disease/Globoid Cell Leukodystrophy</td>
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<tr>
<td>Irritability, hyperpyrexia, vomiting, seizures, hypertonia,</td>
</tr>
<tr>
<td>blindness</td>
</tr>
<tr>
<td>Test: galactocerebrosidase (GALC) enzyme activity</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy</td>
</tr>
<tr>
<td>Late infantile form—stiffening and ataxia of gait, spasticity,</td>
</tr>
<tr>
<td>optic atrophy, intellectual deterioration, absent reflexes</td>
</tr>
<tr>
<td>Juvenile and adult forms</td>
</tr>
<tr>
<td>Test: 1. arylsulfatase A (ARSA) enzyme activity</td>
</tr>
<tr>
<td>2. If ARSA activity is &lt;10% of controls, exclude ARSA</td>
</tr>
<tr>
<td>pseudodeficiency with genetic testing of ARSA and/or abnormal</td>
</tr>
<tr>
<td>urinary sulfatide excretion</td>
</tr>
<tr>
<td>NEURONAL CEROID LIPOFUSCINOSES</td>
</tr>
<tr>
<td>Visual loss, progressive dementia, seizures, motor deterioration</td>
</tr>
<tr>
<td>Test: Diagnostic algorithm depends on age of symptom onset,</td>
</tr>
<tr>
<td>and replies on stepwise testing for palmitoyl-protein</td>
</tr>
<tr>
<td>thioesterase 1 (PPT1) and tripeptidyl-peptidase 1 (TPP-1)</td>
</tr>
<tr>
<td>enzyme activity</td>
</tr>
<tr>
<td>X-LINKED ADRENOLEUKODYSTROPHY</td>
</tr>
<tr>
<td>Classic Adrenoleukodystrophy</td>
</tr>
<tr>
<td>Academic difficulties, behavioral disturbances, hypoadrenalism,</td>
</tr>
<tr>
<td>seizures, spasticity, ataxia, and swallowing difficulties.</td>
</tr>
<tr>
<td>Adrenomyeloneuropathy</td>
</tr>
<tr>
<td>Spastic paraparesis, urinary incontinence, adrenal insufficiency</td>
</tr>
<tr>
<td>Test: very long chain fatty acids</td>
</tr>
<tr>
<td>MUCOPOLYSACCHARIDOSES (MPS)</td>
</tr>
<tr>
<td>Short stature, kyphoscoliosis, coarse facies, hepatosplenomegaly,</td>
</tr>
<tr>
<td>cardiovascular abnormalities, and corneal clouding</td>
</tr>
<tr>
<td>Hurler (MPS type I-H)</td>
</tr>
</tbody>
</table>

Continued
patient with a degenerative neurologic condition of unknown cause should have leukocytes or skin fibroblasts harvested for measurement of a standard battery of lysosomal, peroxisomal, and mitochondrial enzymes (Chapters 56, 57). Neuroimaging, usually with brain magnetic resonance imaging (MRI), is also typically warranted. The diagnosis of leukodystrophy usually can be made confidently on the basis of extensive cerebral white matter changes on MRI. Histologic and biochemical studies may be normal in gray matter encephalopathy, making the diagnosis much less secure. Acquired lesions (infectious, inflammatory, vascular, toxic) are difficult to exclude completely. Brain biopsy is not likely to be helpful.

Sphingolipidoses

The sphingolipidoses are characterized by intracellular storage of lipid substrates resulting from defective catabolism of the sphingolipids comprising cellular membranes. They are inherited in an autosomal recessive pattern. In most cases, there are several forms of these diseases, typically corresponding to the amount of residual activity in the relevant enzyme.

The infantile forms are generally the most severe, usually presenting in the first or second year of life with rapid disease progression; affected individuals have virtually no normal enzyme activity. Juvenile and chronic forms are manifest somewhat later in childhood or even adulthood and have a less fulminant disease course because of some residual enzyme activity.

Classic Niemann-Pick disease is caused by a deficiency of sphingomyelinase and should be suspected in infants who exhibit the combination of hepatosplenomegaly, developmental delay, interstitial lung disease, and retinal cherry-red spots. The ganglion cells of the retina and macula are distended and appear as a large area of white surrounding a small red fovea that is not covered by ganglion cells. Cognitive regression, myoclonic seizures, hypotonia, and jaundice are also noted within the first year of life. Genetic testing for SMPD1 mutations is clinically available.

Although the most common form of Gaucher disease is an indolent illness of adults, there is a rapidly fatal infantile form featuring severe neurologic involvement caused by deficiency of the enzyme glucocerebrosidase. Glucocereamide accumulates in the liver, spleen, and bone marrow. The characteristic neurologic signs are opisthotonos (arching of the trunk), trismus (difficulty opening mouth), eye movement abnormalities, and bulbar signs including difficulty swallowing.

Tay-Sachs disease (GM2 gangliosidosis) is caused by deficiency of hexosaminidase A and results in the accumulation of GM2 ganglioside in cerebral gray matter and cerebellum. Infants are typically normal except for a marked startle response until 6 months of age, when they develop listlessness, irritability, hyperacusis, intellectual retardation, and retinal cherry-red spots. Within months, blindness, convulsions, spasticity, and opisthotonos develop.

Metachromatic leukodystrophy (MLD) is a lipidosid caused by deficiency of arylsulfatase that results in demyelination of the central nervous system (CNS) and peripheral nervous system. Children with the late-infantile form present between 1 and 2 years of age. After a period of normal development, progressive stiffening and ataxia of gait, spasticity, optic atrophy, intellectual deterioration, and absent reflexes occur. Diagnostic testing reveals increased cerebral spinal fluid protein (a sign of CNS demyelination) and slowing of motor nerve conduction velocity (a sign of peripheral demyelination). Older school-age children with the juvenile form of MLD may present with gradual onset of behavior difficulties and declining academic abilities, succeeded by gait difficulties, clumsiness, slurred speech, and sometimes seizures. Relentless progression is the rule. Bone marrow transplant is a treatment option, particularly if a sibling is diagnosed with MLD before symptom onset.

Krabbe disease (globoid cell leukodystrophy) is caused by a deficiency of galactocerebrosidase. Individuals with the infantile form (85% to 90% of cases) appear to be normal during the first months of life. Symptoms begin by 6 months of age and include extreme irritability, hyperpyrexia, vomiting, seizures, hypertonia, and blindness. Demyelination of the CNS and peripheral nervous system results in upper and lower motor neuron signs.
Neuronal Cereoid Lipofuscinoses

The neuronal ceroid lipofuscinoses are a group of inherited, neurodegenerative lysosomal storage disorders characterized by progressive vision loss, seizures, declining cognitive abilities, motor deterioration, and early death. Ten different types have been characterized, including infantile, late-infantile, and juvenile types.

Adrenoleukodystrophy

The adrenoleukodystrophies (ALD) are a group of X-linked neurodegenerative disorders that are often associated with adrenocortical insufficiency. ALD is caused by accumulation of very long chain fatty acids in neuronal and adrenal tissue (Chapter 178) and is diagnosed by abnormal very long chain fatty acid testing. The most common leukodystrophy is classic X-linked adrenoleukodystrophy, caused by a mutation in the ABCD1 gene. Boys present between ages 5 and 15 years with academic difficulties, behavioral disturbances, and gait abnormalities, progressing to seizures, spasticity, ataxia, and swallowing difficulties. Brain MRI demonstrates a classic pattern of symmetric abnormal white matter signal in the periaqueductal regions, with contrast enhancement at the anterior margin. Symptomatic adrenocortical insufficiency with fatigue, vomiting, and hypotension develops in 20% to 40% of patients with X-linked ALD. ALD should be considered in any male with primary adrenocortical insufficiency, even in the absence of clear-cut neurological abnormalities. Adrenomyeloneuropathy, a chronic disorder of spinal cord and peripheral nerves, presents in the third decade of life. Female carriers of the ABCD1 mutation may also have symptoms similar to adrenomyeloneuropathy, beginning later in life (>35 years of age).

Mucopolysaccharidoses

Mucopolysaccharidoses are caused by defective lysosomal hydrolases resulting in the accumulation of mucopolysaccharides within lysosomes (see Chapter 56). The clinical manifestations include coarse features, short stature, kyphoscoliosis, hepatosplenomegaly, cardiovascular abnormalities, and corneal clouding. Neurologic involvement is seen in mucopolysaccharidosis types I (Hurler syndrome), II (Hunter syndrome), III (Sanfilippo syndrome), and VII (Sly syndrome). Children with Hurler syndrome, the most severe of these illnesses, appear normal during the first 6 months of life, then develop the characteristic skeletal and neurologic features. Intellectual disability, spasticity, deafness, and optic atrophy are progressive. Hydrocephalus frequently occurs because of obstruction to cerebrospinal fluid (CSF) flow by thickened leptomeninges.

Mitochondrial Disorders

Mitochondrial diseases represent a clinically heterogeneous group of disorders that fundamentally share a disturbance in oxidative phosphorylation (adenosine triphosphate synthesis) (Chapter 57). Abrupt symptoms are often manifest concurrent with periods of physiologic stress such as febrile illness or fasting. Specific genetic diagnoses are often difficult to identify because clinical features are pleotropic within individual defects and overlap between different defects, and because analysis of mitochondrial protein function is technically demanding. Specific syndromes include MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes); MERRF (myoclonus, epilepsy, and ragged red fibers) which can also manifest as combinations of dementia, sensorineural hearing loss, optic nerve atrophy, peripheral neuropathy, and occasionally cardiomyopathy with Wolff-Parkinson-White syndrome; and NARP (neuropathy, ataxia, and retinitis pigmentosa).

Rett Syndrome

Rett syndrome is a neurodevelopmental disorder that classically affects girls. Typically, development appears normal during the first 6 to 18 months of life, followed by regression, loss of purposeful hand movements, loss of verbal communication skills, gait apraxia, and stereotypic repetitive hand movements that resemble washing, wringing, or clapping of the hands. Girls also develop acquired microcephaly. Episodic apnea and/or hyperpnea, peripheral vasomotor disturbances, growth retardation, abnormal muscle tone, and prolonged QTc interval often occur. The regression plateaus and stabilizes, but seizures, spasticity, and kYPHOSCOLIOSIS develop. The etiology is a mutation on an X chromosome gene coding for methyl-CpG-binding protein 2 transcription factor. Boys with MECP2 mutations usually do not survive to delivery, but can present with severe neonatal encephalopathy, seizures, microcephaly, abnormal tone, and respiratory insufficiency.

Degenerative Diseases with Focal Manifestations

Some neurodegenerative disorders have predilections to target specific regions or systems within the neuraxis, producing symptoms referable to the affected region.

Wilson disease is a treatable degenerative condition that exhibits signs of cerebellar and basal ganglia dysfunction. It is an autosomal recessive inborn error of copper metabolism. Serum ceruloplasmin levels are low. Abnormal copper deposition is found in the liver, producing cirrhosis; in the peripheral cornea, producing a characteristic green-brown (Kayser-Fleischer) ring; and in the CNS, producing neuronal degeneration and protoplasmic astrogliosis. Neurologic symptoms characteristically begin in the early teenage years with dysarthria, dysphasia, drooling, fixed smile, tremor, dystonia, and emotional lability. MRI shows abnormalities of the basal ganglia. Treatment is with a copper-chelating agent, such as oral penicillamine.

Subacute necrotizing encephalomyelopathy, or Leigh disease, is a neuropathologically defined, degenerative inherited CNS disease primarily involving the periaqueductal region of the brainstem, caudate, and putamen. Symptoms usually begin before 2 years of age and consist of hypotonia, feeding difficulties, respiratory irregularity, weakness of extraocular movements, and ataxia. Blood and CSF lactate and pyruvate levels are elevated. Several alterations of mitochondrial function produce this clinical syndrome.
ACQUIRED ILLNESSES MIMICKING DEGENERATIVE DISEASES

Children with poorly controlled epilepsy may be continuously in either an ictal or a postictal state and may appear stuporous because of their epileptic encephalopathy. Antiepileptic drugs that are sedating or affect mood, memory, motivation, or attention may contribute to the lack or loss of developmental abilities and school failure. Use of high doses or multiple anticonvulsants may compound this problem.

Chronic drug use or overuse (sedatives, tranquilizers, anticholinergics) can bring about progressive confusion, lethargy, and ataxia. Intoxications with heavy metals, such as lead, may cause chronic learning difficulties or may present acutely with irritability, listlessness, anorexia, and pallor, progressing to fulminant encephalopathy. Vitamin deficiency of thiamine, niacin, vitamin B₁₂, and vitamin E can produce encephalopathy, peripheral neuropathy, and ataxia.

Congenital and acquired hypothyroidism impairs cognition and retards developmental progress. Unrecognized congenital hypothyroidism produces irreversible damage if it is not treated immediately after birth (Chapter 175).

Structural brain diseases, such as hydrocephalus and slowly growing tumors, may mimic dementia. Certain indolent brain infections, such as rubella (measles, causing subacute sclerosing panencephalitis), rubella (German measles), syphilis, and some fungal infections, cause neurologic deterioration over months and years. Congenital human immunodeficiency virus infection causes failure of normal development and regression of acquired skills.

Psychiatric disorders, such as depression and severe psychosocial deprivation in infancy, can give rise to apathy and failure to attain developmental milestones (Chapter 21). Children with autism spectrum disorder may go through a phase of developmental stagnation or disintegration at about 12 to 18 months of age after a period of early normal milestones. Depression in older children can lead to blunting of affect, social withdrawal, and poor school performance, which raise the question of encephalopathy or dementia.

The cardinal features of neurofibromatosis are café au lait spots, axillary or inguinal freckling, cutaneous neurofibromas, and iris hamartomas (Lisch nodules). Café au lait spots are present in more than 90% of patients who have NF1 (Fig. 186-1). They typically appear in the first few years of life and increase in number and size over time. The presence of six or more café au lait spots on the trunk without a family history of NF1 is suggestive of the disease.

NEUROFIBROMATOSIS TYPE 1

Etiology

Neurofibromatosis type 1 (NF1), also known as von Recklinghausen disease, is an autosomal-dominant disorder with an incidence of approximately 1 in 3000. It is caused by mutations of the NF1 gene, which codes for a tumor suppressor gene, neurofibromin. Neurofibromin is a major negative regulator of a key signal transduction pathway, the Ras pathway. Mutations result in increased downstream mitogenic signaling. Somatic mosaicism, in which an abnormality in one copy of the NF1 gene is present in some cells but not others, indicates a postzygotic mutation and is called segmental neurofibromatosis.

Clinical Manifestations

The cardinal features of neurofibromatosis are café au lait spots, axillary or inguinal freckling, cutaneous neurofibromas, and iris hamartomas (Lisch nodules). Café au lait spots are present in more than 90% of patients who have NF1 (Fig. 186-1). They typically appear in the first few years of life and increase in number and size over time. The presence of six or more café au lait spots on the trunk without a family history of NF1 is suggestive of the disease.

Decision-Making Algorithms

Available @ StudentConsult.com

Hearing Loss
Gynecomastia

more café-au-lait spots larger than 5 mm in a prepubescent child suggests the diagnosis. **Lisch nodules** also increase in frequency with age and are present in more than 90% of adults who have NF1.

**Neurofibromatosis** are composed of various combinations of Schwann cells, fibroblasts, mast cells, and vascular elements. Dermal neurofibromas are nearly universal and consist of discrete, small, soft lesions that lie within the dermis and epidermis and move passively with the skin. They rarely cause any symptoms, but can cause significant cosmetic concerns. Neurofibromas may also be situated within viscera or along blood vessels and peripheral nerves. Plexiform neurofibromas are large, occasionally nodular, subcutaneous lesions that lie along the major peripheral nerve trunks. They often cause symptoms including pain, weakness, and invasion of adjacent viscera, bone, or spinal cord. Sarcomatous degeneration may occur. Surgical treatment may be attempted, but results are often unsatisfactory.

Common complications are learning disability, scoliosis, seizures, and cerebral vasculature abnormalities. Other tumors that occur in NF1 are optic nerve gliomas, astrocytomas of brain and spinal cord, and malignant peripheral nerve tumors. T2-weighted magnetic resonance images (MRI) reveal hyperintense lesions (hamartomas) in the optic tracts, internal capsule, thalamus, cerebellum, and brainstem that are common and distinctive for the disease. They are benign and disappear in adulthood.

The average life expectancy of patients with NF1 may be reduced by 10 to 15 years. Malignancy is the most common cause of death. Genetic and psychological counseling are important components of care for this chronic disorder. Although it is an autosomal dominant disorder, spontaneous mutations account for 30% to 50% of cases.

**Neurofibromatosis Type 2**

Neurofibromatosis type 2 (NF2) is an autosomal-dominant disorder with an incidence of 1 in 25,000. Half the cases have no family history. The NF2 gene is a tumor suppressor gene, and disease results in neurologic, eye, and skin lesions. NF2 predisposes patients to multiple intracranial and spinal tumors, including bilateral acoustic schwannomas, schwannomas of other cranial and spinal nerves, meningoïdomas, and gliomas. Posterior capsular or cortical cataracts are common, and skin lesions include plaque-like lesions, subcutaneous nodules, and cutaneous schwannomas. Lisch nodules, café au lait spots, and axillary freckling are not features of NF2.

**TUBEROUS SCLEROSIS COMPLEX**

**Etiology**

Tuberous sclerosis complex (TSC), an autosomal dominant disorder, is characterized by hamartomas in many organs, especially the brain, eyes, skin, kidneys, and heart. The incidence is 1 in 10,000 births. Two thirds of cases are sporadic and thought to represent new mutations. Germline mosaicism is uncommon, but explains how parents who apparently do not have the disease can have multiple children with tuberous sclerosis. Mutations affecting either of the presumed tumor suppressor genes, TSC1 or TSC2, cause tuberous sclerosis. The TSC1 and TSC2 genes encode distinct proteins, hamartin and tuberin, which are widely expressed in the brain and result in constitutive activation of the protein kinase mTOR (mammalian target of rapamycin), leading to the formation of numerous benign tumors (hamartomas).

**Clinical Manifestations**

TSC is an extremely heterogeneous disease with variable expression and a wide clinical spectrum varying from normal intelligence without seizures to severe mental retardation with refractory seizures, often within the same family. Tuberous sclerosis is one of the most common causes of infantile spasms. These children often develop intractable epilepsy, mental retardation, autism, and hyperactivity. Patients may have retinal lesions (retinal hamartomas, white depigmented patches) and brain lesions (cortical tubers, subependymal nodules, hydrocephalus). **Tubers** in the cerebral cortex are areas of dysplasia that, in combination with other microscopic areas of abnormal development, are responsible for the symptoms of mental retardation and epilepsy. **Subependymal nodules** are hamartomas that may mutate into a growth phase and become subependymal giant cell astrocytomas causing obstruction of cerebrospinal fluid outflow and resultant hydrocephalus. **Extracerebral manifestations** include typical skin findings of hypomelanotic macules (**ash leaf spots**) which are easiest to visualize under a Wood ultraviolet lamp and are apparent in infancy. Facial angiofibromas (**adenoma sebaceum**) appear as small red nodules over the nose and cheeks that are sometimes confused with acne. **Shagreen patches** are elevated, rough plaques of skin with a predilection for the lumbar and gluteal regions that develop in late childhood or early adolescence. Cardiac rhabdomyomas are largest during prenatal life and infancy and are rarely symptomatic. Occasionally, they may cause arrhythmias or cardiac outflow obstruction. Renal angiomyolipomas may undergo malignant transformation and are the most common cause of death in adults with TSC. Interstitial pulmonary disease also affects adults with TSC (pulmonary lymphangioleiomyomatosis).

**STURGE-WEBER SYNDROME**

Sturge-Weber syndrome is sporadic (not inherited) and characterized by abnormal blood vessels (**angiomas**) of the leptomeninges overlying the cerebral cortex in association with an ipsilateral facial **port-wine stain** involving the ophthalmic division of the trigeminal nerve (forehead and upper eyelid) and, often, glaucoma. The port-wine stain, also known as nevus flammeus, is due to an ectasia of superficial venules and may have a much more extensive and even bilateral distribution. Not all children with a facial port-wine stain have Sturge-Weber syndrome.

MRI with contrast demonstrates leptomeningeal angiomia and white matter abnormalities thought to be due to chronic hypoxia and atrophy. Angiomas produce venous engorgement and, presumably, stasis within the involved areas, which are thought to result in hypoxia. Patients present with seizures, hemiparesis, stroke-like episodes, headaches, mental retardation, and learning disabilities. Seizures are the most common associated neurologic abnormality, occurring in 75% of patients, and develop because of ischemic injury to the brain. Many children with Sturge-Weber syndrome are intellectually normal, and seizures are well controlled with standard anticonvulsants. However, progressive ischemia of the underlying
brain develops in some children with Sturge-Weber syndrome, resulting in hemiparesis, hemianopia, intractable focal seizures, and cognitive impairment. Hemispherectomy has been proposed for individuals with unilateral disease whose seizures are difficult to control. Intellectual and motor outcome seems improved, compared with ongoing anticonvulsant drug treatment, but the surgical risks and sequelae of the procedure are considerable. Pulse dye laser surgery is the most promising therapeutic option for cosmetic management of the facial nevus flammeus. Expert ophthalmologic management of glaucoma is required. Endocrinology evaluations are also necessary, as these patients often have growth hormone deficiency and/or hypothyroidism.

### CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM

Central nervous system malformations include disorders of spinal cord and neural tube formation, structure specification (neuronal migration, gray matter), brain growth and size, and skull growth and shape.

The precursor of the nervous system is the neural plate of the embryonic ectoderm, which develops at 18 days of gestation. The neural plate gives rise to the neural tube, which forms the brain and spinal cord, and neural crest cells, which form the peripheral nervous system, meninges, melanocytes, and adrenal medulla. The neural tube begins to form on day 22 of gestation. The rostral end forms the brain, and the caudal region forms the spinal cord. The lumen of the neural tube forms the ventricles of the brain and the central canal of the spinal cord. Most brain malformations are produced by a variety of injuries occurring during a vulnerable period of gestation. Precipitating factors include chromosomal, genetic, and metabolic abnormalities; infections (toxoplasmosis, rubella, cytomegalovirus, herpes); and exposure to irradiation, certain drugs, and maternal illness during pregnancy.

#### CONGENITAL ANOMALIES OF THE SPINAL CORD

**Etiology and Clinical Manifestations**

Defective closure of the caudal neural tube at the end of week 4 of gestation results in anomalies of the lumbar and sacral vertebrae or spinal cord called spina bifida. These anomalies range in severity from clinically insignificant defects of the L5 or S1 vertebral arches to major malformations, leaving the spinal cord uncovered by skin or bone on the infant’s back. The latter severe defect, called a myelomeningocele, results in flaccid paralysis and loss of sensation in the legs and incontinence of bowel and bladder, with the extent and degree of neurologic deficit dependent on the location of the myelomeningocele. In addition, affected children usually have an associated Chiari type II malformation (downward displacement of the cerebellar tonsils and medulla), resulting in hydrocephalus and weakness of face and swallowing. In a meningocele, the spinal canal and cystic meninges are exposed on the back, but the underlying spinal cord is anatomically and functionally intact. In spina bifida occulta, the skin of the back is apparently intact, but defects of the underlying bone or spinal canal are present. Meningoceles and spina bifida occulta may be associated with a lipoma, dermoid cyst, or tethering of the cord to a thick filum terminale. A dimple or tuft of hair may be present over the affected area. Patients may also have an associated dermoid sinus, an epithelial tract extending from the skin surface to the meninges; this increases the risk of meningitis. Patients with spina bifida occulta or meningocele may have weakness and numbness in the feet that can result in recurrent ulcerations, or difficulties controlling bowel or bladder function that may result in recurrent urinary tract infections, reflux nephropathy, and renal insufficiency. In diastematomyelia, a bone spicule or fibrous band divides the spinal cord into two longitudinal sections. An associated lipoma that infiltrates the cord and tethers it to the vertebrae may be present. Symptoms include weakness and numbness of the feet and urinary incontinence.

#### Diagnostic Studies

Myelomeningocele in the fetus is suggested by an elevated alpha-fetoprotein in the mother’s blood and confirmed by ultrasound and high concentrations of alpha-fetoprotein and acetylcholinesterase in the amniotic fluid. After birth, screening ultrasound may be used with magnetic resonance imaging to confirm less dramatic underlying spinal abnormalities.

#### Treatment and Prevention

Neonates with myelomeningocele must undergo operative closure of the open spinal defects (fetal or postnatal surgery) and often require treatment of hydrocephalus by placement of a ventriculoperitoneal shunt. Toddlers and children with lower spinal cord dysfunction require physical therapy, bracing of the lower extremities, and intermittent bladder catheterization. In the absence of associated brain anomalies, most survivors have normal intelligence, but learning problems and epilepsy are more common than in the general population.

Spina bifida can be prevented in many cases by folate administration to the pregnant mother. Because the defect occurs so early in gestation, all women of childbearing age are advised to take oral folic acid daily.

#### CONGENITAL MALFORMATIONS OF THE BRAIN

Defective closure of the rostral neural tube produces anencephaly or encephaloceles. Neonates with anencephaly have a rudimentary brainstem or midbrain, but no cortex or cranium. This is rapidly fatal after delivery. Patients with encephalocele usually have a skull defect and exposure of meninges alone or meninges and brain. The recurrence risk in subsequent
pregnancies for either cranial or spinal neural tube defects is 3% to 4%. Within a family, an anencephalic birth may be followed by the birth of a child affected with a lumbosacral myelomeningocele. The inheritance of neural tube defects is polygenic.

**Agenesis of the corpus callosum** may be partial or complete and may occur in an isolated fashion or in association with other anomalies of cellular migration. **Dandy-Walker malformation** is diagnosed on the basis of the classic triad: complete or partial agenesis of the cerebellar vermis, cystic dilation of the fourth ventricle, and enlarged posterior fossa. There may be associated hydrocephalus, absence of the corpus callosum, and neuronal migration abnormalities. Intelligence may be normal or impaired, depending on the degree of associated cerebral dysgenesis.

**Holoprosencephaly** represents varying degrees of failure of the forebrain (prosencephalon) to divide into two distinct cerebral hemispheres. Holoprosencephaly is often associated with midline facial defects (hypotelorism, cleft lip, cleft palate). This anomaly may be isolated or associated with a chromosomal or genetic disorder. The prognosis for infants with severe (alobar) holoprosencephaly is uniformly poor, but those with milder forms (semilobar, or lobar) may have less severe neurological outcomes. Children with trisomy 13 and trisomy 18 characteristically have varying degrees of holoprosencephaly.

**Hydranencephaly** is a condition in which the brain presumably develops normally, but then is destroyed by an intrauterine, probably vascular, insult. The result is virtual absence of the cerebrum with an intact skull. The thalamus, brainstem, and some occipital cortex are typically present. Children may have a normal external appearance at the time of birth, but do not achieve developmental milestones.

### Table 187-1 | Causes of Macrocephaly

<table>
<thead>
<tr>
<th>Macrocrania (increased skull thickness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achondroplasia</td>
</tr>
<tr>
<td>Hypochondroplasia</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
</tr>
<tr>
<td>Osteopetrosis</td>
</tr>
<tr>
<td>Chronic, severe anemia</td>
</tr>
<tr>
<td>Hydrocephalus (enlargement of the ventricles; see Chapter 184)</td>
</tr>
<tr>
<td>Masses</td>
</tr>
<tr>
<td>Cysts</td>
</tr>
<tr>
<td>Arteriovenous malformations</td>
</tr>
<tr>
<td>Subdural fluid collections/hematoma</td>
</tr>
<tr>
<td>Neoplasm</td>
</tr>
<tr>
<td>Megalencephaly (enlargement of the brain)</td>
</tr>
<tr>
<td>Embryologic disorder causing abnormal proliferation of brain tissue</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td>Sturge-Weber syndrome</td>
</tr>
<tr>
<td>Sotos syndrome</td>
</tr>
<tr>
<td>Riley-Smith syndrome</td>
</tr>
<tr>
<td>Hemi-megalencephaly</td>
</tr>
<tr>
<td>Accumulation of abnormal metabolic substances</td>
</tr>
<tr>
<td>Alexander disease</td>
</tr>
<tr>
<td>Canavan disease</td>
</tr>
<tr>
<td>Gangliosidoses</td>
</tr>
<tr>
<td>Mucopolysaccharidoses</td>
</tr>
<tr>
<td>Benign causes</td>
</tr>
<tr>
<td>Benign extracerebral collections of infancy</td>
</tr>
<tr>
<td>Familial macrocephaly</td>
</tr>
</tbody>
</table>

### Macrocephaly and Microcephaly

Macrocephaly represents a head circumference above the 97th percentile and may be the result of macrocrania (increased skull thickness), hydrocephalus (enlargement of the ventricles; see Chapter 184), or megalencephaly (enlargement of the brain). Diseases of bone metabolism or hypertrophy of the bone marrow cause macrocrania. Megalencephaly may be the result of a significant disorder of brain development or an accumulation of abnormal metabolic substances (Table 187-1). Most often, however, macrocephaly is a familial trait of no clinical significance. If the child is developmentally normal but has macrocephaly, plotting the parents’ head circumference on a growth chart can provide reassurance and help to avoid unnecessary neurodiagnostic testing.

Microcephaly represents a head circumference below the 3rd percentile. Myriad syndromes and metabolic disorders are associated with microcephaly, some of which are hereditary (Table 187-2). In most instances, a small head circumference is a reflection of a small brain. Brain growth is rapid during the perinatal period, and any insult (infectious, metabolic, toxic, vascular) sustained during this period or during early infancy is likely to impair brain growth and result in microcephaly. Rarely, a small head is the result of premature closure of one or more skull sutures, called craniosynostosis. This diagnosis is readily made by the abnormal shape of the skull. As a rule, macrocephaly and microcephaly raise a concern about cognitive ability, but head circumference alone should never be used to establish a prognosis for intellectual development.

### Disorders of Neuronal Migration

Many malformations result from the failure of normal migration of neurons from the periventricular germinal matrix zone to the cortical surface at 1 to 5 months of gestation. Multiple malformations may exist in the same patient. Neurologic development with these anomalies varies and depends on the type and extent of the malformation.

**Schizencephaly** is characterized by clefts within the cerebral hemispheres that extend from the cortical surface to the ventricular cavity. Unilateral clefts may cause isolated congenital hemiparesis, whereas bilateral schizencephaly causes spastic quadriplegia and associated intellectual disability. Affected individuals are at high risk for focal epilepsy.

A severe defect in cortical migration, **lissencephaly** results in a smooth brain without sulcation (agyria). The normal six-layered cortex does not develop. Affected children have difficult-to-control seizures and profound developmental retardation. This anomaly most commonly is part of a genetic disorder, which may be X-linked (DCX mutations) or caused by de novo autosomal dominant gene mutations (Lis-1 mutations). In **pachygyria**, the gyri are few in number and too
broad. In **polymicrogyria**, the gyri are too many and too small. Sometimes pachygyria and polymicrogyria affect an entire hemisphere, producing enlargement of that hemisphere and a clinical syndrome of severe, medically intractable seizures that begin in early infancy. **Gray matter heterotopias** are abnormal islands within the central white matter of neurons that have never completed the migratory process.

**ACKNOWLEDGMENT**
The authors thank Dr. James Dowling for his generous help in preparing Chapter 182 on weakness and hypotonia.

**Table 187-2 Causes of Microcephaly**

<table>
<thead>
<tr>
<th>PRIMARY MICROCEPHALY</th>
<th>SECONDARY (ACQUIRED) MICROCEPHALY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microcephaly vera</strong></td>
<td>Infections (congenital)</td>
</tr>
<tr>
<td>Chromosomal disorders</td>
<td>Rubella</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>Syphilis</td>
</tr>
<tr>
<td>5p microdeletion</td>
<td>Human immunodeficiency virus (HIV)</td>
</tr>
<tr>
<td>Angelman syndrome</td>
<td></td>
</tr>
<tr>
<td>Prader-Willi syndrome</td>
<td></td>
</tr>
<tr>
<td>Central nervous system (CNS) malformation</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Encephalocoele</td>
<td>Stroke</td>
</tr>
<tr>
<td>Hydranencephaly</td>
<td>Toxic</td>
</tr>
<tr>
<td>CNS migrational disorder</td>
<td>Radiation exposure—fetal</td>
</tr>
<tr>
<td>Lissencephaly</td>
<td>Fetal alcohol syndrome</td>
</tr>
<tr>
<td>Schizencephaly</td>
<td>Maternal phenylketonuria</td>
</tr>
<tr>
<td>Pachygyria</td>
<td>Hypoxic-ischemic or other severe brain injury</td>
</tr>
<tr>
<td>Micropolygyria</td>
<td>Periventricular leukomalacia</td>
</tr>
<tr>
<td>Agenesis of the corpus callosum</td>
<td>Systemic disease</td>
</tr>
<tr>
<td>Sex-linked microcephaly syndromes</td>
<td>Chronic cardiac or pulmonary disease</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>Chronic renal disease</td>
</tr>
<tr>
<td>Cornelia de Lange syndrome</td>
<td>Malnutrition</td>
</tr>
<tr>
<td>Seckel dwarfism syndrome</td>
<td></td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>Craniosynostosis totalis</td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
<td></td>
</tr>
<tr>
<td>Hallermann-Streiff syndrome</td>
<td></td>
</tr>
</tbody>
</table>

**Suggested Reading**
ASSESSMENT

Approximately one in three Americans of any age has at least one recognizable skin disorder at any time. The most common cutaneous diseases encountered in community settings are dermatophytosis, acne vulgaris, seborrheic dermatitis, atopic dermatitis (eczema), verrucae (warts), tumors, psoriasis, vitiligo, and infections such as herpes simplex and impetigo. In children attending pediatric dermatology clinics, atopic dermatitis, impetigo, tinea capitis, acne vulgaris, verrucae vulgaris, and seborrheic dermatitis are the most common diagnoses.

HISTORY

The age of the patient, onset, duration, progression, associated cutaneous symptoms (pain, pruritus), and associated systemic signs or symptoms (fever, malaise, weight loss) are important clues. Obtaining an accurate description of the original lesion improves diagnostic accuracy. Over-the-counter remedies may alter the appearance of a rash dramatically. Patients often do not consider a topical antibiotic or anti-itch medication as treatment. Thus it is important to probe deeply with related questions in the history. Other important information includes a history of allergies, environmental exposure, travel history, previous treatment, affected contacts, and family history.

PHYSICAL EXAMINATION

A careful examination of the skin requires a visual and a tactile assessment. Examination of the skin over the entire body must be performed systematically. Mucous membranes, hair, nails, and teeth, all of ectodermal origin, also may be involved in cutaneous disorders and should be assessed.

COMMON MANIFESTATIONS

<table>
<thead>
<tr>
<th>Table 188-1</th>
<th>Primary Skin Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LESION</strong></td>
<td><strong>DESCRIPTION</strong></td>
</tr>
<tr>
<td>Macule</td>
<td>Flat, nonpalpable lesion &lt;1 cm in diameter</td>
</tr>
<tr>
<td>Patch</td>
<td>Similar to macule, but &gt;1 cm in diameter</td>
</tr>
<tr>
<td>Papule</td>
<td>Elevated, solid lesion &lt;1 cm in diameter</td>
</tr>
<tr>
<td>Plaque</td>
<td>Similar to papule, but &gt;1 cm in diameter; has a flat and broad surface in contrast to a nodule</td>
</tr>
<tr>
<td>Nodule</td>
<td>Similar to papule, but &gt;1 cm in diameter; has a rounded surface in contrast to a plaque</td>
</tr>
<tr>
<td>Tumor</td>
<td>Similar to nodule, but implies a neoplastic growth rather than an inflammatory process</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Fluid-filled (usually clear or straw-colored) epidermal lesion &lt;1 cm in diameter</td>
</tr>
<tr>
<td>Bulla</td>
<td>Similar to vesicle, but &gt;1 cm in diameter</td>
</tr>
<tr>
<td>Pustule</td>
<td>Pus-filled epidermal lesion, which may have an initial papular phase and often is surrounded by erythema</td>
</tr>
<tr>
<td>Purpura</td>
<td>Macule or papule resulting from extravasated blood into the skin; does not blanch with pressure</td>
</tr>
<tr>
<td>Petechia</td>
<td>Similar to purpura, but less than a few millimeters in diameter</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>Larger, hemorrhagic patch or plaque resulting from extravasated blood</td>
</tr>
<tr>
<td>Wheal (hive)</td>
<td>Pink, edematous papules and plaques that vary greatly in size and configuration; characterized by transient nature with individual lesions resolving within 24 hours</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>Collection of small superficial red blood vessels</td>
</tr>
<tr>
<td>Milia</td>
<td>Superficial, white, small epidermal keratin cysts</td>
</tr>
<tr>
<td>Comedo</td>
<td>Plug of keratin and sebum within the orifice of a hair follicle, which can be open (whitehead) or closed (blackhead); characteristic lesion of acne vulgaris</td>
</tr>
<tr>
<td>Cyst</td>
<td>Papule or nodule with an epidermal lining composed of fluid or solid material</td>
</tr>
</tbody>
</table>

A descriptive nomenclature of skin lesions helps with generating a differential diagnosis and also with communication between health care providers. Determination of the primary lesion and secondary change is the cornerstone of dermatologic diagnosis. A **primary lesion** is defined as the basic lesion that arises de novo and is most characteristic of the disease process (Table 188-1 and Fig. 188-1). Primary lesions are rarely seen on a patient at the time of presentation, as most lesions are altered by time or external factors such as...
medication applied, secondary infection, or physical manipulation (e.g., scratching). A search for the primary lesion often proves worthwhile and focuses the differential diagnosis to a category of lesion that is specific for the underlying diagnosis. On occasion, two different types of primary lesions may be present. In most cases, secondary lesions are the residue, or result, of the effects of the primary lesion. They may be created by scratching or secondary infection and may be seen in the absence of a primary lesion (Table 188-2).

The color, texture, configuration, location, and distribution of the lesion should be recorded. A localized or grouped eruption may suggest a cutaneous infection, whereas widespread, symmetrical involvement of extensor surfaces may suggest a primary skin disorder, such as psoriasis. Herpesvirus lesions are usually grouped lesions. Annular lesions may suggest Lyme disease, syphilis, and fungal infections. Lesions on mucous membranes are usually short-lived, and lesions in thick-skinned areas, such as the palms and soles, may be particularly difficult to characterize.

### INITIAL DIAGNOSTIC EVALUATION AND TESTS

A thorough history and physical examination are usually sufficient for diagnosis because of the visibility of the skin. Adjunctive tests at the time of examination include potassium hydroxide (KOH) examination for fungi and dermatophytes, skin scrapings for scabies, cytologic examination (Tzanck test) for herpesvirus and varicella-zoster virus infection, and Wood light examination for the yellowish gold fluorescence of tinea versicolor. A skin biopsy may be performed to help with the diagnosis. The biopsy specimen can be accomplished by either shave or punch biopsy, and both are simple, in-office procedures. Occasionally, laboratory or imaging studies are necessary.

<table>
<thead>
<tr>
<th>Table 188-2</th>
<th>Secondary Skin Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LESION</strong></td>
<td><strong>DESCRIPTION</strong></td>
</tr>
<tr>
<td>Scale</td>
<td>Results from abnormal keratinization; may be fine or sheetlike</td>
</tr>
<tr>
<td>Crust</td>
<td>Dried collection of serum and cellular debris</td>
</tr>
<tr>
<td>Erosion</td>
<td>Shallow depression with loss of the superficial epidermis</td>
</tr>
<tr>
<td>Ulcer</td>
<td>Deeper depression with loss of the entire epidermis into dermis; heals with scarring</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Thinning of epidermis (surface appears shiny and translucent) or dermis (skin is depressed)</td>
</tr>
<tr>
<td>Scar</td>
<td>Thickened, firm, and discolored collection of connective tissue that results from dermal damage; initially pink, but lightens with time</td>
</tr>
<tr>
<td>Sclerosis</td>
<td>Circumscribed or diffuse hardening of skin</td>
</tr>
<tr>
<td>Lichenification</td>
<td>Accentuated skin lines/markings that result from thickening of the epidermis</td>
</tr>
<tr>
<td>Excoriation</td>
<td>Superficial linear erosion that is caused by scratching</td>
</tr>
<tr>
<td>Fissure</td>
<td>Linear break within the skin surface that usually is painful</td>
</tr>
</tbody>
</table>
ACNE

ETIOLOGY
Acne vulgaris (or acne) is a chronic inflammatory disorder that affects areas with the greatest concentration of sebaceous glands, such as the face, chest, and back. The pathogenesis of acne is multifactorial. Gender, age, genetic factors, and environment are all major contributing factors. Stress may trigger acne, possibly by affecting hormone levels. There is no evidence linking chocolate, candy, or fried foods to acne.

Acne is caused by chronic inflammation of the pilosebaceous unit (hair follicle with an associated sebaceous gland). The primary event in all acne lesions is the development of the micro-comedo, which results from the obstruction of the hair follicle with keratin, increased sebum production from sebaceous glands, and overgrowth of normal skin flora, leading to pilosebaceous occlusion and enlargement. Androgens are a potent stimulus of the sebaceous gland. The subsequent inflammatory component and pustule formation results from proliferation of Propionibacterium acnes, a commensal organism of the skin. The pathogenesis of acne thus involves three components: increased sebum production, hyperkeratosis, and bacterial proliferation. Effective treatment focuses on minimizing these factors.

CLINICAL MANIFESTATIONS
Acne primarily affects areas with increased sebaceous gland density, such as the face, upper chest, and back. Superficial plugging of the pilosebaceous unit results in noninflammatory small (1- to 2-mm) open (blackhead) and closed (whitehead) comedones. An open comedo is less likely to become inflammatory than a closed comedo. Rupture of a comedo into adjacent dermis and proliferation of P. acnes induce an inflammatory response and development of inflammatory papules and pustules. Larger, skin-colored or red cysts and nodules represent deeper plugging and cystic acne. Increased and persistent inflammation, especially with rupture of a deep cyst, increases the risk of scarring.

The diagnosis of acne is usually not difficult because of the characteristic and chronic lesions. Laboratory studies and imaging studies are usually not necessary to diagnose acne. Screening tests may be necessary if there are signs of hyperandrogenism due to polycystic ovarian syndrome (irregular menses, hirsutism, insulin resistance) or an underlying androgen-secreting tumor (irregular menses, hirsutism, deepening voice, clitoromegaly).

COMPLICATIONS
Acne has significant and frequently devastating effects on an adolescent’s body image and self-esteem. There may be little correlation between severity and psychosocial impact. Scarring may result in permanent morbidity.

PROGNOSIS
Classically, acne lasts 3 to 5 years, although some individuals may have disease for 15 to 20 years. Only early treatment with isotretinoin may alter the natural course of acne. Acne lesions often heal with temporary postinflammatory erythema and hyperpigmentation. Depending on the severity, chronicity, and depth of involvement, pitted, atrophic, or hypertrophic scars may develop. Cystic acne has the highest incidence of
scarring because rupture of a deep cyst induces the greatest inflammation, though scarring may be caused by milder pustular or even comedonal acne.

**PREVENTION**
Greasy hair and cosmetic preparations should be avoided because they exacerbate preexisting acne. There are no effective means for preventing acne, and there is little evidence that diet is associated with acne. Repetitive cleansing with soap and water or use of astringents or abrasives removes only surface lipids. Their use makes the skin appear less oily but does not prevent formation of microcomedones and may paradoxically worsen acne.

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**ATOPIC DERMATITIS**

**ETIOLOGY**
Atopic dermatitis is a chronic inflammatory disease with no known cure. It is associated with significant psychosocial morbidity and decreased health-related quality of life. For many affected individuals, atopic dermatitis is the skin manifestation of atopy accompanied by asthma and allergic rhinitis.

Atopic dermatitis manifests with a defective skin barrier, reduced innate immune responses, and exaggerated immune responses to allergens and microbes. Both genetic predisposition and environmental factors play a role in the development of atopic dermatitis. Genes associated with skin barrier dysfunction and inflammation have been linked with atopic dermatitis. Inflammatory mediators involved include predominantly T helper cells, with the Th2 pathway implicated early in acute lesions and a Th1 predominance found in chronic lesions. Langerhans cells, IgE, and eosinophils play a prominent role, as well as many other inflammatory mediators. Environmental and contact allergens, infections, irritants, extremes of temperature, sweat, and lack of humidity can exacerbate the condition, as can scratching or rubbing. Triggers are somewhat variable from individual to individual.

**EPIDEMIOLOGY**
Atopic dermatitis is the most common skin disease in children, with an estimated prevalence of up to 20% of children. Only 1% to 2% of adults manifest disease. In addition to genetic factors, an environmental influence contributes. Atopic dermatitis occurs more frequently in urban areas and in higher socioeconomic classes. Prevalence is lower in areas where industrial pollution is less and where eosinophil-mediated infections such as helminthic infections are endemic.

Patients generally have a family history of atopy. Children with atopic dermatitis are predisposed to the development of allergy and allergic rhinitis, referred to as the atopic march. Asthma develops in up to half of children with atopic dermatitis, and allergic rhinitis even more frequently. Food allergies are commonly associated with atopic dermatitis.

**CLINICAL MANIFESTATIONS**
Atopic dermatitis is a chronic, relapsing skin disease characterized by xerosis, pruritus, and characteristic skin findings. The condition generally improves with age and remits in adulthood, although some childhood cases will continue into adulthood.

Characteristic lesions of atopic dermatitis are erythematous papules or plaques with ill-defined borders and overlying scale or hyperkeratosis. Lesions can be secondarily excoriated or have an overlying crust that is yellow or hemorrhagic. Weeping may be present in acute stages. Lichenification is found in older lesions. Formation of fissures is common in both acute and chronic lesions. Temporary hypo- and hyperpigmentation can be seen after lesions resolve, but atopic dermatitis is not usually scarring unless secondary features become severe (e.g., infection or physical manipulation [scratching]).

Characteristic locations vary with the age of the patient. Infantile atopic dermatitis typically affects the face and extensor surfaces of the extremities and is often generalized. Childhood lesions predominate in flexural surfaces (ante-cubital and popliteal fossae), wrists, ankles, hands, and feet (Fig. 190-1). The adult phase occurs after puberty and manifests in the flexural areas including the neck, as well as predominant involvement on the face, dorsa of the hands, fingers and toes, and the upper arms and back.

Secondary bacterial infection, most commonly with Staphylococcus aureus or less commonly with Streptococcus pyogenes, is frequently present. Patients are at increased risk for infections with cutaneous viruses and can develop disseminated skin infections with viruses such as herpes simplex virus (eczema herpeticum), varicella-zoster virus, smallpox virus (eczema vaccinatum), and molluscum contagiosum. Atopic skin is more susceptible to fungal infections as well.

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**Figure 190-1** Atopic dermatitis (arm).
Signs of concomitant infection include acute worsening of disease in an otherwise well-controlled patient, resistance to standard therapy, fever, and presence of pustules, fissures, or exudative or crusted lesions (Fig. 190-2). Eczema herpeticum and eczema vaccinatum can be life threatening if not treated.

LABORATORY AND IMAGING STUDIES
Diagnosis of atopic dermatitis is based on clinical signs and symptoms. Skin biopsy findings are generally characteristic but not exclusively diagnostic and can overlap with other skin conditions. Peripheral blood eosinophilia and elevated IgE levels can be found but are not specific. Skin prick testing or measurement of specific IgE antibody levels can detect sensitization to food and environmental allergens, although false-positive findings occur.

DIFFERENTIAL DIAGNOSIS
The differential diagnosis of atopic dermatitis is extensive, but the history of a relapsing pruritic condition in the setting of atopy and skin lesions in a characteristic distribution is typical.

The lesions of seborrheic dermatitis have circumscribed and well-defined borders. The scale or hyperkeratosis is thicker, greasy, and yellowish. The distribution of seborrheic dermatitis is different from that of atopic dermatitis, typically involving the scalp, eyebrows, perinasal region, upper chest, and back. Occasionally the two conditions coexist.

Psoriasis tends to localize on the elbows, knees, lower back, and scalp. The lesions of psoriasis on exposed surfaces are salmon color at the base with an overlying hyperkeratosis that is much thicker with silver coloration. They are generally very well demarcated, oval or round, thick plaques.

Allergic contact dermatitis has a distribution limited to one area of the body corresponding to contact with the allergen. The lesions generally make bizarre, linear, square, or angulated shapes corresponding to the source. Nickel dermatitis is common and results from contact sensitization to nickel in metals. It occurs in characteristic locations, such as the periumbilical area (where metal from pant buttons rub against skin); on the ear lobe or neck (where earrings contact skin); circumferentially around the neck (necklaces); and under rings or wristbands. Patients with atopic dermatitis can have concomitant contact dermatitis as well.

TREATMENT
Ideal therapy for atopic dermatitis includes three main components: frequent liberal use of bland emollients to restore the skin barrier, avoidance of triggers of inflammation, and use of topical anti-inflammatory medication to affected areas of skin when needed. Control of pruritus and infection should be considered on an individual basis. If topical therapy and these measures are inadequate, systemic therapy with immunosuppressive agents or ultraviolet light therapy may be indicated.

A daily short bath with warm but not hot water is generally recommended, although this is controversial and there are some who advocate less frequent bathing. A moisturizing cream or ointment should be applied to the entire body immediately afterward to trap moisture. Application of topical medications is also most effective immediately after bathing. Additional information for patients and families can be found at the website of the National Eczema Association for Science and Education (http://www.nationaleczema.org).

Common triggers of inflammation in atopic dermatitis include rubbing or scratching, contact with saliva or foods that are acidic, soaps and detergents, fabric softeners, wool or other harsh materials, fragranced personal care products, sweat, highly chlorinated pools, low humidity, tobacco smoke, dust mites, animal dander, environmental pollens, and molds. Exposure to these triggers should be limited whenever possible. Infections that are unrelated to skin disease, such as an upper respiratory infection, can also exacerbate atopic dermatitis. Food allergy is commonly seen in patients with atopic dermatitis but typically presents with urticaria or anaphylaxis rather than exacerbation of the atopic dermatitis.

Topical corticosteroids are the mainstay of anti-inflammatory therapy for atopic dermatitis. Hundreds of topical corticosteroids are available and are classified according to strength from I to VII. Class I is the highest potency and class VII is the lowest potency. Potency varies according to the steroid molecule (active ingredient), and, for a given ingredient, strength can vary according to relative concentration and vehicle base. Enhanced penetration occurs in areas of natural occlusion (flexures such as axillae and groin), with external occlusion (diapers or bandages), in areas of open skin (excoriations), and with heat or hydration. Use of wet wraps with topical corticosteroid application takes advantage of this principle of heat and hydration for enhanced penetration for recalcitrant lesions. Class I and II steroids are typically avoided in young children or in areas of thinner skin or enhanced penetration.

Corticosteroids are available in different vehicles. In general, ointments are preferred because of their increased efficacy, occlusive nature, and tolerability. Creams may be slightly less effective for a given steroid ingredient but may be more cosmetically acceptable for older patients or in warmer climates. Lotions may have more preservatives that can cause irritation and are generally less potent. Sprays, foams, solutions, and gels can be especially useful for hair-bearing areas. Creams, lotions, sprays, solutions, and gels can be particularly irritating when applied to atopic skin and should generally be avoided on areas of open skin.

Figure 190-2 Atopic dermatitis with Staphylococcus superinfection.
Topical corticosteroids should be used in conjunction with adequate skin care, such as avoiding triggers of inflammation and frequent application of emollients. Twice-daily application of corticosteroids is recommended. The goal is to limit the need for anti-inflammatory medications and thereby avoid potential for adverse effects. Local side effects such as skin atrophy, striae, acne, and hypopigmentation are related to corticosteroid potency, site of application, and duration of application. Systemic side effects of adrenal suppression or Cushing syndrome can result with application of a potent topical corticosteroid to large surface areas or occluded areas at risk of enhanced penetration.

Topical calcineurin inhibitors (also referred to as topical immune modulators) such as topical tacrolimus and pimecrolimus may be part of the treatment regimen for atopic dermatitis. These agents selectively inhibit T-cell proliferation by inhibiting calcineurin and subsequent interleukin 2 production. There is no potential for skin atrophy; thus these agents are particularly useful for face or genital lesions. They are currently approved for intermittent therapy as second-line treatments for mild to moderate atopic dermatitis. Long-term studies, combined with other modalities for treatment, are underway.

Sedating antihistamines (e.g., diphenhydramine, hydroxyzine) are useful adjunctive therapy, especially during flares. These may have only mild effect on pruritus but can improve the sleeplessness due to scratching during the night. A dose before bedtime is most effective, and additional daytime doses can be added on an individual basis when needed. Non-sedating antihistamines are of little benefit in controlling the pruritus of atopic dermatitis.

Short-term administration of systemic corticosteroids is rarely indicated for cases of severe disease and may be considered when adequate topical therapy failed or is being instituted. Systemic corticosteroid courses should be adequately tapered and used in conjunction with an appropriate atopic skin care regimen. Rebound flare of atopic dermatitis is common following withdrawal of corticosteroids and should be anticipated to avoid misinterpretation of the natural disease severity. Long-term and frequent repeated courses should be avoided to prevent adverse effects.

Ultraviolet light therapy (UVB, narrow band UVB, UVA, or UVA1) can be an option for moderate to severe cases in older children. Typically, light therapy is administered two to three times weekly until improvement is seen, and then is tapered or discontinued once the acute flare has resolved. More frequent use of light therapy in children is hindered by requirements for frequent office visits, ability to cooperate with standing in a light box while wearing protective goggles, and risk of long-term skin damage, including the potential for skin cancer development with excessive UV light exposure. Systemic cyclosporine (up to 5 mg/kg/day) can be effective therapy for atopic dermatitis in severe cases. It is used for periods of up to 1 year to gain control of severe disease and should be tapered once the atopic dermatitis is controlled.

An increased tendency toward bacterial, viral, and fungal skin infections is due to an impaired skin barrier and decrease in innate immune proteins in the skin as well as maladaptive secondary immune responses.

**Secondary impetigo** with *S. aureus* is the most common secondary skin infection found in atopic dermatitis. Group A streptococcus infection is also common. Infection manifests with pusules, erythema, crusting, scabbing, flare of disease, or lack of response to adequate anti-inflammatory therapy. Localized lesions can be treated with topical mupirocin. Widespread and generalized lesions require oral antibiotic therapy, most commonly with a first-generation cephalosporin, such as cephalaxin. Methicillin-resistant *S. aureus* infection is increasingly common, and antibiotic therapy should be tailored based on local resistance rates and patient factors. Diagnosis of superinfection may be made clinically, but a superficial bacterial culture can confirm the diagnosis and provide antimicrobial susceptibilities. Treatment should include a concomitant atopic skin care routine including the continued use of topical corticosteroids. Although secondary skin infection with *S. aureus* is common, progression to cellulitis or septicemia is unusual. Rarely, intravenous antibiotics may nevertheless be required. Children with colonization and frequent infections may benefit from dilute bleach baths two to three times weekly; ¼ to ½ cup of household bleach is added to a half-full or full bathtub.

**Eczema herpeticum** (Kaposi’s varicelliform eruption) is one of the potentially serious infectious complications in atopic dermatitis. After herpes simplex virus (HSV) infection, an eruption of multiple, pruritic, vesiculopustular lesions occurs in a disseminated pattern, both within plaques of atopic dermatitis and on normal-appearing skin. These characterize rupture and form crusted umbilicated papules and punched-out hemorrhagic erosions (Fig. 190-3). Irritability, anorexia, and fever can also be seen. Systemic and central nervous system disease have been reported. Bacterial superinfection of eroded areas of the skin often occurs. Diagnosis can be made rapidly from a scraping of the skin lesion stained with Giemsa or Wright’s stain (Tzanck test), though these are not highly sensitive. These stains allow

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**COMPLICATIONS**

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![Decision-Making Algorithm](Available @ StudentConsult.com)

**Fever and Rash**

Figure 190-3 Eczema herpeticum (hand).
microscopic visualization of the presence of multinucleated giant cells indicative of herpes simplex virus or varicella-zoster virus infection. Vesicle fluid can also be sent for polymerase chain reaction (PCR) detection of herpes simplex virus DNA, rapid direct fluorescent antibody testing, or viral culture. Laboratory confirmation of infection is important because similar clinical manifestations can occur with bacterial infections.

The psychosocial impact of atopic dermatitis can be significant. There is often disfigurement, lack of sleep from pruritus resulting in irritability and fatigue, and limitations on participation in sports. Significant time, as well as financial strain, is involved in caring for a child with atopic dermatitis. Thus, management should address these potential issues and provide adequate anticipatory guidance.

**PROGNOSIS**

Atopic dermatitis frequently remits during childhood and is much less common after puberty. The condition is generally most severe and widespread in infancy and early childhood. Relapse of disease in adults can occur and commonly manifests as face or hand dermatitis. Frequently, adults have generalized dry skin and are aware that their skin is sensitive to many over-the-counter preparations. Patients with atopic dermatitis can also develop asthma and allergic rhinitis. Asthma is more commonly associated with more severe skin disease.

**PREVENTION**

Individual flares of atopic dermatitis can be prevented by avoiding triggers of inflammation and can be lessened with frequent emollient application. Some evidence suggests that breastfeeding for at least 4 months prevents or delays the occurrence of atopic dermatitis in early childhood. For infants with a parent or sibling with atopic disease and who are not exclusively breastfed for 4 to 6 months, there is modest evidence that the onset of atopic dermatitis may be delayed or prevented by the use of extensively hydrolyzed casein-based formulas. There is insufficient evidence that soy-based formulas, delaying the introduction of complementary foods beyond 4 to 6 months of age, or other dietary intervention prevents the development of atopic disease. There is no convincing evidence that women who avoid peanuts or other foods during pregnancy or while breastfeeding lower their child’s risk of allergies.

**CONTACT DERMATITIS**

**ETIOLOGY AND EPIDEMIOLOGY**

Inflammation in the top layers of the skin, caused by direct contact with a substance, is divided into two subtypes: irritant contact dermatitis and allergic contact dermatitis. **Irritant contact dermatitis** is observed after the skin surface is exposed to an irritating chemical or substance. **Allergic contact dermatitis** is a cell-mediated immune reaction, also called type IV or delayed-type hypersensitivity. The antigens, or hapten, involved in allergic contact dermatitis readily penetrate the epidermis and are bound by Langerhans cells, the antigen-presenting cells of the skin. The hapten is presented to T lymphocytes, and an immune cascade follows. Contact dermatitis may occur in any age, and girls are more frequently affected than boys.

**CLINICAL MANIFESTATIONS**

Irritant contact dermatitis is characterized by ill-defined, scaly, pink or red patches and plaques (Fig. 191-1). The eruption is localized to skin surfaces that are exposed to the irritant. Irritant contact dermatitis is observed frequently on the dorsal surfaces of the hands in patients, often from repeated hand washing or exposure to irritating chemicals.

Diaper dermatitis is a common problem in infants and most commonly is a form of irritant contact dermatitis. The dermatitis is caused by irritation from urine and feces, typically affecting the perianal region and the buttocks while sparing the protected groin folds and other occluded areas. Secondary infection by *Candida albicans* or bacterial pathogens may complicate diaper dermatitis as well.

Allergic contact dermatitis may be acute (such as *Rhus dermatitis*) or chronic (such as nickel dermatitis). Acute lesions are bright pink, pruritic patches, often in linear or sharply margined bizarre configurations. Within the patches are clear vesicles and bullae (Fig. 191-2). Signs and symptoms of the disease may be delayed for 7 to 14 days after exposure if the patient has not been sensitized previously. On reexposure, symptoms begin within hours and are usually more severe. The eruption may persist for weeks. Chronic lesions are pink, scaly, pruritic plaques, often mimicking atopic dermatitis. Even intermittent exposure can result in a persistent dermatitis.

**LABORATORY AND IMAGING STUDIES**

The diagnosis is established by clinical presentation and history of exposure to a recognized irritant or allergen. Skin-prick testing and serum IgE levels are not helpful in determining the cause of allergic contact dermatitis. Patch testing may be used to determine the allergen causing the reaction in difficult cases.
Chapter 192  Seborrheic Dermatitis

DIFFERENTIAL DIAGNOSIS
The distribution and appearance of the dermatitis and a detailed exposure history are the most useful diagnostic tools. Involvement of the lower legs and distal arms suggests exposure to plants of the *Rhus* species (poison ivy or poison oak), especially when linear configurations of lesions are present. Dermatitis of the ears (earrings), wrist (bracelet or watch), or periumbilical region (belt buckle or pant buttons) suggests a metal allergy to nickel. Distribution on the dorsal surfaces of the feet indicates a shoe allergy, usually to dyes, rubber, or leather. Topical antibiotics (neomycin) and fragrances (soaps, perfumes, cosmetics) are frequent causes of allergic contact dermatitis.

Diaper rashes caused by *Candida* are quite common. Irritant contact dermatitis primarily affects the prominent, exposed surfaces, whereas *Candida* primarily affects intertriginous areas. The two are frequently present simultaneously, as secondary *Candida* infection may complicate irritant dermatitis.

Psoriasis, seborrheic dermatitis, and Langerhans cell histiocytosis can present with an erythematous rash in the diaper area. Referral to a dermatologist should be considered for any child with severe rash or with diaper rash that does not respond to conventional therapy.

TREATMENT
Topical corticosteroids are effective in treatment of allergic and irritant contact dermatitis. High-potency corticosteroids, and even short courses of oral corticosteroids, may be necessary for severe reactions of allergic contact dermatitis. Oral antihistamines may be required to control itching.

Treatment of candidal diaper dermatitis consists of topical nystatin or topical azole antifungals. Low-potency topical corticosteroids are frequently used in addition to topical antifungal therapy to treat the irritant component of the diaper dermatitis when present concomitantly.

COMPLICATIONS
In addition to superinfection of diaper dermatitis by *C. albicans*, bacterial superinfection may complicate any form of contact dermatitis. This is especially common if the skin barrier is no longer intact because of blistering or scratching.

PREVENTION
Every effort should be made to identify the trigger of allergic or irritant contact dermatitis. With allergic contact dermatitis, reexposure often leads to increasingly severe reactions.

SEBORRHEIC DERMATITIS

ETIOLOGY
Seborrheic dermatitis is a common, chronic inflammatory disease that has different clinical presentations at different ages. Seborrheic dermatitis classically presents in infants as cradle cap or dermatitis in the intertriginous areas of the axillae, groin, antecubital and popliteal fossae, and umbilicus. It is seen in adolescents as dandruff. The pathogenesis of seborrheic dermatitis is unclear, but it is theorized that there is an abnormal inflammatory response to commensal *Malassezia* species in sebum-rich areas. Areas prone to seborrheic dermatitis include the scalp, eyebrows, eyelids, nasolabial folds, external auditory canals, and posterior auricular folds.

CLINICAL MANIFESTATIONS
Seborrheic dermatitis in infants begins during the first month and persists during the first year of life. It is also called cradle cap because of the thick, greasy and waxy, yellow-white scaling and crusting of the scalp (Fig. 192-1). It is usually prominent on the vertex of the scalp, but it may be diffuse. Greasy, scaly, erythematous, nonpruritic patches and plaques may extend to the face and posterior auricular folds, sometimes involving the entire body. Diaper and intertriginous areas can have sharply demarcated, shiny, erythematous patches with yellow, greasy, or waxy-appearing scale. Hypopigmentation may persist after the inflammation has faded. The eruption is usually asymptomatic, which helps differentiate it from infantile atopic dermatitis, which is pruritic.

Classic seborrheic dermatitis during adolescence is typically localized to the scalp. The mild form is commonly known as dandruff, a fine, white, dry scaling of the scalp with minor itching. Additional findings of seborrheic dermatitis vary from diffuse, brawny scaling to focal areas of thick, oily, yellow crusts with underlying erythema. The external auditory canals, eyebrows, eyelids, and intertriginous areas may be involved as well. Pruritus may be minimal or severe.
Seborrheic dermatitis does not cause permanent hair loss. Cradle cap is self-limited and resolves during the first year of life. Seborrheic dermatitis does not cause permanent hair loss.

**LABORATORY AND IMAGING STUDIES**

Laboratory studies and imaging studies are not necessary to diagnose seborrheic dermatitis. Fungal cultures and potassium hydroxide studies may be necessary to help differentiate seborrheic dermatitis of the scalp from tinea capitis (see Chapter 98).

**DIFFERENTIAL DIAGNOSIS**

Seborrheic dermatitis in an infant may be difficult to differentiate from atopic dermatitis, and in fact, some cases may represent an overlap. In a teenager, seborrheic dermatitis of the scalp and psoriasis of the scalp may have very similar clinical findings; it may be very difficult to differentiate the two disorders, especially if there are no other cutaneous findings to provide additional clues. Intractable, severe, generalized seborrheic dermatitis suggests Langerhans cell histiocytosis. Intractable seborrheic dermatitis, accompanied by chronic diarrhea and failure to thrive, suggests Leiner disease or acquired immunodeficiency syndrome (AIDS).

**TREATMENT**

Seborrheic dermatitis of the scalp is usually asymptomatic and generally does not require treatment. Minor amounts of scale can be removed easily by frequent shampooing. For infants with cradle cap, oil (such as mineral oil or olive oil) may be gently massaged into the scalp and left on for a few minutes before gently brushing out the scale and shampooing. Daily shampooing with ketoconazole, zinc pyrithione, selenium sulfide, or salicylic acid shampoos can treat scalp scale. Seborrheic dermatitis with inflamed lesions responds rapidly to treatment with low-potency steroids two times daily.

The response to treatment is usually rapid. Secondary bacterial infection can occur but is uncommon. Intractable disease and other complications warrant further evaluation for other etiologies.

**PROGNOSIS**

Cradle cap is self-limited and resolves during the first year of life. Seborrheic dermatitis does not cause permanent hair loss. For teenagers, continued use of an antiseborrheic shampoo is often required for control of dandruff.

**PREVENTION**

Frequent shampooing, especially with early signs of seborrheic dermatitis, may help prevent progression.

**OTHER PAPULOSQUAMOUS DERMATOSES**

**Pityriasis Rosea**

Pityriasis rosea is a benign, self-limited eruption that may occur at any age, with peak incidence during adolescence. A solitary, 2- to 5-cm, pink, oval patch with central clearing, the so-called herald patch, is the first manifestation of the eruption. The herald patch typically is found on the breast, lower torso, or proximal thigh and is often misdiagnosed as fungal or eczematous in origin. One to 2 weeks later, a generalized eruption occurs on the torso and proximal extremities. Multiple 0.5- to 2-cm, oval to oblong, red or tan macules with a fine, branlike scale are characteristically arranged parallel to skin tension lines (Christmas tree pattern). Rarely, the eruption may have an inverse distribution involving the axillae and groin or a papular or papulovesicular appearance. Mild prodromal symptoms may be present with the appearance of the herald patch, and pruritus is present in 25% of cases. The eruption lasts 4 to 14 weeks, with gradual resolution. Residual hyperpigmentation or hypopigmentation can take additional months to clear. Treatment is unnecessary, though pruritus can be managed with oral antihistamines, phototherapy, and low-potency topical corticosteroids.

**Psoriasis**

Psoriasis is a common papulosquamous condition characterized by well-demarcated, erythematous, scaling papules and plaques. Psoriasis occurs at all ages, including infancy, with onset of 30% of cases during childhood. The disease is characterized by a chronic and relapsing course, although spontaneous remissions can occur. Infections (especially Streptococcus pyogenes), stress, trauma, and medications may cause disease exacerbations. Various subtypes of psoriasis exist. The most common variety is plaque-type psoriasis (psoriasis vulgaris), which can be localized or generalized. The lesions consist of round, well-demarcated, red plaques measuring 1 to 7 cm with micaceous scale, which is distinctive in its thick, silvery appearance with pinpoint bleeding points revealed on removal of the scales (Auspitz sign). The lesions of psoriasis have a distinctive distribution involving the extensor aspect of the elbows and knees, posterior occipital scalp, periumbilical region, lumbar-sacral region, and intergluteal cleft. Children often have facial lesions involving the superomedial aspect of the eyelids. Nail plate involvement is common and includes pitting, onycholysis, subungual hyperkeratosis, and oil staining (reddish brown subungual macular discoloration). Guttate (numerous small plaques diffusely distributed on the torso), erythrodermic (covering large body surface areas), inverse (moist red patches affecting body folds), and pustular forms may occur.

The foundation of therapy is topical corticosteroids. Treatment of psoriasis with oral corticosteroids can induce pustular psoriasis and should be avoided. Because of the risk of atrophy, striae, and telangiectases, especially when potent fluorinated...
corticosteroid preparations are administered long-term, the goal is to use the least potent corticosteroid necessary. Topical vitamin D analogs, salicylic acid, and tar preparations are useful adjuvants to topical corticosteroids. Phototherapy with ultraviolet B (UVB) light can be useful as secondary therapy in older children. Extensive plaque or guttate, erythrodermic, and pustular psoriasis may necessitate systemic treatments with immune suppressive medication (methotrexate, cyclosporine, tumor necrosis factor-α antagonists). Disease triggers such as infection or medications should be identified and removed.

**DERMAL MELANOSIS**

The most frequently encountered pigmented lesion is dermal melanosis, which occurs in 70% to 90% of African-American, Hispanic, Asian, and Native American infants and in approximately 5% of white infants. This is a congenital lesion caused by entrapment of melanocytes in the dermis during their migration from the neural crest into the epidermis. Although most of these lesions are found in the lumbosacral area (Mongolian spot), they also occur at other sites such as the buttocks, flank, extremities, or, rarely, the face (Fig. 193-1). Single or multiple, poorly demarcated, gray-blue patches up to 10 cm in size may be present. Most lesions gradually disappear during the first few years of life; aberrant lesions in unusual sites are more likely to persist.

**CAFÉ AU LAIT MACULES**

Café au lait macules are pigmented macules or patches, which may be present in a newborn but tend to develop during childhood (Fig. 193-2). They range in color from very light brown to a chocolate brown. Up to five café au lait macules are found in 1.8% of newborns and 25% to 40% of normal children, and have no significance. Children with six or more café au lait macules (0.5 cm in diameter before puberty or greater than 1.5 cm in diameter after puberty), especially when accompanied by axillary or inguinal freckling, should be evaluated carefully.

**Table 193-1: Common Birthmarks**

<table>
<thead>
<tr>
<th>COLOR/LESION</th>
<th>BIRTHMARK</th>
<th>LOCATION</th>
<th>OTHER FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown/macule or patch</td>
<td>Café au lait macule</td>
<td>Variable</td>
<td>May be associated with genetic syndromes</td>
</tr>
<tr>
<td>Brown (&lt;20 cm)/plaque</td>
<td>Congenital melanocytic nevus</td>
<td>Variable</td>
<td>Low risk of melanoma</td>
</tr>
<tr>
<td>Brown (&gt;20 cm)/plaque</td>
<td>Giant congenital melanocytic nevus</td>
<td>Trunk most common</td>
<td>Risk of melanoma and neutromelanosis</td>
</tr>
<tr>
<td>Brown-“flesh-colored”/plaque</td>
<td>Epidermal nevus</td>
<td>Variable, trunk and neck</td>
<td>May enlarge with time</td>
</tr>
<tr>
<td>Red/patch</td>
<td>Port-wine stain (nevus flammeus)</td>
<td>Variable, face most common</td>
<td>May be associated with Sturge-Weber syndrome</td>
</tr>
<tr>
<td>Red/papule or plaque</td>
<td>Salmon patch (nevus simplex)</td>
<td>Glabella, eyelids, nape of neck</td>
<td>Improves or resolves with time</td>
</tr>
<tr>
<td>Red/papule or plaque</td>
<td>Hemangioma</td>
<td>Variable</td>
<td>May be associated with liver hemangiomas, airway hemangiomas, and PHACE syndrome</td>
</tr>
<tr>
<td>Gray-blue/patch</td>
<td>Dermal melanosis</td>
<td>Lower trunk (Mongolian spot); face (nevus of Ota); posterior shoulder (nevus of Ito)</td>
<td>Nevus of Ota may be associated with ocular pigmentation</td>
</tr>
<tr>
<td>Blue-purple/nodule</td>
<td>Cephalohematoma</td>
<td>Scalp</td>
<td>Resolves with time</td>
</tr>
<tr>
<td>Blue-purple/plaque</td>
<td>Venous, lymphatic, or mixed malformation</td>
<td>Variable</td>
<td>Intermittent swelling and pain</td>
</tr>
<tr>
<td>Yellow-orange/plaque</td>
<td>Nevis sebaceous</td>
<td>Head and neck</td>
<td>Malignant and benign tumors may arise within</td>
</tr>
<tr>
<td>Yellow-orange/nodule</td>
<td>Juvenile xanthogranuloma</td>
<td>Head and neck most common</td>
<td>Spontaneously involutes</td>
</tr>
<tr>
<td>Yellow-brown/papule or nodule</td>
<td>Mastocytoma</td>
<td>Variable</td>
<td>Spontaneously involutes</td>
</tr>
<tr>
<td>Hypertrichosis/plaque</td>
<td>Smooth muscle hamartoma</td>
<td>Trunk</td>
<td></td>
</tr>
<tr>
<td>Hypertrichosis/tumor</td>
<td>Plexiform neurofibroma</td>
<td>Trunk most common</td>
<td>Associated with neurofibromatosis type 1</td>
</tr>
<tr>
<td>White/patch</td>
<td>Nevis anemicus</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>White/patch</td>
<td>Nevis depigmentosus</td>
<td>Variable</td>
<td></td>
</tr>
</tbody>
</table>
for additional stigmata of neurofibromatosis type 1. Other dis-
orders also associated with café au lait macules include the other
forms of neurofibromatosis, Legius syndrome, tuberous sclero-
sis, McCune-Albright syndrome, multiple lentigines/LEOPARD
syndrome, Noonan syndrome, and Russell-Silver syndrome.

CONGENITAL MELANOCYTIC NEVI
Approximately 1% to 2% of newborns have congenital mela-
ocytic nevi. Smaller lesions (as opposed to giant pigmented
nevi) are brown patches or plaques, often with an oval or
lancet configuration. Lesions may resemble café au lait mac-
ules initially, but darker pigmentation, variegated speckles,
textural changes, and elevation develop with time and help
to differentiate these lesions (Fig. 193-3). Thick, dark, coarse
hair frequently is associated with congenital melanocytic nevi
(Fig. 193-4). These lesions vary in site and size but are most
often solitary. Congenital melanocytic nevi pose a very slightly
increased risk for the development of malignant melanoma,
usually developing during adulthood. Surgical removal may
be considered to improve the cosmetic appearance of the
patient or to reduce the likelihood of malignant transforma-
tion, although some patients and physicians elect for observa-
tion. Excisional biopsy is indicated when malignant change is
suspected.

CONGENITAL GIANT MELANOCYTIC NEVI
Giant congenital melanocytic nevi are defined as nevi that
would be approximately 20 cm in length in adulthood; in a
neonate, this translates to 9 cm on the head and neck and 6 cm
on the rest of the body. These lesions appear as color variegated,
light brown to black patch or plaques, sometimes with smaller
macules and papules (satellite nevi) in addition. The affected
skin may be smooth, nodular, or leathery. Prominent, dark
hypertrichosis is often present. Neuromelanosis, the presence
of melanocytes in the central nervous system, may be associ-
ated with giant congenital melanocytic nevi. Affected patients
may be asymptomatic or have hydrocephalus and seizures; in symptomatic patients, death often results during early childhood. Malignant melanoma develops in approximately 2% to 10% of patients with giant congenital melanocytic nevi, in either the cutaneous lesion or the neural melanocytes. In contrast to small and medium congenital melanocytic nevi, melanoma is more likely to develop during childhood. Because of the incidence of malignant degeneration and extensive deformity, surgical excision should be considered for resectable lesions. The use of tissue expansion techniques has greatly improved the capability for surgical removal of large lesions.

ACQUIRED NEVI

Acquired melanocytic nevi are common skin lesions. Melanocytic nevi may occur at any age; however, the lesions develop most rapidly in prepubertal children and teenagers. Melanocytic nevi are well-delineated, round to oval, brown macules and papules. Lesions are most common on the face, upper torso, and arms. Family history, fair skin, and sun exposure are considered major risk factors. Irregular pigmentation, rapid growth, bleeding, and a change in configuration or borders suggest signs of malignant degeneration and biopsy should be performed. Malignant melanoma is rare in childhood; however, there is an alarming increase in incidence in adolescence, especially in those who use indoor tanning. Education of parents and children regarding the risks of sun exposure, appropriate sun protection, and recognition of worrisome lesions is important.

Chapter 194

VASCULAR ANOMALIES

Vascular anomalies can be divided into two major categories: tumors and malformations. Vascular tumors are characterized by hypercellularity, proliferation, and growth. Vascular malformations, however, are developmental defects derived from the capillary, venous, arterial, or lymphatic vessels. In contrast to hemangiomas, vascular malformations remain relatively static over time. Differentiating between these entities is important because they have different prognoses and clinical implications.

VASCULAR TUMORS

Hemangiomas

Hemangiomas are the most common soft tissue tumors of infancy, occurring in approximately 5% to 10% of 1-year-old infants. In newborns, hemangiomas may originate as a pale white macule with threadlike telangiectasia. When the tumor proliferates, it assumes its most recognizable form as a bright red, lobulated plaque or nodule (superficial component, Fig. 194-1). Hemangiomas that lie deeper in the skin are soft, warm masses with a slightly bluish discoloration (deeper component). Frequently, hemangiomas have both a superficial and a deep component. They range from a few millimeters to several centimeters in diameter and are usually solitary; 20% involve multiple lesions. Hemangiomas occur predominantly in females (3:1) and have an increased incidence in premature infants. Approximately 55% are present at birth; the rest develop in the first weeks of life. Superficial hemangiomas reach their maximal size by 6 to 8 months, but deep hemangiomas may grow for 12 to 14 months. They then undergo slow, spontaneous resolution, which takes 3 to 10 years.

Despite the benign nature of most cutaneous hemangiomas, there may be the risk of functional compromise or permanent disfigurement depending on the location and extent. Ulceration, the most frequent complication, can be painful and increases the risk of infection, hemorrhage, and scarring. Areas frequently associated with complications include the periorcular region, lip, nasal tip, beard, face (large lesions), groin, and buttocks.

Periorbital hemangiomas pose considerable risk to vision and should be monitored carefully. Amblyopia can result from the hemangioma causing obstruction of the visual axis or pressure on the globe, resulting in astigmatism. If there is any concern, the patient should have urgent evaluation by an ophthalmologist. Treatment may be indicated to prevent blindness. Subglottic hemangiomas manifest as hoarseness and stridor; progression to respiratory failure may be rapid. Symptomatic airway hemangiomas develop in more than 50% of infants with extensive facial hemangiomas on the chin and jaw (beard distribution); any infant with a beard hemangioma should be referred for laryngoscopy. Multiple cutaneous (diffuse hemangiomatosis) and large facial hemangiomas may be associated with visceral hemangiomas. Extensive cervicofacial hemangiomas may be associated with multiple anomalies, including posterior fossa malformations, hemangiomas, arterial anomalies of the cerebrovasculature, coarctation of aorta and cardiac defects, and eye abnormalities (PHACE syndrome). Lumbosacral hemangiomas suggest an occult spinal dysraphism with or without anorectal and urogenital anomalies. Magnetic resonance imaging of the spine is
indicated in all patients with midline cutaneous hemangiomas in the lumbosacral area.
Most hemangiomas do not necessitate medical intervention and involute spontaneously; however, if complications arise and treatment is warranted, oral propranolol is the mainstay of therapy.

**Pyogenic Granuloma**
A pyogenic granuloma is an acquired, benign vascular tumor commonly seen in children. Initially, the lesions appear as pink-red papules that often arise after minor trauma, growing rapidly over a period of weeks into a bright red, vascular, often pedunculated papule measuring 2 to 10 mm. The lesions often have the appearance of granulation tissue and are very friable. They may occur anywhere on the body, but the head, neck, and upper extremities are most commonly affected. When traumatized, these lesions may bleed profusely, often requiring emergent medical attention. Surgical excision is the most definitive treatment option, though pulsed dye laser can be useful for very small lesions.

**VASCULAR MALFORMATIONS**

**Port-Wine Stain**
Port-wine stains (nevus flammeus, capillary malformation) are malformations of the superficial capillaries of the skin. These lesions are present at birth and should be considered permanent developmental defects. They do not enlarge after birth; any apparent increase in size is caused by growth of the child. A port-wine stain may be localized to any body surface, but facial lesions are the most common. They are pink-red, sharply demarcated macules and patches in infancy (Fig. 194-2). With time, they darken to a purple or port-wine color and may develop a pebbly or slightly thickened surface. Vascular blebs may form within the lesions and become symptomatic or bleed. The most successful treatment modality in use is the pulsed dye laser, which can result in 80% to 90% improvement in these lesions after a series of treatment sessions and can avoid future complications associated with vascular dilation. Treatment is more effective if undertaken in infancy. Overgrowth of underlying bone can occur and is frequently seen with facial lesions. Affected patients often need maxillofacial intervention from malalignment that develops.

Most port-wine stains occur as isolated defects and do not indicate systemic malformations. Rarely, they may suggest ocular defects or specific neurocutaneous syndromes. **Sturge-Weber syndrome** (encephalotrigeminal angiomatosis) may occur with a facial port-wine stain, usually in the cutaneous distribution of the first branch of the trigeminal nerve. Other features include leptomeningeal angiomatosis, mental retardation, seizures, hemiparesis contralateral to the facial lesions, ipsilateral intracortical calcification, and frequent ocular manifestations such as buphthalmos, glaucoma, angiooma of the choroid, hemianoptic defects, and optic atrophy. Anticonvulsant therapy and neurosurgical procedures have been of value in some patients. Glaucoma can occur in association with port-wine stains located on the eyelid, even in the absence of Sturge-Weber syndrome, and these patients need lifelong monitoring of ocular pressures. **Klippel-Trénaunay-Weber syndrome** is characterized by the triad of capillary and venous malformations, venous varicosities, and hyperplasia of the soft tissues—and often bone—of the involved area. The lower limb is most commonly affected. A port-wine stain overlying the spine may rarely be a marker of spinal dysraphism or an intraspinal vascular malformation.

**Salmon Patch (Nevus Simplex)**
A salmon patch (nevus simplex, stork bite, angel’s kiss) is a variant of nevus flammeus that is present in 70% of normal newborns. They are red, irregular, macular patches resulting from dilation of dermal capillaries and are usually found on the nape of the neck, the eyelids, and the glabella. Most of the facial lesions fade by 1 year of age, but lesions on the neck may persist for life. Surveys of adult populations confirm the persistence of the nuchal lesions in approximately 25% of the population.

**ERYTHEMA MULTIFORME, STEVENS-JOHNSON SYNDROME, AND TOXIC EPIDERMAL NECROLYSIS**
Erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are acute hypersensitivity reactions characterized by cutaneous and mucosal necrosis. These syndromes represent a hypersensitivity reaction to a precipitating cause, usually infectious organisms or drugs. These disorders were historically thought to represent a spectrum of
the same disease process, and inconsistent use of these disease names led to further confusion. A consensus definition was published in 1993, and current literature favors that EM is distinct from the SJS/TEN spectrum of disease. The differential diagnosis of vesiculobullous eruptions is listed in Table 195-1.

**Decision-Making Algorithm**

**Available @ StudentConsult.com**

**Vesicles and Bullae**

### Table 195-1 Vesiculobullous Eruptions

<table>
<thead>
<tr>
<th>ENTITY</th>
<th>CLINICAL CLUES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFECTION</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
</tr>
<tr>
<td>Staphylococcal scalded skin syndrome</td>
<td>Generalized, tender erythema, Nikolsky sign. Occasionally associated with underlying infection such as osteomyelitis, septic arthritis, pneumonia. Desquamation and moist erosions observed, especially in intertriginous areas. More common in children younger than 5 years of age.</td>
</tr>
<tr>
<td>Bullous impetigo</td>
<td>Localized blisters from staphylococcal infection.</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>Grouped vesicles on erythematous base. May be recurrent at same site—lips, eyes, cheeks, hands. Reactivated by fever, sunlight, trauma, stress.</td>
</tr>
<tr>
<td>Varicella</td>
<td>Crops of vesicles on erythematous base (“dewdrops on rose petal”). Highly contagious. May see multiple stages of lesions simultaneously. Associated with fever.</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Grouped vesicles on erythematous base limited to one or several adjacent dermatomes. Thoracic dermatomes most commonly involved in children. Usually unilateral. Bursa, pruritus.</td>
</tr>
<tr>
<td><strong>HYPERSENSITIVITY</strong></td>
<td></td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Target lesions on acral sites. May have involvement of mucosal surfaces. Associated with herpes simplex virus infection.</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome and toxic epidermal necrolysis</td>
<td>Prodrome of fever, headache, malaise, sore throat, cough, vomiting, diarrhea. Extensive epidermal necrosis with mucosal involvement. Frequently related to drugs (e.g., sulfonamides, anticonvulsants). Nikolsky sign.</td>
</tr>
<tr>
<td><strong>EXTRINSIC</strong></td>
<td></td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Irritant or allergic. Distribution dependent on the irritant or allergen. Distribution helpful in identifying cause.</td>
</tr>
<tr>
<td>Insect bites</td>
<td>Occur occasionally following flea or mosquito bites. May be hemorrhagic bullae. Often in linear or irregular clusters. Very pruritic.</td>
</tr>
<tr>
<td>Friction</td>
<td>Usually on acral surfaces. May be related to footwear. Often activity-related.</td>
</tr>
<tr>
<td><strong>MISCELLANEOUS</strong></td>
<td></td>
</tr>
<tr>
<td>Miliaria crystallina</td>
<td>Clean, 1- to 2-mm superficial vesicles occurring in crops. Rupture spontaneously. Intertriginous areas, especially neck and axillae.</td>
</tr>
<tr>
<td>Hereditary: epidermolysis bullosa, incontinentia pigmenti, epidermolytic hyperkeratosis</td>
<td></td>
</tr>
<tr>
<td>Autoimmune: linear IgA disease, bullous pemphigoid, dermatitis herpetiformis</td>
<td></td>
</tr>
</tbody>
</table>

and involves less than 10% of the body surface area. Cutaneous lesions are symmetrical and commonly involve acral areas such as the hands, feet, elbows, and knees. Involvement of the ocular, oral, and genital mucosa can be seen in some cases.

Most EM cases in children are precipitated by herpes simplex virus infection, though the infection may no longer be apparent by the time EM develops. *Mycoplasma pneumoniae* and other infectious organisms may also trigger EM. Systemic treatment is usually sufficient. Oral antihistamines help suppress pruritus, stinging, and burning. The use of systemic corticosteroids is controversial but may be considered for severe mucosal disease. Antiviral medications targeting herpes simplex virus do not alter the course of the EM, though children with recurrent EM may be candidates for prophylactic antivirals. The prognosis is excellent, with most lesions lasting no more than 2 weeks. Healing occurs without scarring.

**STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS**

SJS, TEN, and SJS/TEN overlap are severe, life-threatening disorders thought to represent the same disease continuum. They are usually preceded by a prodrome of fever, malaise, and upper respiratory symptoms 1 to 14 days before the onset of cutaneous lesions. Red macules appear suddenly and tend to coalesce into large patches, with a predominant distribution over the face and trunk. Atypical targets may be present, causing diagnostic confusion initially with EM, although the atypical targets lack the characteristic three zones. Skin lesions evolve rapidly into bullae and areas of necrosis. SJS is defined as epidermal detachment of less than 10% of the body surface area, whereas SJS/TEN overlap has 10% to 30% and TEN has greater than 30% body surface area involvement. Any mucosal surface may be involved. The upper and lower lips are generally swollen and bright red with erosions and hemorrhagic crusts, and the remainder of the oral mucosa may also be involved. Early in the disease process, there is bilateral conjunctival injection; however, this usually progresses to conjunctival erosions. There may be erosions of the penile, vaginal, or perianal mucosa. Urogenital, esophageal, and tracheal surfaces may be involved in the most severe cases.

Drugs and *Mycoplasma pneumoniae* infections are the most common causes of SJS/TEN in children. The most common drugs implicated are nonsteroidal anti-inflammatory drugs, sulphonamides, anticonvulsants, and antibiotics. Other precipitating factors are viral infections, bacterial infections, syphilis, and deep fungal infections.

SJS/TEN can occur at any age. The diagnosis of SJS/TEN is clinical; there are no diagnostic tests. Confusion with EM, Kawasaki disease, and bacterial toxin-mediated diseases (scarlet fever, toxic shock syndrome, and staphylococcal scalded skin syndrome) may occur. Patients with Kawasaki disease have conjunctival injection and hyperemia of the mucous membranes. Necrosis of the mucosal surfaces does not occur; blistering, erosions, and severe crusting are not observed. The mucosal changes of staphylococcal scalded skin syndrome are minor, and frank erosions are not present. The blistering of the skin is more superficial and favors intertriginous regions.

SJS/TEN is a serious illness with a mortality rate as high as 35% for severe cases of TEN. Prompt discontinuation of the offending agent is key. No controlled clinical trials regarding medical therapy exist, though early initiation of intravenous immunoglobulin has been proposed. Supportive care is another essential component of therapy, and a multidisciplinary care team is often necessary. Sepsis is the major cause of morbidity and mortality, so meticulous wound care is crucial, with stringent surveillance for cutaneous infections and use of antibiotics as warranted. Parenteral or nasogastric feeding should be instituted early to accelerate the healing process. Careful fluid management and monitoring of electrolytes are critical. Occlusive complications are a major cause of long-term morbidity, so early involvement of an ophthalmologist is important.

**CUTANEOUS INFESTATIONS**

Arthropods are common in the environment. Although many can bite or sting humans, only a few infest humans. Arachnids (mites) are the most common, parasitizing humans and animals by burrowing into the skin and depositing eggs within the skin.

**SCABIES**

Scabies is caused by the mite *Sarcoptes scabiei*. The female mite burrows into the epidermis and deposits her eggs, which mature in 10 to 14 days. The disease is highly contagious because infested humans do not manifest the typical signs or symptoms for 3 to 4 weeks, facilitating transmission. An immunocompetent person with scabies typically harbors only 10 to 20 mites.

The clinical presentation varies depending on the age of the patient, duration of infestation, and immune status of the patient. Severe and paroxysmal itching is the hallmark, with complaints of itching that is frequently worse than the eruption would suggest. Most children exhibit an eczematous eruption composed of red, excoriated papules and nodules. The classic linear papule or burrow is often difficult to find. Distribution is the most diagnostic finding; the papules are found in the axillae, umbilicus, groin, penis, instep of the foot, and web spaces of the fingers and toes (Fig. 196-1). Infants infested with scabies have diffuse erythema, scaling, and pinpoint papules. Pustules, vesicles, and nodules are much more common in infants and may be more diffusely distributed. The face and scalp usually are spared in adults and older children, but these areas are usually involved in infants. Nodular lesions may represent active infection or prolonged hypersensitivity lesions following resolution of infestation. Immunocompromised or neurologically impaired persons may develop a severe form
of the disease known as **Norwegian** or **crusted scabies**, with infestation of 2 million live mites at one time.

The diagnosis of scabies can be confirmed by microscopic visualization of the mite, eggs, larvae, or feces in scrapings of papules or burrows examined under oil immersion. Skin biopsy is rarely necessary but may be useful if lesions have become nodular.

Curative treatment is achieved by a 12-hour (overnight) application of permethrin 5% cream applied to the entire body. Because permethrin is not effective against the eggs, the treatment should be repeated 1 week later to kill any subsequently hatched larvae. All household members and close contacts should be treated simultaneously, even if asymptomatic. Bed linens, towels, and clothes worn for the previous 2 days before treatment should be machine-washed in hot water and machine-dried using high heat; heat is the most effective scabicide. Items that are not washable may be dry-cleaned or placed in a sealed plastic bag for 7 days.

Secondary bacterial infection may occur but is uncommon. In contrast to the pediculoses, scabies is not a vector for infections. Pruritus may persist for 7 to 14 days after successful therapy because of a prolonged hypersensitivity reaction, which does not indicate treatment failure. Inadequate treatment or reinfection should be suspected if new lesions develop after treatment.

**PEDICULOSES**

Three species of lice infest humans: **Pediculus humanus capitis**, the **head louse**; **Pthirus pubis**, the **pubic louse** or **crab louse**; and **Pediculus humanus** (also known as **Pediculus humanus corporis**), the **body louse**. Lice are wingless insects 2 to 4 mm in length that cannot fly or jump. Transmission usually occurs by direct contact with another infested individual. Indirect spread through contact with fomites or personal belongings, such as hairbrushes, combs, or caps, is much less frequent.

Pediculosis differs from scabies infestation in that the louse resides on the hair or clothing and intermittently feeds on the host by piercing the skin. The **bite** causes small urticarial papules and itching. Head lice live close to the skin and may live for 30 days, depositing 100 to 400 eggs as **nits** on hair shafts, usually within 6 mm of the scalp.

Head lice are seen most frequently in early school-age children. Head lice infestations are unrelated to hygiene and are not more common among children with long hair or with dirty hair. It is estimated that 6 to 12 million persons in the United States and 1% to 3% of persons in developed countries are infested with head lice each year. In the United States, head lice infestation is rare among African Americans and may be more common in girls, which is attributed to their tendency to play more closely with one another than boys do.

Pubic lice are transmitted by sexual contact. Their presence in children may be a sign of child abuse. Body lice are firm evidence of poor hygiene, such as infrequent washing and clothing changes.

**Itching**, if present, is the primary symptom. Pediculosis capitis usually causes pruritus behind the ears or on the nape of the neck, or a crawling sensation in the scalp. Pediculosis pubis usually causes pruritus in the groin. Eyelash involvement in children may cause crusting and blepharitis. Pediculosis corporis causes pruritus that, because of repeated scratching, may result in lichenification or secondary bacterial infection. Excoriations and crusting, with or without associated regional lymphadenopathy, may be present.

Infestation with the head louse may be asymptomatic and has little morbidity. The diagnosis can be confirmed by visualizing a live louse. A fine-toothed comb to trap lice is more effective than simply looking at the hair. Wet combing is more time-consuming, but dry combing produces static that may propel the lice away from the comb.

Nits represent the outer casing of the louse ova. Viable nits have an intact operculum (cap) on the nonattached end and a developing louse within the egg. **Brown nits** located on the proximal hair shaft suggest active infestation. **White nits** located on the hair shaft 4 cm or farther from the scalp indicate previous infestation. Because nonviable nits can remain stuck in the hair for weeks to months after an infestation has resolved, many children with nits do not have active lice infestation.

The treatment of head lice is controversial because of resistance to many established options. Over-the-counter permethrin (1%) and pyrethrin-based products (0.17% to 0.33%) are the first choices of therapy. Because 20% to 30% of eggs may survive one treatment, a second treatment should be applied in 7 to 10 days. Drug resistance is on the rise, and malathion (0.5%) lotion may be used as an alternative for resistant cases.

Everyone in the family should be checked for head lice and treated if live lice are found to reduce the risk of reinfection. Bed linens, towels, and clothes worn for the previous 2 days before treatment should be machine-washed in hot water and machine-dried using high heat. Items that are not washable may be dry-cleaned or placed in a sealed plastic bag for 2 weeks. Brushes and combs should be soaked in dish detergent or rubbing alcohol for 1 hour. Rugs, furniture, mattresses, and car seats should be vacuumed thoroughly.

Manual removal of nits after treatment is not necessary to prevent spread. Children treated for head lice should return to school immediately after completion of the first effective treatment or first wet combing, regardless of the presence of remaining nits. There is no evidence that **no nit or nit-free** policies reduce transmission of head lice. If required for return
to school, nit removal is best achieved by wetting the hair and combing with a fine-toothed metal comb.

Excoriations can become secondarily infected with skin bacteria, usually *Staphylococcus* and *Streptococcus*. The body louse functions as a vector for potentially serious infectious diseases, including epidemic typhus, caused by *Rickettsia prowazekii*; louse-borne relapsing fever, caused by *Borrelia recurrentis*; and trench fever, caused by *Bartonella quintana*. These louse-borne infections are rare in the United States. In contrast to body lice, head lice and pubic lice are not associated with transmission of other infections.

**Suggested Reading**
ORTHOPEDICS ASSESSMENT

To care for the pediatric patient, one must understand the growth and development of the musculoskeletal system as well as common orthopedic terms (Table 197-1). Practitioners should recognize common mechanisms for congenital and acquired orthopedic disorders (Table 197-2).

GROWTH AND DEVELOPMENT

The ends of the long bones contain a much higher proportion of cartilage in the skeletally immature child than in an adult (Figs. 197-1 and 197-2). The high cartilage content allows for a unique vulnerability to trauma and infection (particularly in the metaphysis).

The physis is responsible for the longitudinal growth of the long bones. Articular cartilage allows the ends of the bone to enlarge and accounts for growth of smaller bones, such as the tarsals. The periosteum can provide circumferential growth.

Trauma, infection, nutritional deficiency (rickets), inborn errors of metabolism (mucopolysaccharidoses), and other metabolic disorders (renal tubular acidosis, hypothyroid) may affect each of the growth processes and produce distinct aberrations.

<table>
<thead>
<tr>
<th>Table 197-1</th>
<th>Common Orthopedic Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abduction</td>
<td>Movement away from midline</td>
</tr>
<tr>
<td>Adduction</td>
<td>Movement toward or across midline</td>
</tr>
<tr>
<td>Apophysis</td>
<td>Bone growth center that has a muscular insertion but is not considered a growth plate (example: tibial tubercle)</td>
</tr>
<tr>
<td>Arthroscopy</td>
<td>Surgical exploration of a joint using an arthroscope</td>
</tr>
<tr>
<td>Arthroplasty</td>
<td>Surgical reconstruction of a joint</td>
</tr>
<tr>
<td>Arthrotomy</td>
<td>Surgical incision into a joint; an “open” procedure</td>
</tr>
<tr>
<td>Deformation</td>
<td>Changes in limb, trunk, or head due to mechanical force</td>
</tr>
<tr>
<td>Dislocation</td>
<td>Displacement of bones at a joint</td>
</tr>
<tr>
<td>Equinus</td>
<td>Plantar flexion of the forefoot, hindfoot, or entire foot</td>
</tr>
<tr>
<td>Femoral anteversion</td>
<td>Increased angulation of the femoral head and neck with respect to the frontal plane</td>
</tr>
<tr>
<td>Malformation</td>
<td>Defect in development that occurs during fetal life (example: syndactyly)</td>
</tr>
<tr>
<td>Osteotomy</td>
<td>Surgical division of a bone</td>
</tr>
<tr>
<td>Pes cavus</td>
<td>High medial arch of the foot</td>
</tr>
<tr>
<td>Pes planus</td>
<td>Flat foot</td>
</tr>
<tr>
<td>Rotation, internal</td>
<td>Inward rotation (toward midline)</td>
</tr>
<tr>
<td>Rotation, external</td>
<td>Outward rotation (away from midline)</td>
</tr>
<tr>
<td>Subluxation</td>
<td>Incomplete loss of contact between two joint surfaces</td>
</tr>
<tr>
<td>Tibial torsion</td>
<td>Rotation of the tibia in an internal or external fashion</td>
</tr>
<tr>
<td>Valgus/valgum</td>
<td>Angulation of a bone or joint in which the apex is toward the midline (example: knock-knee)</td>
</tr>
<tr>
<td>Varus/varum</td>
<td>Angulation of a bone or joint in which the apex is away from the midline (example: bowlegs)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 197-2</th>
<th>Mechanisms of Common Pediatric Orthopedic Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATEGORY</td>
<td>MECHANISM</td>
</tr>
<tr>
<td>CONGENITAL</td>
<td>Malformation</td>
</tr>
<tr>
<td></td>
<td>Disruption</td>
</tr>
<tr>
<td></td>
<td>Deformation</td>
</tr>
<tr>
<td>DEFORMATION</td>
<td>Dysplasia</td>
</tr>
<tr>
<td>ACQUIRED</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td>TUMOR</td>
<td>Tumor</td>
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</tbody>
</table>
DEVELOPMENTAL MILESTONES

Neurologic maturation, marked by achievement of developmental motor milestones, is important for normal musculoskeletal development (see Section 2). A neurologic disorder may cause a secondary musculoskeletal abnormality (e.g., extremity contractures in Duchenne muscular dystrophy). Thus, normal motor development must be included in the definition of a normal musculoskeletal system.

Infants

The in utero position of the fetus can affect the angular and torsional alignment (temporary or permanent) of the skeletal system, especially of the lower extremity (Fig. 197-3). The newborn's hips are externally rotated. Pes planus and genu varum are common. Infants are usually born with a flexed posture. This position usually decreases to neutral within the first 4 to 6 months. The foot is often flat and tucked under at birth; the ankle will be inverted and the forefoot is adducted when compared with the hindfoot. The lateral border of the foot must straighten out, even with dorsiflexion, to be considered secondary to in utero positioning.

The head and neck may also be distorted by in utero positioning. The spine and upper extremities are less likely to be affected. By the age of 3 to 4 years, the effects of in utero positioning have usually resolved.

Gait

Normal gait has a stance phase and swing phase; each leg should have symmetrical timing with each phase. The stance phase represents 60% of the gait and begins with foot contact (usually the heel strike) and ends with the toe-off. During the swing phase (40%), the foot is off the ground. The gait cycle is the interval between stance phases on the same limb.

Toddlers will generally walk independently by 18 months of age. Their externally rotated gait is usually inconsistent, is characterized by short, rapid steps, and does not have the reciprocal arm swing. Gait coordination improves over time, with a normal gait usually achieved by the time a child enters elementary school.

The Limping Child

The differential diagnosis for a limping child is often categorized by age and presence or absence of a painful limp (Table 197-3). The gluteus medius muscle stabilizes the pelvis during the stance phase, preventing the pelvis from dropping toward the leg in swing phase. An antalgic gait is a painful limp; the stance phase and stride of the affected limb are shortened to decrease the discomfort of weight bearing on the affected limb. The Trendelenburg gait has a normal stance phase, but excessive swaying of the trunk. Waddling gait refers to a bilateral decrease in function of the gluteus muscles.

Toe walking is a common complaint in early walkers. A physician should evaluate any child older than 3 years of age who still toe walks. Although this is most likely habit, a neuromuscular disorder (cerebral palsy, tethered cord), Achilles tendon contracture (heel cord tightness), or a leg-length discrepancy should be considered.
Orthopedics Assessment

Chapter 197

Uterine compression

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligohydramnios</td>
<td>Small pelvis</td>
</tr>
<tr>
<td>Uterine hypertonia</td>
<td>Bony lumbar spines</td>
</tr>
<tr>
<td>Multiple fetuses</td>
<td>Increased abdominal tone</td>
</tr>
<tr>
<td>Large fetus</td>
<td>Abnormal fetal posture (including breech)</td>
</tr>
<tr>
<td>Uterine deformities (bicorne)</td>
<td>Abnormal fetal muscular tone</td>
</tr>
</tbody>
</table>

Increased mechanical forces

Fetal constraint

Deformations

Craniofacial

- Scaphocephaly
- Plagiocephaly
- Mandibular asymmetry
- Flattened facies
- Deviated nasal septum
- Crumpled ear
- Craniostenosis

Extremity

- Dislocated hips
- Metatarsus adductus
- Equinovarus foot
- Calcaneovalgus foot
- Tibial bowing
- Hyperflexed hips
- Hyperextended knees
- Contractures
- Internal tibial torsion

Other

- Torticollis
- Lung hypoplasia
- Scoliosis

Figure 197-3 Deformation abnormalities resulting from uterine compression.

Table 197-3 Differential Diagnosis of Limping in Children

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>DIAGNOSTIC CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early walker: 1 to 3 years of age</td>
<td>Painful Limp</td>
</tr>
<tr>
<td></td>
<td>Septic arthritis and osteomyelitis</td>
</tr>
<tr>
<td></td>
<td>Transient monarticular synovitis</td>
</tr>
<tr>
<td></td>
<td>Occult trauma (“toddler’s fracture”)</td>
</tr>
<tr>
<td></td>
<td>Intervertebral diskitis</td>
</tr>
<tr>
<td></td>
<td>Malignancy</td>
</tr>
<tr>
<td></td>
<td><em>Painless Limp</em></td>
</tr>
<tr>
<td></td>
<td>Developmental dysplasia of the hip</td>
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<tr>
<td></td>
<td>Neuromuscular disorder</td>
</tr>
<tr>
<td></td>
<td>Cerebral palsy</td>
</tr>
<tr>
<td></td>
<td>Lower extremity length inequality</td>
</tr>
</tbody>
</table>

| Child: 3 to 10 years of age       | Painful Limp                                                   |
|                                  | Septic arthritis, osteomyelitis, myositis                      |
|                                  | Transient monarticular synovitis                              |
|                                  | Trauma                                                        |
|                                  | Rheumatologic disorders                                       |
|                                  | - Juvenile idiopathic arthritis                               |
|                                  | - Intervertebral diskitis                                     |
|                                  | Malignancy                                                    |
|                                  | *Painless Limp*                                               |
|                                  | Developmental dysplasia of the hip                             |
|                                  | Legg-Calve-Perthes disease                                    |
|                                  | Lower extremity length inequality                              |
|                                  | Neuromuscular disorder                                        |
|                                  | Cerebral palsy                                                |
|                                  | Muscular dystrophy (Duchenne)                                 |

| Adolescent: 11 years of age to maturity | Painful Limp                                                  |
|                                        | Septic arthritis, osteomyelitis, myositis                     |
|                                        | Trauma                                                       |
|                                        | Rheumatologic disorder                                       |
|                                        | - Slipped capital femoral epiphysis: acute; unstable          |
|                                        | Malignancy                                                   |
|                                        | *Painless Limp*                                              |
|                                        | Slipped capital femoral epiphysis: chronic; stable            |
|                                        | Developmental dysplasia of the hip: acetabular dysplasia      |
|                                        | Lower extremity length inequality                              |
|                                        | Neuromuscular disorder                                        |
FRACTURES

Fractures account for 10% to 15% of all childhood injuries. The anatomic, biomechanical, and physiologic differences in children account for unique fracture patterns and management. Fracture terminology helps describe fractures (Table 198-1).

The pediatric skeleton has a higher proportion of cartilage and a thicker, stronger, and more active periosteum, capable of producing a larger callus more rapidly than in an adult. The thick periosteum may decrease the rate of displaced fractures and stabilize fractures after reduction. Because of the higher proportion of cartilage, the skeletally immature patient can withstand more force before deformation or fracture than adult bone. As children mature into adolescence, the rate of healing slows and approaches that of adults.

PEDIATRIC FRACTURE PATTERNS

Buckle or torus fractures occur after compression of the bone; the bony cortex does not truly break. These fractures will typically occur in the metaphysis and are stable fractures that heal in approximately 4 weeks with immobilization. A common example is a fall onto an outstretched arm causing a buckle fracture in the distal radius.

Complete fractures occur when both sides of bony cortex are fractured. This is the most common fracture and may be classified as comminuted, oblique, transverse, or spiral, depending on the direction of the fracture line.

Greenstick fractures occur when a bone is angulated beyond the limits of plastic deformation. The bone fails on the tension side and sustains a bend deformity on the compression side. The force is insufficient to cause a complete fracture (Fig. 198-1).

Bowing fractures demonstrate no fracture line evident on radiographs, but the bone is bent beyond its limit of plastic deformation. This is not a true fracture, but will heal with periosteal reaction.

Physeal Fractures

Fractures involving the growth plate constitute about 20% of all fractures in the skeletally immature patient. These fractures are more common in males (2:1 male-female ratio). The peak incidence is 13 to 14 years in boys and 11 to 12 years in girls. The distal radius, distal tibia, and distal fibula are the most common locations.

Ligaments frequently insert onto epiphyses. Thus, traumatic forces to an extremity may be transmitted to the physis, which is not as biomechanically strong as the metaphysis; it may fracture with mechanisms of injury that may cause sprains in the adult. The growth plate is most susceptible to torsional and angular forces.

Physeal fractures are described using Salter-Harris classification, which allows for prognostic information regarding premature closure of the growth plate and poor functional outcomes. The higher the type number, the more likely the patient will have complications. There are five main groups (Fig. 198-2):

Type I: transverse fracture through the physis; growth disturbance is unusual
Type II: fracture through a portion of the physis and metaphysis; most common type of Salter-Harris fracture (75%)
Type III: fracture through a portion of the physis and epiphysis into the joint that may result in complication because of intra-articular component and because of disruption of the growing or hypertrophic zone of the physis

Table 198-1 Useful Fracture Terminology

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>The bone fragments separate completely</td>
</tr>
<tr>
<td>Incomplete</td>
<td>The bone fragments are still partially joined</td>
</tr>
<tr>
<td>Linear</td>
<td>Referring to a fracture line that is parallel to</td>
</tr>
<tr>
<td></td>
<td>the bone’s long axis</td>
</tr>
<tr>
<td>Transverse</td>
<td>Referring to a fracture line that is at a right</td>
</tr>
<tr>
<td></td>
<td>angle to the bone’s long axis</td>
</tr>
<tr>
<td>Oblique</td>
<td>Referring to a fracture line that is diagonal to</td>
</tr>
<tr>
<td></td>
<td>the bone’s long axis</td>
</tr>
<tr>
<td>Spiral</td>
<td>Referring to a twisting fracture</td>
</tr>
<tr>
<td>Commination</td>
<td>A fracture that results in several fragments</td>
</tr>
<tr>
<td>Compaction</td>
<td>The bone fragments are driven into each other</td>
</tr>
<tr>
<td>Angulation</td>
<td>The fragments have angular malalignment</td>
</tr>
<tr>
<td>Rotation</td>
<td>The fragments have rotational malalignment</td>
</tr>
<tr>
<td>Shortening</td>
<td>The fractured ends of the bones overlap</td>
</tr>
<tr>
<td>Open</td>
<td>A fracture in which the bone has pierced the skin</td>
</tr>
</tbody>
</table>

Figure 198-1 The greenstick fracture is an incomplete fracture. (Modified from White N, Sty R: Radiological evaluation and classification of pediatric fractures, Clin Pediatr Emerg Med 3:94–105, 2002.)
Type IV: fracture through the metaphysis, physis, and epiphysis with a high risk of complication
Type V: a crush injury to the physis with a poor functional prognosis

Types I and II fractures can often be managed by closed reduction and do not require perfect alignment. A major exception is the type II fracture of the distal femur, which is associated with a poor outcome unless proper anatomic alignment is obtained. Types III and IV fractures require anatomic alignment for successful treatment. Type V fractures are rare and often result in premature closure of the physis.

**MANAGEMENT OF PEDIATRIC FRACTURES**
The majority of pediatric fractures can be managed with closed methods. Some fractures need closed reduction to improve alignment. Approximately 4% of pediatric fractures require internal fixation. Patients with open physes are more likely to require internal fixation if they have one of the following fractures:
- Displaced epiphyseal fractures
- Displaced intra-articular fractures
- Fractures in a child with multiple injuries
- Open fractures
- Unstable fractures

The goal of internal fixation is to improve and maintain anatomic alignment. This is usually done with Kirschner wires, Steinmann pins, and cortical screws with subsequent external immobilization in a cast until healing is satisfactory. After healing, the hardware is frequently removed to prevent incorporation into the callus and prevent physeal damage.

External fixation without casting may be necessary for pelvic fractures causing hemodynamic instability. Fractures associated with soft tissue loss, burns, and neurovascular damage may benefit from external fixation.

**SPECIAL CONCERNS**

**Remodeling**
Fracture remodeling occurs because of a combination of periosteal resorption and new bone formation. Many pediatric fractures do not need perfect anatomic alignment for proper healing. Younger patients have greater potential for fracture remodeling. Fractures that occur in the metaphysis, near the growth plate, may undergo more remodeling. Fractures angulated in the plane of motion also remodel very well. Intra-articular fractures, angulated or displaced diaphyseal fractures, rotated fractures, and fracture deformity not in the plane of motion tend not to remodel as well.

**Overgrowth**
Overgrowth occurs in long bones as the result of increased blood flow associated with fracture healing. Femoral fractures in children younger than 10 years of age will frequently overgrow 1 to 3 cm. This is the reason end-to-end alignment for femur and long-bone fractures may not be indicated. After 10 years of age, overgrowth is less of a problem, so end-to-end alignment is recommended.

**Progressive Deformity**
Fractures and injuries to the physis can result in premature closure. If it is a partial closure, the consequence may be an angular deformity. If it is a complete closure, limb shortening may occur. The most commonly affected locations are the distal femur and the distal and proximal tibia.

**Neurovascular Injury**
Fractures and dislocations may damage adjacent blood vessels and nerves. The most common location is the distal humerus (supracondylar fracture) and the knee (dislocation and physeal fracture). It is necessary to perform and document a careful neurovascular examination distal to the fracture (pulse, sensory, and motor function).

**Compartment Syndrome**
Compartment syndrome is an orthopedic emergency that results from hemorrhage and soft tissue swelling within the tight fascial compartments of an extremity. This can result in muscle ischemia and neurovascular compromise unless it is surgically decompressed. The most common sites are the lower leg (tibial fracture) and arm (supracondylar fracture).

Affected patients have severe pain and will eventually have decreased sensation in the dermatomes supplied by the nerves.

**Figure 198-2** The types of growth plate injury as classified by Salter and Harris. See text for descriptions of types I to V. (From Salter RB, Harris WR: Injuries involving the epiphyseal plate, J Bone Joint Surg Am 45:587–622, 1963.)
located in the compartment. Swollen and tight compartments and pain with passive stretching are present. This can happen underneath a cast and may actually occur when a cast is applied too tightly. It is important to educate all patients with fractures on the signs of compartment syndrome and ensure that they realize it is an emergency.

**Toddler’s Fracture**

This is an oblique fracture of the distal tibia without a fibula fracture. There is often no significant trauma. Patients are usually 1 to 3 years old, but can be as old as 6 and present with limping and pain with weight bearing. There may be minimal swelling and pain. Initial radiographs do not always show the fracture; if symptoms persist, a repeat x-ray in 7 to 10 days may be helpful.

**Child Abuse**

Child abuse must always be considered in the differential diagnosis of a child with fractures, especially in those younger than 3 years (see Chapter 22). Common fracture patterns that should increase the index of suspicion include multiple fractures in different stages of radiographic healing, metaphyseal corner fractures (shaking), fractures too severe for the history, or fractures in nonambulatory infants. Although spiral fractures of long bones were historically considered pathognomonic for abuse, they can be seen in nonabuse situations.

When there is concern for child abuse, the child should have a full evaluation, which may include admission to the hospital. A thorough and well-documented physical examination should focus on soft tissue injuries, the cranium, and a funduscopic examination for retinal hemorrhages or detachment. A skeletal survey or a bone scan may be helpful in identifying other fractures.

**DEVELOPMENTAL DYSPLASIA OF THE HIP**

In developmental dysplasia of the hip (DDH), the hips at birth may be dislocated or dislocatable. The femoral head and acetabulum develop from the same mesenchymal cells; by 11 weeks’ gestation, the hip joint is formed. There are two types of DDH: teratologic and typical. Teratologic dislocations occur early in utero and are usually associated with neuromuscular disorders (spina bifida, arthrogryposis). Typical dislocations occur in the neurologically normal infant and can occur before or after birth. The true incidence of DDH is unknown, but it may be as high as 1.5 cases per 1000 infants.

**Etiology**

Newborn infants have ligamentous laxity that, if significant enough in the hip, may lead to spontaneous dislocation and reduction of the femoral head. Persistence of this spontaneous pattern can lead to pathologic changes, such as flattening of the acetabulum, muscle contractures that limit motion, and joint capsule tightening. The left hip is affected three times as often as the right hip, possibly because of in utero positioning.

Physiologic risk factors for DDH include a generalized ligamentous laxity, perhaps from maternal hormones that are associated with pelvic ligament relaxation (estrogen and relaxin). Female infants are at higher risk (9:1); family history is positive in 20% of all patients with DDH.

Other risk factors include breech presentation, firstborn child (60%), oligohydramnios, and postnatal infant positioning. In breech presentations, the fetal pelvis is situated in the maternal pelvis. This can increase hip flexion and limit overall fetal hip motion, causing further stretching of the already lax joint capsule and exposing the posterior aspect of the femoral head. The altered relationship between the acetabulum and femoral head causes abnormal acetabular development. Postnatal positioning of the hips in a tight swaddle with the hips adducted and extended can displace the hip joint.

Congenital muscular torticollis, metatarsus adductus, and clubfoot are associated with DDH. An infant with any of these three conditions should receive a careful examination of the hips.

**Clinical Manifestations**

Every newborn requires a screening physical examination for DDH; further evaluation through at least the first 18 months of life is part of the physical examination for toddlers. DDH evolves over time, so the examination may change as the patient ages. The examination starts with inspection for asymmetrical thigh and gluteal folds with the hips and knees flexed. A relative shortening of the femur with asymmetrical skin folds is a positive Galeazzi sign and indicates DDH. Range of motion should be assessed with the pelvis stabilized and the child supine on the examining table, not in the parent's lap (Fig. 199-1). Hip abduction should easily reach or exceed 75°, and hip adduction should reach 30°. Limitations may indicate contractures associated with DDH, especially decreased abduction.
The Barlow test attempts to dislocate an unstable hip (Fig. 199-2). The examiner should stabilize the infant’s pelvis with one hand and grasp the abducted and flexed thigh in the other hand. The hip should be flexed to 90°. Next, begin to adduct the hip, while applying a posterior force to the anterior hip. A hip that can be dislocated in this method is readily felt (clunk feeling) and is a positive test. It may reduce spontaneously once the posterior force is removed, or the examiner may need to perform the Ortolani test.

The Ortolani test may reduce a dislocated hip (Fig. 199-3). The examiner should stabilize the pelvis and hold the leg in the same method as for the Barlow test. The infant’s hip should be in 90° of flexion. Abduct the hip while applying anterior pressure to the posterior thigh. A positive test is the palpable reduction of the dislocation, which may be felt (clunk). After 2 months of age, the hip may develop muscular contractures, preventing positive Ortolani tests.

These tests should be performed with only gentle force and done one hip at a time. The test may need to be repeated multiple times, as they can be difficult to interpret. A click, which is not pathologic, may occur from breaking the surface tension of the hip joint or snapping gluteal tendons.

Bilateral fixed dislocations present a diagnostic dilemma because of the symmetry on exam. The Klisic test is useful in this situation; it is done by placing the third finger over the greater trochanter and the index finger over the anterior superior iliac spine, then drawing an imaginary line between the two. The line should point to the umbilicus in a normal child. However, in a dislocated hip, the greater trochanter is elevated, which causes the line to project lower (between the umbilicus and pubis). This test is helpful identifying bilateral DDH, which can otherwise be difficult to diagnose because of the symmetry found on examination.

Older children with unrecognized DDH may present with limping. A patient with increased lumbar lordosis and a waddling gait may have an unrecognized bilateral DDH.

\textbf{Figure 199-1} Hip abduction test. Place the infant supine, flex the hips 90°, and fully abduct the hips. Although the normal abduction range is broad, hip disease should be suspected in any patient who lacks more than 30° to 45° of abduction. (From Chung SMK: Hip Disorders in Infants and Children, Philadelphia, 1981, Lea & Febiger, p 69.)

\textbf{Figure 199-2} Barlow (dislocation) test. Reverse of Ortolani test. If the femoral head is in the acetabulum at the time of examination, the Barlow test is performed to discover any hip instability. A, The infant’s thigh is grasped as shown and adducted with gentle downward pressure. B, Dislocation is palpable as the femoral head slips out of the acetabulum. Diagnosis is confirmed with the Ortolani test.

\textbf{Figure 199-3} Ortolani (reduction) test. With the infant relaxed and content on a firm surface, the hips and knees are flexed to 90°. The hips are examined one at a time. The examiner grasps the infant’s thigh with the middle finger over the greater trochanter and lifts the thigh to bring the femoral head from its dislocated posterior position to opposite the acetabulum. Simultaneously the thigh is gently abducted, reducing the femoral head in the acetabulum. In a positive finding, the examiner senses reduction by a palpable, nearly audible clunk.
Radiographic Evaluation
Ultrasound is used for initial evaluation of infants with DDH. Ultrasonography is necessary for girls with a positive family history or breech presentation in both sexes. This should be obtained after 6 weeks of age to avoid confusion with physiologic laxity. Because the femoral head begins to ossify at 4 to 6 months of age, plain radiographs can be misleading until patients are older.

Complications
The most important and severe complication of DDH is iatrogenic avascular necrosis of the femoral head. This can occur from excessive flexion or abduction during positioning of the Pavlik harness or hip spica cast. Infants under 6 months of age are at highest risk. Pressure ulcers can occur with prolonged casting. Redislocation or subluxation of the femoral head and residual acetabular dysplasia can occur.

TRANSPORT MONOARTICULAR SYNOVITIS
Transient synovitis, also known as toxic synovitis, is a common cause of limping in children. It is a diagnosis of exclusion, because septic arthritis and osteomyelitis of the hip must be excluded (see Chapters 117 and 118).

Etiology and Epidemiology
The etiology of transient synovitis is uncertain, but possible causes are viral illness and hypersensitivity. Approximately 70% of children diagnosed with transient synovitis have an upper respiratory tract viral infection in the preceding 7 to 14 days. Biopsies have revealed nonspecific synovial hyper trophy. Hip joint aspirations, when necessary, are negative for bacterial culture or signs of bacterial infection.

Clinical Manifestations and Evaluation
The patient or family will describe an acute onset of pain in the groin/hip, anterior thigh, or knee. Irritation of the obturator nerve can cause referred pain in the thigh and knee when the pathology is at the hip. Patients with transient synovitis are often afebrile, walk with a painful limp, and have normal to minimally elevated white blood cell count, C-reactive protein, and erythrocyte sedimentation rate compared with bacterial diseases of the hip (Table 199-1). Table 197-3 lists the differential diagnosis of a limping child.

Treatment
The mainstay of treatment is bed rest and minimal weight bearing until the pain resolves. Nonsteroidal anti-inflammatory medication is usually sufficient to decrease pain. Limiting strenuous activity and exercise for 1 to 2 weeks following recovery is helpful. Follow-up will help ensure that there is no deterioration. Lack of improvement necessitates further evaluation for more serious disorders.

LEGG-CALVE-PERTHES DISEASE
Etiology and Epidemiology

Table 199-1

<table>
<thead>
<tr>
<th>Differences between Bacterial Infection and Transient Synovitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BACTERIAL INFECTION</strong></td>
</tr>
<tr>
<td>Elevated joint fluid cell count</td>
</tr>
<tr>
<td>Fever—temperature &gt;38.5°C</td>
</tr>
<tr>
<td>Leukocytosis</td>
</tr>
<tr>
<td>ESR &gt;20 mm/hour</td>
</tr>
<tr>
<td>Refusal to walk</td>
</tr>
<tr>
<td>Hip held in external rotation, abduction, and flexion</td>
</tr>
<tr>
<td>Severe pain and tenderness</td>
</tr>
<tr>
<td><strong>TRANSIENT SYNOVITIS</strong></td>
</tr>
<tr>
<td>Afebrile</td>
</tr>
<tr>
<td>Normal WBC count</td>
</tr>
<tr>
<td>Normal ESR and CRP</td>
</tr>
<tr>
<td>Painful limp</td>
</tr>
<tr>
<td>Hip held normally</td>
</tr>
<tr>
<td>Moderate pain and mild tenderness</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell.

*Examples: Septic arthritis, osteomyelitis of hip.
Legg-Calve-Perthes disease (LCPD) is idiopathic avascular necrosis (osteonecrosis) of the capital epiphysis of the femoral head. The etiology is unclear, but it is likely caused by an interruption of the blood supply to the capital femoral epiphysis. There may be an associated hypercoagulability state (factor V Leiden).

LCPD commonly presents in patients 3 to 12 years of age, with a mean age of 7 years. It is four to five times more common in boys.

Clinical Manifestations
Patients may not present for several weeks because of minimal discomfort; the classic presentation is a child with an atraumatic, painless limp. There may be mild or intermittent hip/groin, anterior thigh, or knee pain. Decreased internal rotation and abduction with some discomfort, thigh muscle spasm, and anterior thigh muscular atrophy may be present. Patients have delayed bone age.

Radiologic Evaluation
Anteroposterior and frog-leg radiographs of both hips are usually adequate for diagnosis and management. It is necessary to document the extent of the disease and follow its progression. MRI and bone scan are helpful to diagnose early LCPD.

Treatment and Prognosis
LCPD is usually a self-limited disorder that should be followed by a pediatric orthopedist. Initial treatment focuses on pain control and restoration of hip range of motion. The goal of treatment is prevention of complications, such as femoral head deformity and secondary osteoarthritis.

Containment is important in treating LCPD; the femoral head is contained inside the acetabulum, which acts like a mold for the capital femoral epiphysis as it reossifies. Nonsurgical containment uses abduction casts and orthoses, whereas surgical containment is accomplished with osteotomies of the proximal femur and pelvis.

The short-term prognosis is determined by the magnitude of the femoral head deformity after healing has completed. It is improved by early diagnosis, good follow-up, and compliance with the treatment plan. Older children and children with a residual femoral head deformity are more likely to develop osteoarthritis (OA). The incidence of OA in patients who developed LCPD after 10 years of age is close to 100%; it is negligible in children with onset before 5 years of age. Patients between 6 and 9 years of age have a risk of OA of less than 40%.

Classification
SCFE is classified as stable or unstable. Unstable patients refuse to ambulate even with crutches. Stable patients have an antalgic gait. SCFE can also be characterized as acute (symptoms less than 3 weeks) or chronic (symptoms over 3 weeks). Acute-on-chronic SCFE is seen when more than 3 weeks of symptoms are accompanied by an acute exacerbation of pain and difficulty/inability to bear weight.

Radiologic Evaluation
Anteroposterior and frog-leg radiographs are indicated. Patients with known SCFE or with a high index of suspicion should not undergo frog-leg lateral radiographs. Instead, a cross table lateral radiograph reduces the risk of iatrogenic progression. The earliest sign of SCFE is widening of the physis without displacement. Klein’s line (Fig. 199-4) is helpful in assessing the anteroposterior radiograph for SCFE. The slippage can be classified radiographically as type I (0% to 33% displacement), type II (34% to 50%), or type III (>50%). The likelihood of complications increases with degree of displacement.

Treatment
Patients with SCFE should be immediately made non–weight bearing and referred to a pediatric orthopedist. The goal is to prevent further slippage, enhance physesal closure, and minimize complications, which is usually accomplished with internal fixation in situ with a single cannulated screw. More severe cases may require surgical hip dislocation and reduction to realign the epiphysis. There is controversy surrounding the prophylactic fixation of the nonaffected side. Assessment for endocrine disorders is important, particularly in children outside the range of 10 to 16 years of age.
Internal femoral torsion or anteversion is the most common cause of in-toeing in children 2 years or older (Table 200-1). It is at its worst between 4 and 6 years of age, and then resolves. It occurs twice as often in girls. Many cases are associated with generalized ligamentous laxity. The etiology of femoral anteversion is likely congenital and is common in individuals with abnormal sitting habits such as W-sitting.

Clinical Manifestations. The family may give a history of W-sitting, and there may be a family history of similar concerns when the parents were younger. The child may have kissing kneecaps due to increased internal rotation of the femur. While walking, the entire leg will appear internally rotated, and with running the child may appear to have an egg-beater gait where the legs flip laterally. The flexed hip will have internal rotation increased to 80° to 90° (normal 60° to 70°) and external rotation limited to about 10°. Radiographic evaluation is usually not indicated.

### In-Toeing, Out-Toeing, and Toe-Walking

**Femoral Anteversion**

Internal femoral torsion or femoral anteversion is the most common cause of in-toeing in children 2 years or older (Table 200-1). It is at its worst between 4 and 6 years of age, and then resolves. It occurs twice as often in girls. Many cases are associated with generalized ligamentous laxity. The etiology of femoral anteversion is likely congenital and is common in individuals with abnormal sitting habits such as W-sitting.

**Clinical Manifestations.** The family may give a history of W-sitting, and there may be a family history of similar concerns when the parents were younger. The child may have kissing kneecaps due to increased internal rotation of the femur. While walking, the entire leg will appear internally rotated, and with running the child may appear to have an egg-beater gait where the legs flip laterally. The flexed hip will have internal rotation increased to 80° to 90° (normal 60° to 70°) and external rotation limited to about 10°. Radiographic evaluation is usually not indicated.

### Internal Tibial Torsion

The two most serious complications of SCFE are chondrolysis and avascular necrosis. Chondrolysis is destruction of the articular cartilage. It is associated with more severe slips and with intra-articular penetration of operative hardware. This can lead to severe osteoarthritis (OA) and disability. Avascular necrosis occurs when there is a disruption of the blood supply to the capital femoral epiphysis. This usually happens at the time of injury, but may occur during forced manipulation of an unstable slip. Avascular necrosis may occur in up to 50% of unstable SCFEs and may lead to OA.

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**Table 200-1** Common Causes of In-Toeing and Out-Toeing

<table>
<thead>
<tr>
<th>IN-TOEING</th>
<th>OUT-TOEING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal femoral torsion or anteversion</td>
<td>External femoral torsion or retroversion</td>
</tr>
<tr>
<td>Internal tibial torsion</td>
<td>External tibial torsion</td>
</tr>
<tr>
<td>Metatarsus adductus</td>
<td>Calcaneevalgus feet</td>
</tr>
<tr>
<td>Talipes equinovarus (clubfoot)</td>
<td>Hypermobile pes planus (flatfoot)</td>
</tr>
<tr>
<td>Developmental dysplasia</td>
<td>Slipped capital femoral epiphysis</td>
</tr>
</tbody>
</table>

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**Figure 199-4** Slipped capital femoral epiphysis (SCFE). A, Anteroposterior radiograph reveals a widened physis (small arrows) and decreased height of the epiphysis on the left. In addition, there is loss (large arrow) of the Capener triangle (c) (normal double density of the medial metaphysis superimposed on the posterior acetabular rim on right) and an abnormal lateral femoral neck line (normal on right). B, Frog, lateral view confirms the inferomedial position of the SCFE. (From Blickman H: Pediatric Radiology, the Requisites, ed 2, St Louis, 1998, Mosby, p 244.)
This is the most common cause of in-toeing in a child younger than 2 years old. When it is the result of in utero positioning, it may be associated with metatarsus adductus.

Clinical Manifestations. The child will present with a history of in-toeing. The degree of tibial torsion may be measured using the thigh-foot angle (Fig. 200-1). The patient lies prone on a table with the knee flexed to 90°. The long axis of the thigh is compared to the long axis of the foot to determine the thigh-foot angle. Negative angles are associated with internal tibial torsion, and positive angles are associated with external tibial torsion.

Treatment of In-toeing
The mainstay of management is to identify patients who have pathologic reasons for in-toeing and reassurance and follow-up to document improvement for patients with femoral anteversion and internal tibial torsion. It can take until 7 to 8 years of age for correction, so it is important to inform families of the appropriate timeline. Braces (Denis Browne splint) do not improve these conditions. Fewer than 1% of all patients with in-toeing will need surgical intervention because of functional disability or cosmetic appearance.

Out-Toeing

External Tibial Torsion
External tibial torsion is the most common cause of out-toeing and may be associated with a calcaneovalgus foot (see Chapter 201). This is often related to in utero positioning. It may improve over time, but because the tibia rotates externally with age, external tibial torsion can worsen. It may be an etiologic factor for patellofemoral syndrome, especially when combined with femoral anteversion. Treatment is usually observation and reassurance, but patients with dysfunction and cosmetic concerns may benefit from surgical intervention.

Angular Variations

The majority of patients who present with knock-knees (genu valgum) or bowlegs (genu varum) are normal (Fig. 200-2). Infants are born with maximum genu varum. The lower extremity straightens out around 18 months of age. Children typically progress to maximal genu valgum around 4 years. The legs are usually straight to a slight genu valgum in adulthood.

It is important to inquire about family history and assess overall height. A child who is 2 standard deviations below normal with angular deformities may have skeletal dysplasia. Dietary history should be obtained, as rickets (see Chapter 31) may cause angular deformities. For genu valgum, following the intermalleolar distance (distance between the two tibial medial malleoli with the knees touching) is used. Measurement of the intercondylar distance (the distance between the medial femoral condyles with the medial malleoli touching) is used for genu varum. These measurements track improvement or progression. When obtaining...
radiographs, it is important to have the patella, not the feet, facing forward. In the child with external tibial torsion, having the feet facing forward gives the false appearance of bowlegs.

**Genu Valgum**

Physiologic knock-knees are most common in 3- to 4-year-olds and usually resolve between 5 and 8 years of age. Patients with asymmetrical genu valgum or severe deformity may have underlying disease causing their knock-knees (e.g., renal osteodystrophy, skeletal dysplasia). Treatment is based on reassurance of the family and patient. Surgical intervention may be indicated for severe deformities, gait dysfunction, pain, and cosmesis.

**Genu Varum**

Physiologic bowlegs are most common in children older than 18 months with symmetrical genu varum. This will generally improve as the child approaches 2 years of age. The most important consideration for genu varum is differentiating between physiologic genu varum and Blount disease (tibia vara).

**Tibia Varus (Blount Disease)**

Tibia vara is the most common pathologic disorder associated with genu varum. It is characterized by abnormal growth of the medial aspect of the proximal tibial epiphysis, resulting in a progressive varus deformity. Blount disease is classified according to age of onset:
- Infantile (1 to 3 years)
- Juvenile (4 to 10 years)
- Adolescent (>11 years)

Late-onset Blount disease is less common than infantile disease. The cause is unknown, but it is felt to be secondary to growth suppression from increased compressive forces across the medial knee.

**Clinical Manifestations**

Infantile tibia vara is more common in African Americans, females, and obese patients. Many patients were early walkers. Nearly 80% of patients with infantile Blount disease have bilateral involvement. It is usually painless. The patients will often have significant internal tibial torsion and lower extremity leg-length discrepancy. There may also be a palpable medial tibial metaphyseal beak.

*Late-onset* Blount disease is more common in African Americans, males, and markedly obese patients. Only 50% have bilateral involvement. The initial presentation is usually painful bowlegs. Late-onset Blount disease is usually not associated with palpable metaphyseal beaking, significant internal tibial torsion, or significant leg-length discrepancy.

**Radiologic Evaluation**

Weight-bearing anteroposterior and lateral radiographs of both legs are necessary for the diagnosis of tibia vara. Fragmentation, wedging, and beak deformities of the proximal medial tibia are the major radiologic features of infantile Blount disease. In late-onset Blount disease, the medial deformity may not be as readily noticeable. It can be very difficult to tell the difference between physiologic genu varum and infantile Blount disease on radiographs in patients younger than 2 years of age.

**Treatment**

Once the diagnosis of Blount disease is confirmed, treatment should begin immediately. Orthotics to unload the medial compressive forces can be used in children younger than 3 years of age with a mild deformity. Compliance with this regimen can be difficult. Nonoperative management of more severe Blount disease is contraindicated. Any patient older than 4 years should undergo surgical intervention. Patients with moderate to severe deformity and patients who fail orthotic treatment also require surgical intervention. Proximal tibial valgus osteotomy with fibular diaphyseal osteotomy is the usual procedure performed.

**LEG-LENGTH DISCREPANCY**

Leg-length discrepancy (LLD) is common and may be due to differences in the femur, tibia, or both bones. The differential diagnosis is extensive, but common causes are listed in Table 200-2. The majority of the lower extremity growth comes from the distal femur (38%) and the proximal tibia (27%).

**Measuring Leg-Length Discrepancy**

Clinical measurements using bony landmarks (anterior superior iliac spine to medial malleolus) are inaccurate. The *teloradiograph* is a single radiograph of both legs that can be done in very young children. The *orthoradiograph* consists of three slightly overlapping exposures of the hips, knees, and ankles. The *scanogram* consists of three standard radiographs of the hips, knees, and ankles with a ruler next to the extremities. A
computed tomography (CT) scanogram is the most accurate measure of LLD, but also has the highest radiation exposure. Technology such as EOS/slot scanning is an extremely accurate, reduced-radiation alternative to CT scan. The measured discrepancy is followed using Moseley and Green-Anderson graphs.

### Treatment
Treating LLD is complex. The physician must take into account the estimated adult height, discrepancy measurements, skeletal maturity, and the psychological aspects of the patient and family. LLD greater than 2 cm usually requires treatment. Shoe lifts can be used, but they will often cause psychosocial problems for the child and may make the shoes heavier and less stable. Surgical options include shortening of the longer extremity, lengthening of the shorter extremity, or a combination of the two procedures. Discrepancies less than 5 cm are treated by epiphysiodesis (surgical physeal closure) of the affected side, whereas discrepancies greater than 5 cm are treated by lengthening. Current use of removable implants, which permit growth modulation without permanent impact on growth plates, has allowed for early and more accurate treatment.

### KNEE

The knee joint is constrained by soft tissues rather than the usual geometric fit of articulating bones. The medial and lateral collateral ligaments as well as the anterior and posterior cruciate ligaments maintain knee stability. Weight and force transmission can cross articular cartilage and the meniscus. The patellofemoral joint is the extensor mechanism of the knee and a common site of injury in the adolescent (Fig. 200-3).

Knee effusion or swelling is a common sign of injury. When the fluid accumulates rapidly after an injury, it is usually a hemarthrosis (blood in the joint) and may indicate a fracture, ligamentous disruption (often of the anterior cruciate ligament [ACL]), or meniscus tear. Unexplained knee effusion may occur with arthritis (septic, Lyme disease, viral, postinfectious, juvenile idiopathic arthritis, systemic lupus erythematosus). It may also occur as a result of overactivity and hypermobile joint syndrome (ligamentous laxity). An aspiration and laboratory evaluation of unexplained effusion can help expedite a diagnosis.

#### Discoid Lateral Meniscus
Each meniscus is normally semilunar in shape; rarely the lateral meniscus will be disk shaped. A normal meniscus is attached at the periphery and glides anteriorly and posteriorly with knee motion. The discoid meniscus is less mobile and may tear more easily. When there is inadequate posterolateral attachment, the discoid meniscus can displace anteriorly with knee flexion, causing an audible click. Most commonly, patients will present in late childhood or early adolescence after an injury with knee pain and swelling. The anteroposterior radiographs can show increased joint space and a squared-off appearance of the lateral femoral condyle; magnetic resonance imaging (MRI) can confirm the diagnosis. Treatment is usually arthroscopic excision of tears and reshaping of the meniscus.

#### Popliteal Cyst
A popliteal cyst (Baker cyst) is commonly seen in the middle childhood years. The cause is the distension of the gastrocnemius and semimembranous bursa along the posteromedial aspect of the knee by synovial fluid. In adults, Baker cysts are associated with meniscus tears. In...
childhood, the cysts are usually painless and benign. They often spontaneously resolve, but it may take several years. Knee radiographs are normal. The diagnosis can be confirmed by ultrasound. Treatment is reassurance, because surgical excision is indicated only for progressive cysts or cysts that cause disability.

### Osteochondritis Dissecans

Osteochondritis dissecans (OCD) most commonly involves the knee. It occurs when an area of bone adjacent to the articular cartilage suffers a vascular insult and separates from the adjacent bone. It most commonly affects the lateral aspect of the medial femoral condyle. Patients may complain of knee pain or swelling. The lesions can be seen on anteroposterior, lateral, and tunnel view radiographs. MRI can be helpful in determining the extent of the injury. In young patients with intact articular cartilage, the lesion will often revascularize and heal with rest from activities. The healing process may take several months and requires radiographic follow-up to document healing. With increasing age, the risk for articular cartilage damage and separation of the bony fragment increases. Older patients are more likely to need surgical intervention. Any patient with a fracture of the articular cartilage will not improve without surgical intervention. Patients with OCD should be referred to a specialist.

### Osgood-Schlatter Disease

Osgood-Schlatter disease is a common cause of knee pain at the insertion of the patellar tendon on the tibial tubercle. The stress from a contracting quadriceps muscle is transmitted through the developing tibial tubercle, which can cause a microfracture or partial avulsion fracture in the ossification center. It usually occurs after a growth spurt and is more common in boys. The age at onset is typically 11 years for girls and 13 to 14 years for boys.

Patients will present with pain during and after activity as well as have tenderness and local swelling over the tibial tubercle. Radiographs may be necessary to rule out infection, tumor, or avulsion fracture.

Rest and activity modification are paramount for treatment. Pain control medications and icing may be helpful. Lower extremity flexibility and strengthening exercise programs are important. Some patients may require immobilization. The course is usually benign, but symptoms frequently last 1 to 2 years. Complications can include bony enlargement of the tibial tubercle and avulsion fracture of the tibial tubercle.

### Patellofemoral Disorders

The patellofemoral joint is a complex joint that depends on a balance between restraining ligaments of the patella, muscular forces around the knee, and alignment for normal function. The interior surface of the patella has a V-shaped bottom that moves through a matching groove in the femur called the trochlea. When the knee is flexed, the patellar ligaments and the majority of the muscular forces pulling through the quadriceps tendon move the patella in a lateral direction. The vastus medialis muscle counteracts the lateral motion, pulling the patella toward the midline. Problems with function of this joint usually result in anterior knee pain.

**Idiopathic anterior knee pain** is a common complaint in adolescents. It is particularly prevalent in adolescent female athletes. Previously, this was referred to as chondromalacia of the patella, but this term is incorrect as the joint surfaces of the patella are normal. It is now known as **patellofemoral pain syndrome** (PFPS). The patient will present with anterior knee pain that worsens with activity, going up and down stairs, and soreness after sitting in one position for an extended time. There is usually no associated swelling. The patient may complain of a grinding sensation under the kneecap. Palpating and compressing the patellofemoral joint with the knee extended elicits pain. Patients often have weak hip musculature or poor flexibility in the lower extremities. Radiographs are rarely helpful but may be indicated to rule out other diagnoses such as osteochondritis dissecans.

Treatment is focused on correcting the biomechanical problems that are causing the pain. This is usually done using an exercise program emphasizing hip girdle and vastus medialis strengthening with lower extremity flexibility. Anti-inflammatory medication, ice, and activity modifications may also be helpful. Persistent cases should be referred to an orthopedic or sports medicine specialist.

One must exclude **recurrent patellar subluxation** and **dislocation** when evaluating a patient with PFPS. Acute traumatic dislocation will usually cause significant disability and weight bearing seen in an initial dislocation. Patients with recurrent dislocations often have associated ligamentous laxity, genu valgum, and femoral anteverision. The initial treatment is non-operative and may involve a brief period of immobilization, followed by an aggressive physical therapy program designed to strengthen the quadriceps and improve function of the patellofemoral joint. Continued subluxation or recurrent dislocation is failure of this treatment plan, and surgical repair is usually necessary.
FOOT

In newborns and non-weight-bearing infants, the difference between posturing and deformity is important. Posturing is the habitual position in which the infant holds the foot; passive range of motion is normal. Deformity produces an appearance similar to posturing, but passive motion is restricted. Most pediatric foot disorders are painless. Foot pain is more common in older children (Table 201-1).

CLUB FOOT (TALIPES EQUINOVARUS)

A clubfoot deformity involves the entire leg, not just the foot. It affects 1 in 1000 newborns and is bilateral in one half of cases. The tarsals in the affected foot are hypoplastic; the talus is most affected. The muscles of the limb are hypoplastic because of the abnormal tarsal interactions, which leads to a generalized limb hypoplasia, mainly affecting and shortening the foot. There is usually atrophy of the calf musculature.

Etiology

Family history is important. Club foot can be congenital, teratologic, or positional. Although congenital clubfoot (75% of all cases) is usually an isolated abnormality, every infant should be assessed for developmental dysplasia of the hip. Teratologic clubfoot is associated with a neuromuscular disorder, such as myelomeningocele, arthrogryposis, or other syndromes. Positional clubfoot is a normal foot that was held in the deformed position in utero.

Clinical Manifestations

The diagnosis is seldom confused with other disorders (Fig. 201-1). The presence of clubfoot should prompt a careful search for other abnormalities. The infant will have hindfoot equinus and varus, forefoot adduction, and varying degrees of rigidity. All are secondary to the abnormalities of the talonavicular joint. Calf atrophy and foot shortening are more noticeable in older children.

Radiologic Evaluation

In infants, radiographs and advanced imaging are rarely necessary for assessment because their tarsals have incomplete ossification. The navicular ossifies at about 3 years of age for girls and 4 years for boys. As children age, radiographs can be used to follow the tibial calcaneal and lateral talocalcaneal angles and to assess navicular positioning.

Table 201-1

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>DIAGNOSTIC CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 6 years</td>
<td>Poorly fitting shoes, Fracture, Puncture wound, Foreign body, Osteomyelitis, Cellulitis, Juvenile idiopathic arthritis, Hair tourniquet, Leukemia</td>
</tr>
<tr>
<td>6 to 12 years</td>
<td>Poorly fitting shoes, Trauma (fracture, sprain), Juvenile idiopathic arthritis, Puncture wound, Sever disease, Accessory tarsal navicular, Hypermobile flatfoot, Oncologic (Ewing sarcoma, leukemia)</td>
</tr>
<tr>
<td>12 to 18 years</td>
<td>Poorly fitting shoes, Stress fracture, Trauma (fracture, sprain), Foreign body, Ingrown toenail, Metatarsalgi, Plantar fascitis, Achilles tendinopathy, Accessory ossicles (navicular, os trigonum), Tarsal coalition, Avascular necrosis of metatarsal (Freiberg infarction) or navicular (Kohler disease), Plantar warts</td>
</tr>
</tbody>
</table>


Decision-Making Algorithm

Available @ StudentConsult.com

In-Toeing, Out-Toeing, and Toe-Walking

Treatment

The goal of treatment is to correct the deformity and preserve mobility. Nonoperative treatment involves the Ponseti method of serial casting. The Ponseti method also relies on a percutaneous tenotomy of the Achilles tendon to help correct the equinus deformity.
Metatarsus adductus is the most common foot disorder in infants. It is characterized by a convexity of the lateral foot (Fig. 201-2) and is caused by in utero positioning. It is bilateral in half of cases. Occurring equally in boys and girls, it is more common in first-born children because of the smaller primigravid uterus. Two percent of infants with metatarsus adductus have developmental dysplasia of the hip.

Clinical Manifestations
The forefoot is adducted and sometimes supinated, but the midfoot and hindfoot are normal. The lateral border of the foot is convex, while the medial border is concave. Ankle dorsiflexion and plantar flexion are normal. With the midfoot and hindfoot stabilized, the deformity can be pushed beyond a neutral position (into abduction). Older children may present with an in-toeing gait.

Treatment
True metatarsus adductus resolves spontaneously over 90% of the time without treatment, so reassurance is all that is needed. Metatarsus adductus that does not improve within 2 years needs evaluation by a pediatric orthopedist. Persistent cases may benefit from serial casting or bracing, and potentially surgery to help reduce the risk of disability in adulthood.

CALCANEOVALGUS FOOT
The calcaneovalgus foot is another common foot disorder in newborns that is secondary to in utero positioning. It is characterized by a hyperdorsiflexed foot with forefoot abduction and heel valgus. It is usually unilateral. The appearance may be quite severe dorsiflexion, but it is not a rigid deformity like congenital vertical talus. Simulated weight-bearing radiographs may be necessary for questionable diagnoses. The calcaneovalgus foot will appear normal or have minimal hindfoot valgus.

This disorder requires no treatment beyond reassurance. Parents can be taught passive stretching exercises for their infant’s foot. Most affected infants realign by 2 years. A calcaneovalgus foot can be associated with bowing of the tibia, which resolves spontaneously, but a leg length discrepancy may exist.

HYPERMOBILE PES PLANUS (FLEXIBLE FLATFOOT)
Hypermobile or pronated feet are seen in 15% of adults. The child with flatfeet is usually asymptomatic and has no activity limitations. Newborn and toddler flatfoot is the result of ligamentous laxity and fat in the medial longitudinal arch. This is called developmental flatfoot and usually improves by 6 years of age. In older children, flatfoot is typically the result of generalized ligamentous laxity, and there is often a positive family history. Hypermobile flatfoot can be thought of as a normal variant.

Clinical Manifestations
In the non-weight-bearing position, the older child with a flexible flatfoot will have a medial longitudinal arch. When weight bearing, the foot pronates (arch collapse) with varying degrees of hindfoot valgus. Subtalar motion (essentially all ankle motion except plantar and dorsiflexion) is normal. Any loss of subtalar motion may indicate a rigid flatfoot, which can be related to tarsal coalition, neuromuscular disorders (cerebral palsy), and heel cord contractures. Radiographs of hypermobile flatfeet are usually not indicated.

Treatment
Hypermobile pes planus cannot be diagnosed until after 6 years of age; before that, it is developmental pes planus. Reassurance that this is a normal variant is very important. Patients who are symptomatic with activity may require education on proper, supportive footwear, orthotics/arch supports, and heel cord stretching.

TARSAL COALITION
Patients with tarsal coalition will usually present with a rigid flatfoot (loss of inversion and eversion at the subtalar joint). Coalition is produced by a congenital fusion or failure of segmentation of two or more tarsal bones. The attachment may be fibrous, cartilaginous, or osseous. Tarsal coalition can be unilateral or bilateral and will often become symptomatic in
early adolescence. The most common forms of tarsal coalition are calcaneonavicular and talocalcaneal.

**Clinical Manifestations**

The patient will usually present with hindfoot pain, which may radiate laterally because of peroneal muscle spasm. Symptoms are exacerbated by sports, and young athletes can present with frequent ankle sprains. There is a familial component. Pes planus is usually present in both weight bearing and non-weight-bearing positions. There is usually a loss of subtalar motion, and passive attempts at joint motion may produce pain.

**Radiologic Evaluation**

Anteroposterior, lateral, and oblique radiographs should be obtained, but they may not always clearly identify the disorder. The oblique view often identifies the calcaneonavicular coalition. Computed tomography (CT) is the gold standard for diagnosis of tarsal coalition. Even patients with obvious calcaneonavicular coalition on plain radiographs should have a CT scan to rule out a second coalition.

**Treatment**

Coalitions that are asymptomatic (the majority) do not need treatment. Nonoperative treatment for patients with pain consists of cast immobilization for a few weeks and foot orthotics. The symptoms will often return, necessitating surgery. Surgical excision of the coalition and soft tissue interposition to prevent reossification can be very effective.

**CAVUS FOOT**

Cavus foot is characterized by increased height of the medial longitudinal arch (high arch) and frequently hindfoot varus. It can be classified as physiologic or neuromuscular. Most patients with physiologic cavus foot are asymptomatic. A thorough neurologic examination on all patients with a cavus foot is important. Patients with painful high arches have a high risk of neurologic (tethered cord) and neuromuscular disease, and there is a strong association with Charcot-Marie-Tooth disease, a familial neuropathy. The underlying disorder should be treated first. Nonoperative treatment using orthotics is usually not helpful. Progressive, symptomatic cavus foot will likely need surgical reconstruction.

**IDIOPATHIC AVASCULAR NECROSIS**

Kohler disease (tarsal navicular) and Freiberg disease (head of the second metatarsal) are uncommon and due to avascular necrosis. Patients will present with pain at the affected site with activity and weight bearing. Infection, fracture, and neoplasm should be excluded. Treatment consists of immobilization and activity restriction. The majority of the patients will improve upon subsequent revascularization and re-formation of bone.

**SEVER DISEASE (CALCANEAL APOPHYSITIS)**

Sever disease is a common cause of heel pain among active young people. The mean age of presentation for girls is about 9 years of age and for boys about 11 to 12 years. Approximately 60% of cases are bilateral. Sever disease is caused by the forces of the calf musculature through the Achilles tendon at the calcaneal apophysis, causing microfracture. As the child ages and the apophysis begins to close, the pain disappears.

**Clinical Manifestations**

The common presentation is a young athlete who develops heel pain with activity that decreases with rest. Swelling is rare, but limping may be associated with Sever disease. The child will have pain to palpation of the posterior calcaneus and often tight heel cords. Radiographs are rarely indicated, but with persistent pain they should be done to exclude infection or tumor.

**Treatment**

Activity modification, icing, and anti-inflammatory medications can be helpful. A program designed to improve heel cord flexibility and overall ankle strength may decrease symptoms. Heel elevation using heel wedges or heel cups can be helpful.

**TOE DEFORMITIES**

Curly toes are the most common deformity of the lesser toes. The fourth and fifth toes are most commonly affected. Curly toes are characterized by flexion at the proximal interphalangeal joint with lateral rotation of the toe. It is caused by contractures of the flexor digitorum brevis and longus tendons. Some curly toes will spontaneously resolve by 3 to 4 years of age. Persistent deformity may be treated by surgical tenotomy.

Polydactyly (extra toes) is usually found on the initial newborn physical examination. When the extra toe is adjacent to the fifth toe and attached by only a stalk of soft tissue or skin, simple ligation or amputation is effective. When the deformity involves the great toe or middle toes, or when the extra digit has cartilage or bone, delayed surgical intervention is indicated. Syndactyly (fusion of toes) is more common than polydactyly. It is usually a benign cosmetic problem. Both syndactyly and polydactyly may be associated with malformation syndromes (Table 201-2).
### Table 201-2
Disorders Associated with Syndactyly and Polydactyly

<table>
<thead>
<tr>
<th>POLYDACTYLY</th>
<th>SYNDAC T YL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis-van Creveld syndrome</td>
<td>Apert syndrome</td>
</tr>
<tr>
<td>Rubinstein-Taybi syndrome</td>
<td>Carpenter syndrome</td>
</tr>
<tr>
<td>Carpenter syndrome</td>
<td>de Lange syndrome</td>
</tr>
<tr>
<td>Meckel-Gruber syndrome</td>
<td>Holt-Oram syndrome</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>Orofaciodigital syndrome</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>Polysyndactyly</td>
</tr>
<tr>
<td>Orofaciodigital syndrome</td>
<td>Fetal hydantoin syndrome</td>
</tr>
<tr>
<td></td>
<td>Laurence-Moon-Biedl syndrome</td>
</tr>
<tr>
<td></td>
<td>Fanconi pancytopenia</td>
</tr>
<tr>
<td></td>
<td>Trisomy 21</td>
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<td></td>
<td>Trisomy 13</td>
</tr>
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<td></td>
<td>Trisomy 18</td>
</tr>
</tbody>
</table>

### Chapter 202

**SPINE**

**SPINAL DEFORMITIES**
A simplified classification of the common spinal abnormalities, scoliosis and kyphosis, is presented in Table 202-1.

### Clinical Manifestations

Most patients will present for evaluation of an asymmetrical spine, which is usually pain free. A complete physical examination is necessary for any patient with a spinal deformity, because the deformity can indicate an underlying disease. The back is examined from behind (Fig. 202-1). First, the levelness of the pelvis is assessed. Leg-length discrepancy produces pelvic obliquity, which often results in **compensatory scoliosis**. When the pelvis is level, the spine is examined for symmetry and spinal curvature with the patient upright. Cutaneous lesions (hemangioma, skin dimple, or hair tuft) should be noted. The spine should be palpated for areas of tenderness.

The patient is then asked to bend forward with the hands directed between the feet (Adams forward bend test). The examiner should inspect for asymmetry in the spine. The presence of the hump in this position is the hallmark for scoliosis. The area opposite the hump is usually depressed because of spinal rotation. Scoliosis is a rotational malalignment of one vertebra on another, resulting in rib elevation in the thoracic spine and paravertebral muscle elevation in the lumbar spine. With the patient still in the forward flexed position, inspection from the side can reveal the degree of roundback. A sharp forward angulation in the thoracolumbar region indicates a **kyphotic deformity**. It is important to examine the skin for café au lait spots (**neurofibromatosis**), hairy patches, and nevi (**spinal dysraphism**). Abnormal extremities may indicate skeletal dysplasia, whereas heart murmurs can be associated with Marfan syndrome. It is essential to do a full neurologic examination to determine whether the scoliosis is idiopathic or secondary to an underlying neuromuscular disease, and to assess whether the scoliosis is producing any neurologic sequelae.

### Table 202-1
Classification of Spinal Deformities

<table>
<thead>
<tr>
<th>SCOLIOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Infantile</td>
</tr>
<tr>
<td>Juvenile</td>
</tr>
<tr>
<td>Adolescent</td>
</tr>
<tr>
<td><strong>Congenital</strong></td>
</tr>
<tr>
<td>Failure of formation</td>
</tr>
<tr>
<td>Wedge vertebrae</td>
</tr>
<tr>
<td>Hemivertebrae</td>
</tr>
<tr>
<td>Failure of segmentation</td>
</tr>
<tr>
<td>Unilateral bar</td>
</tr>
<tr>
<td>Bilateral bar</td>
</tr>
<tr>
<td>Mixed</td>
</tr>
<tr>
<td><strong>Neuromuscular</strong></td>
</tr>
<tr>
<td>Neuropathic diseases</td>
</tr>
<tr>
<td>Upper motor neuron disease</td>
</tr>
<tr>
<td>Cerebral palsy</td>
</tr>
<tr>
<td>Spinocerebellar degeneration</td>
</tr>
<tr>
<td>Friedreich ataxia</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth disease</td>
</tr>
<tr>
<td>Syringomyelia</td>
</tr>
<tr>
<td>Spinal cord tumor</td>
</tr>
<tr>
<td>Spinal cord trauma</td>
</tr>
<tr>
<td>Lower motor neuron disease</td>
</tr>
<tr>
<td>Myelodysplasia</td>
</tr>
<tr>
<td>Poliomyelitis</td>
</tr>
<tr>
<td>Spinal muscular atrophy</td>
</tr>
<tr>
<td>Myopathic diseases</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
</tr>
<tr>
<td>Arthrogryposis</td>
</tr>
<tr>
<td>Other muscular dystrophies</td>
</tr>
</tbody>
</table>

### Syndromes
- Neurofibromatosis
- Marfan syndrome
- **Compensatory**
- Leg-length inequality

### KYPHOSIS
- Postural roundback
- Scheuermann disease
- Congenital kyphosis

Adapted from the Terminology Committee of the Scoliosis Research Society, 1975.
Radiologic Evaluation
Initial radiographs should include a posteroanterior and lateral standing film of the entire spine. The iliac crests should be visible to help determine skeletal maturity. The degree of curvature is measured from the most tilted or end vertebra of the curve superiorly and inferiorly to determine the Cobb angle (Fig. 202-2). Newer imaging modalities such as slot scanning or EOS provide the ability to obtain accurate measurements with much lower radiation than radiographs.

SCOLIOSIS
Alterations in normal spinal alignment that occur in the anteroposterior plane are termed scoliosis. Most scoliotic deformities...
are idiopathic. Scoliosis may also be congenital, neuromuscular, or compensatory from a leg-length discrepancy.

**Idiopathic Scoliosis**

**Etiology and Epidemiology**

Idiopathic scoliosis is the most common form of scoliosis. It occurs in healthy, neurologically normal children. Approximately 20% of patients have a positive family history. The incidence is slightly higher in girls than boys, and the condition is more likely to progress and require treatment in females. There is some evidence that progressive scoliosis may have a genetic component as well.

Idiopathic scoliosis can be classified in three categories: **infantile** (birth to 3 years), **juvenile** (4 to 10 years), and **adolescent** (>11 years). Idiopathic adolescent scoliosis is the most common cause (80%) of spinal deformity. The right thoracic curve is the most common pattern. Juvenile scoliosis is uncommon, but may be underrepresented because many patients do not seek treatment until they are adolescents. In any patient younger than 11 years of age, there is a greater likelihood that scoliosis is not idiopathic. The prevalence of an intraspinal abnormality in a child with congenital scoliosis is approximately 40%.

**Clinical Manifestations**

Idiopathic scoliosis is a painless disorder 70% of the time. A patient with pain requires a careful evaluation. Any patient presenting with a left-sided curve has a high incidence of intraspinal pathology (syrinx or tumor). Evaluation of the spine with magnetic resonance imaging (MRI) is indicated in these cases.

**Treatment**

Treatment of idiopathic scoliosis is based on the skeletal maturity of the patient, the size of the curve, and whether the spinal curvature is progressive or nonprogressive. Initial treatment for scoliosis is likely observation and repeat radiographs to assess for progression. No treatment is indicated for nonprogressive deformities. The risk factors for curve progression include gender, curve location, and curve magnitude. Girls are five times more likely to progress than boys. Younger patients are more likely to progress than older patients.

Typically, curves under 25° are observed. Progressive curves between 20° and 50° in a skeletally immature patient are treated with bracing. A radiograph in the orthotic is important to evaluate correction. Curves greater than 50° usually require surgical intervention.

**Congenital Scoliosis**

Abnormalities of the vertebral formation during the first trimester may lead to structural deformities of the spine that are evident at birth or early childhood. Congenital scoliosis can be classified as follows (Fig. 202.3):

- Partial or complete failure of vertebral formation (wedge vertebra or hemivertebra)
- Partial or complete failure of segmentation (unsegmented bars)
- Mixed

More than 60% of patients have other associated abnormalities, such as VACTERL association (vertebral defects, imperforate anus, cardiac anomalies, tracheoesophageal fistula, renal anomalies, limb abnormalities such as radial agenesis) or Klippel-Feil syndrome. Renal anomalies occur in 20% of children with congenital scoliosis, with renal agenesis being the most common; 6% of children have a silent, obstructive uropathy suggesting the need for evaluation with ultrasonography. Congenital heart disease occurs in about 12% of patients. **Spinal dysraphism** (tethered cord, intradural lipoma, syringomyelia, diplomyelia, and diastematomyelia) occurs in approximately 20% of children with congenital scoliosis. These disorders are frequently associated with cutaneous lesions on the back and abnormalities of the legs and feet (e.g., cavus foot, neurologic changes, calf atrophy). MRI is indicated in evaluation of spinal dysraphism.

The risk of spinal deformity progression in congenital scoliosis is variable and depends on the growth potential of the malformed vertebrae. A unilateral unsegmented bar typically progresses, but a block vertebra has little growth potential. About 75% of patients with congenital scoliosis will show some progression that continues until skeletal growth is complete, and about 50% will require some type of treatment. Progression can be expected during periods of rapid growth (before 2 years and after 10 years).

**Treatment** of congenital scoliosis hinges on early diagnosis and identification of progressive curves. Orthotic treatment is not helpful in congenital scoliosis. Early spinal surgery should be performed once progression has been documented. This can help prevent major deformities. Patients with large curves that cause thoracic insufficiency should undergo surgery immediately.

**Neuromuscular Scoliosis**

Progressive spinal deformity is a common and potentially serious problem associated with many neuromuscular disorders, such as cerebral palsy, Duchenne muscular dystrophy, spinal curvature.
muscular atrophy, and spina bifida. Spinal alignment must be part of the routine examination for a patient with neuro-muscular disease. Once scoliosis begins, progression is usually continuous. The magnitude of the deformity depends on the severity and pattern of weakness, whether the underlying disease process is progressive, and the amount of remaining musculoskeletal growth. Nonambulatory patients have a higher incidence of spinal deformity than ambulatory patients. In nonambulatory patients, the curves tend to be long and sweeping, produce pelvic obliquity, involve the cervical spine, and also produce restrictive lung disease. If the child cannot stand, then a supine or seated anteroposterior radiograph of the entire spine, rather than a standing posteroanterior view, is indicated.

The goal of treatment is to prevent progression and loss of function. Nonambulatory patients are more comfortable and independent when they can sit in a wheelchair without external support. Progressive curves can impair sitting balance, which affects quality of life. Orthotic treatment is usually ineffective in neuromuscular scoliosis. Surgical intervention may be necessary with frequent fusion to the pelvis.

**Compensatory Scoliosis**

Adolescents with a leg-length discrepancy (Chapter 200) may have a positive screening examination for scoliosis. Before correction of the pelvic obliquity, the spine curves in the same direction as the obliquity. However, with identification and correction of any pelvic obliquity, the curvature should resolve, and treatment should be directed at the leg-length discrepancy. Thus, it is important to distinguish between a structural and compensatory spinal deformity.

---

**Figure 202-3** Types of closed vertebral and extravertebral spinal anomalies that result in congenital scoliosis. **A,** Partial unilateral failure of formation (wedge vertebra). **B,** Complete unilateral failure of formation (hemivertebra). **C,** Unilateral failure of segmentation (congenital bar). **D,** Bilateral failure of segmentation (block vertebra).
KYPHOSIS

Kyphosis refers to a roundback deformity or to increased angulation of the thoracic or thoracolumbar spine in the sagittal plane. Kyphosis can be postural, structural (Scheuermann kyphosis), or congenital.

Postural Roundback
Postural kyphosis is secondary to poor posture. It is voluntarily corrected in the standing and prone positions. The patient may also have increased lumbar lordosis. Radiographs are usually unnecessary if the kyphosis fully corrects. If not, radiographs will reveal no vertebral abnormalities. Treatment, if needed, is aimed at improving the child's posture.

Scheuermann Kyphosis
Scheuermann disease is the second most common cause of pediatric spinal deformity. It occurs equally in males and females. The etiology is unknown, but there may be hereditary factors. Scheuermann kyphosis is differentiated from postural roundback on physical examination and by radiographs.

A patient with Scheuermann disease cannot correct the kyphosis with standing or lying prone. When viewed from the side in the forward flexed position, patients with Scheuermann disease will have an abrupt angulation in the mid to lower thoracic region (Fig. 202-4), and patients with postural roundback show a smooth, symmetrical contour. In both conditions, lumbar lordosis is increased. However, half of patients with Scheuermann disease will have atypical back pain, especially with thoracolumbar kyphosis. The classic radiologic findings of Scheuermann kyphosis include the following:

- Narrowing of disk space
- Loss of anterior height of the involved vertebrae producing wedging of 5° or more in at least three consecutive vertebrae
- Irregularities of the vertebral endplates
- Schmorl nodes

Treatment of Scheuermann kyphosis is similar to idiopathic scoliosis. It is dependent on the degree of deformity, skeletal maturity, and the presence or absence of pain. Nonoperative treatment begins with bracing. Surgical fusion is done for patients who have completed growth, have a severe deformity, or have intractable pain.

Congenital Kyphosis
Congenital kyphosis is a failure of the formation of all or part of the vertebral body (with preservation of posterior elements) or failure of anterior segmentation of the spine, or both. Severe deformities are found at birth and tend to rapidly progress. Progression will not cease until the end of skeletal growth. A progressive spine deformity may result in neurologic deficit. Treatment of congenital kyphosis is often surgical.

TORTICOLLIS

Etiology and Epidemiology
Torticollis is usually first identified in newborns because of a head tilt. Torticollis is usually secondary to a shortened sternocleidomastoid muscle (muscular torticollis). This may result from in utero positioning or birth trauma. Acquired torticollis may be related to upper cervical spine abnormalities or central nervous system pathology (mass lesion). It can also occur in older children during a respiratory infection (potentially secondary to lymphadenitis) or local head or neck infection, and it may herald psychiatric diagnoses.

Clinical Manifestations and Evaluation

Infants with muscular torticollis have the ear tilted toward the clavicle on the ipsilateral side. The face will look upward toward the contralateral side. There may be a palpable swelling or fibrosis in the body of the sternocleidomastoid shortly after birth, which is often the precursor of a contracture. Congenital muscular torticollis is associated with skull and facial asymmetry (plagiocephaly) and developmental dysplasia of the hip.

After a thorough neurologic examination, anteroposterior and lateral radiographs should be obtained. The goal is to rule out a nonmuscular etiology. A computed tomography (CT) scan or MRI of the head and neck is necessary for persistent neck pain, neurologic symptoms, and persistent deformity.

Treatment
Treatment of muscular torticollis is aimed at increasing the range of motion of the neck and correcting the cosmetic deformity. Stretching exercises of the neck can be very beneficial for...
infants. Surgical management is indicated if patients do not improve with adequate stretching exercises in physical therapy. Postoperative physical therapy is needed to decrease the risk of recurrence. Treatment in patients with underlying disorders should target the disorder.

**BACK PAIN IN CHILDREN**

**Etiology and Epidemiology**

Back pain in the pediatric population should always be approached with concern. In contrast to adults, in whom back pain is frequently mechanical or psychological, back pain in children may be the result of organic causes, especially in preadolescents. Back pain lasting longer than a week requires a detailed investigation. In the pediatric population, approximately 85% of children with back pain for greater than 2 months have a specific lesion: 33% are posttraumatic (spondylolysis, occult fracture), 33% are developmental (kyphosis, scoliosis), and 18% have an infection or tumor. In the remaining 15%, the diagnosis is undetermined.

**Clinical Manifestations and Management**

The history must include the onset and duration of symptoms. The location, character, and radiation of pain are important. Neurologic symptoms (muscle weakness, sensory changes, and bowel or bladder dysfunction) must be reviewed. Medical history and family history should be obtained, with a focus on back pain, rheumatologic disorders, and neoplastic processes. The review of systems should include detailed questions on overall health, fever, chills, recent weight loss, and recent illnesses. Physical examination should include a complete musculoskeletal and neurologic evaluation. Spinal alignment, range of motion, areas of tenderness, and muscle spasm should be noted. **Red flags** for childhood back pain include persistent or increasing pain, systemic findings (e.g., fever, weight loss), neurologic deficits, bowel or bladder dysfunction, young age (under 4 is strongly associated with tumor), night waking, pain that restricts activity, and a painful left thoracic spinal curvature.

Anteroposterior and lateral standing films of the entire spine with bilateral oblique views of the affected area should be obtained. Secondary imaging with bone scan, CT scan, or MRI may be necessary for diagnosis. MRI is very useful for suspected intraspinal pathology. Laboratory studies, such as a complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and specialized testing for juvenile idiopathic arthritis and ankylosing spondylitis, may be indicated.

The differential diagnosis of pediatric back pain is extensive (Table 202-2). Treatment depends on the specific diagnosis. If serious pathology has been ruled out and no definite diagnosis has been established, an initial trial of physical therapy with close follow-up for reevaluation is recommended.

**Table 202-2** Differential Diagnosis of Back Pain

<table>
<thead>
<tr>
<th>INFECTION DISEASES</th>
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</thead>
<tbody>
<tr>
<td>Diskitis (most common before the age of 6 years)</td>
</tr>
<tr>
<td>Vertebral osteomyelitis (pyogenic or tuberculous)</td>
</tr>
<tr>
<td>Spinal epidural abscess</td>
</tr>
<tr>
<td>Pyelonephritis</td>
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<tr>
<td>Pancreatitis</td>
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</table>

<table>
<thead>
<tr>
<th>RHEUMATOLOGIC DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Reiter syndrome</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
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<tr>
<td>Inflammatory bowel disease</td>
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</tbody>
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<table>
<thead>
<tr>
<th>DEVELOPMENTAL DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheuermann kyphosis</td>
</tr>
<tr>
<td>Scoliosis (left thoracic)</td>
</tr>
<tr>
<td>Spondylolysis</td>
</tr>
<tr>
<td>Spondylolisthesis</td>
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</tbody>
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<table>
<thead>
<tr>
<th>TRAUMATIC AND MECHANICAL ABNORMALITIES</th>
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<tbody>
<tr>
<td>Hip and pelvic abnormalities (sacroiliac joint dysfunction)</td>
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<tr>
<td>Herniated nucleus pulposus (intervertebral disk)</td>
</tr>
<tr>
<td>Overuse injuries (facet syndrome)</td>
</tr>
<tr>
<td>Vertebral stress fractures (spondylolysis, spondylolisthesis)</td>
</tr>
<tr>
<td>Vertebral compression fracture (steroid, sickle cell anemia)</td>
</tr>
<tr>
<td>Upper cervical spine instability (atlantoaxial instability)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>NEOPLASTIC DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary vertebral tumors (osteogenic sarcoma)</td>
</tr>
<tr>
<td>Metastatic tumor (neuroblastoma)</td>
</tr>
<tr>
<td>Primary spinal tumor (astrocytoma)</td>
</tr>
<tr>
<td>Bone marrow malignancy (leukemia, lymphoma)</td>
</tr>
<tr>
<td>Benign tumors (eosinophilic granuloma, osteoid osteoma)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conversion disorder</td>
</tr>
<tr>
<td>Juvenile osteoporosis</td>
</tr>
</tbody>
</table>

**SPONDYLOLYSIS AND SPONDYLolisthesis**

**Etiology and Epidemiology**

Spondylolysis is a defect in the pars interarticularis. Spondylolisthesis refers to bilateral defects with anterior slippage of the superior vertebra on the inferior vertebra. The lesions are not present at birth, but about 5% of children will have the lesion by 6 years of age. It is most common in adolescent athletes, especially those involved in sports that involve repetitive back extension. Classically, this was an injury seen in gymnasts and divers. However, with increased intensity and year-round sports, the incidence is increasing. Football interior lineman (extension while blocking), soccer players (extension while shooting), and basketball players (extension while rebounding) are examples of athletes at higher risk. The most common location of spondylolysis is L5, followed by L4.

Spondylolisthesis is classified according to the degree of slippage:

- **Grade 1**: less than 25%
- **Grade 2**: 25% to 50%
- **Grade 3**: 50% to 75%
- **Grade 4**: 75% to 99%
- **Grade 5**: complete displacement or spondylolisthesis

The most common location of spondylolisthesis is L5 on S1.
Clinical Manifestations

Patients will often complain of an insidious onset of low back pain persisting over 2 weeks. The pain tends to worsen with activity and with extension of the back and improves with rest. There may be some radiation of pain to the buttocks. A loss of lumbar lordosis may occur due to muscular spasm. Pain is present with extension of lumbar spine and with palpation over the lesion. Patients with spondylolisthesis may have a palpable step off at the lumbosacral area. A detailed neurologic examination should be done, especially because spondylolisthesis can have nerve root involvement.

Radiologic Evaluation

Anteroposterior, lateral, and oblique radiographs of the spine should be obtained. The oblique views may show the classic Scotty dog findings associated with spondylolysis. The lateral view will allow measurement of spondylolisthesis. Unfortunately, plain radiographs do not regularly reveal spondylolysis, so advanced imaging may be needed. The most helpful form of advanced imaging among CT, bone scan, single-photon emission CT (SPECT), or MRI continues to be debated. MRI may be required in patients with neurologic deficits.

Treatment

Spondylolysis

Painful spondylolysis requires activity restriction. Bracing is controversial but may help with pain relief. Patients benefit from an aggressive physical therapy plan to improve lower extremity flexibility and increase core strength and spinal stability. It is most beneficial to begin with flexion exercises and progress to extension exercises as tolerated. There is evidence that some patients with an acute spondylolysis can achieve bony union and that these patients have a decreased incidence of low back pain and degenerative change in the low back as they age when compared with spondylolysis patients with nonunion. Rarely, surgery is indicated for intractable pain and disability.

Spondylolisthesis

Patients with spondylolisthesis require periodic evaluation for progression of their slippage. Treatment of spondylolisthesis is based on grading.

Grade 1: Same treatment as spondylolysis. Failure of nonoperative management may lead to surgical fusion.

Grade 2: Reasonable to try nonoperative management, but if the slippage is progressing, surgical intervention may be needed. Any patient with neurologic symptoms requires surgical intervention.

Grades 3 to 5: Spinal fusion is usually required to prevent further slippage or damage.

Diskitis

Diskitis is an intervertebral disk space infection that does not cause associated vertebral osteomyelitis (see Chapter 117). The most common organism is Staphylococcus aureus. The infection can occur at any age but is more common in patients under 6 years of age.

Clinical Manifestations

Children may present with back pain, abdominal pain, pelvic pain, irritability, and refusal to walk or sit. Fever is an inconsistent symptom. The child typically holds the spine in a straight or stiff position, generally has a loss of lumbar lordosis due to paravertebral muscular spasm, and refuses to flex the lumbar spine. The white blood cell count is normal or elevated, but the ESR and CRP are usually high.

Radiologic Evaluation

Radiographic findings vary according to the duration of symptoms before diagnosis. Anteroposterior, lateral, and oblique radiographs of the lumbar or thoracic spine will typically show a narrow disk space with irregularity of the adjacent vertebral body end plates. In early cases, bone scan or MRI may be helpful, because they will be positive before findings are noticeable on plain radiographs. MRI can also be used to differentiate between diskitis and the more serious condition of vertebral osteomyelitis.

Treatment

Intravenous antibiotic therapy is the mainstay of treatment. Blood cultures may occasionally be positive and identify the infectious agent. Aspiration and needle biopsy are reserved for children who are not responding to empirical antibiotic treatment. Symptoms should resolve rapidly with antibiotics, but intravenous antibiotics should be continued for 1 to 2 weeks and be followed by 4 weeks of oral antibiotics. Pain control can be obtained with medications and temporary orthotic immobilization of the back.
UPPER EXTREMITY

SHOULDER
The shoulder actually comprises four joints: Glenohumeral joint (commonly referred to as the shoulder joint) Acromioclavicular joint Sternoclavicular joint Scapulothoracic joint
The glenohumeral joint has minimal geometric stability because the relatively small glenoid fossa articulates with the proportionately larger head of the humerus. The low level of intrinsic stability allows for a large range of motion. The rotator cuff muscles help give the glenohumeral joint more stability, but they need normal contact of the glenohumeral joint to be successful. The scapulothoracic movement also expands the range of motion of the shoulder, but like the glenohumeral joint, it requires strong, coordinated musculature to function efficiently.

Sprengel Deformity
Sprengel deformity is the congenital elevation of the scapula. There are varying degrees of severity; it is usually unilateral. There is restricted scapulothoracic motion (especially with abduction) so most of the shoulder motion is through the glenohumeral joint. There is usually associated hypoplasia of the parascapular muscles. Webbing of the neck and low posterior hairline can be associated problems. There is an association with congenital syndromes, such as Klippel-Feil anomaly, so a thorough history and examination are necessary. Mild forms with a cosmetic deformity and mild loss of shoulder motion do not need surgical correction. Severe forms may have a bony connection (omovertebral) between the scapula and lower cervical spine. Moderate and severe forms may need surgical repositioning of the scapula in early childhood to improve cosmesis and function.

Brachial Plexus Injuries
Obstetric brachial plexus palsy is discussed in Section 11. Brachial plexopathy is an athletic injury, commonly referred to as a stinger or burner. The symptoms are often likened to a dead arm. There is pain (often burning), weakness, and numbness in a single upper extremity. There are three mechanisms of injury:
Traction caused by lateral flexion of the neck away from the involved upper extremity
Direct impact to the brachial plexus at Erb’s point
Compression caused by neck extension and rotation toward the involved extremity
Symptoms are always unilateral and should resolve within 15 minutes. It is paramount to assess the cervical spine for serious injury. Bilateral symptoms, lower extremity symptoms, persistent symptoms, or recurrent injury are all signs of more serious disease and may need a more extensive workup and cervical spine stabilization. Athletes may return to activity if there are no red flags on history or physical examination and the athlete has full pain-free range of motion and strength in the neck and affected extremity.

Glenohumeral Dislocation
Shoulder dislocation is uncommon in childhood but becomes more frequent in adolescence. The younger the patient is at presentation, the more likely it is that the patient will have recent dislocation. Anterior dislocation is the most common. If assessment of the neurovascular status of the affected extremity reveals any compromise, urgent reduction is needed to prevent further complications. Patients will need radiographs to assess for fractures of the glenoid (Bankhart lesion) and humeral head (Hill-Sachs lesion). Most patients will require a brief period of protection in a sling or shoulder immobilizer, as well as pain control. As symptoms resolve, a gentle range-of-motion program, followed by an aggressive strengthening program, should be done. Recurrence occurs in nearly 90% of athletes participating in contact sports, so orthopedists consider surgical intervention early rather than awaiting further dislocation.

Overuse Injuries
The incidence of overuse injuries is increasing because of increased opportunities for athletic participation as well as higher levels of intensity during sports. Overuse injuries are inflammatory responses in tendons and bursae that are subjected to repetitive motions and trauma (e.g., rotator cuff tendinopathy in swimmers). These injuries are uncommon in children but may be seen in adolescents. Bony injury, such as physeal fractures and apophysitis, must be ruled out before making the diagnosis of a soft tissue overuse injury. Many overuse injuries in the shoulder, such as rotator cuff tendinopathy, are secondary to joint laxity.

The patient will often present with discomfort over the affected area that worsens with activity. Physical examination usually reveals tenderness to palpation and often weakness of the associated muscles due to pain. It is important to assess for glenohumeral stability. Radiographs may be indicated for acute trauma or when symptoms are not improving. Treatment consists of activity modification, icing, anti-inflammatory medication, and a physical therapy program aimed at strengthening, increasing flexibility, and improving posture.

Proximal Humeral Epiphysiodesis
Proximal humeral epiphysiodesis is commonly referred to as Little Leaguer’s shoulder. It most commonly occurs in 9- to 14-year-olds who participate in overhead (tennis, volleyball) and throwing sports, particularly baseball pitchers. It is a stress injury that potentially can be a fracture (epiphysiodesis) of the proximal humeral physis. Most patients present with pain during or after throwing. There may be tenderness to palpation over the proximal humerus; if the athlete has been resting for a few days, examination may be normal. Radiographs should include comparison views to assess the physis. There may be widening of the proximal humeral physis in the affected arm, but the films may be normal. Treatment is rest from the offending activity, followed by a rehabilitation program designed to
improve strength in the shoulder muscles. Pitchers should also be encouraged to follow youth pitching guidelines published by Little League baseball.

**ELBOW**
The elbow consists of three articulations:
- Ulnar-humeral joint
- Radial-humeral joint
- Proximal radioulnar joint

Collectively, these joints produce a hinge-type joint that allows for supination (palm up) and pronation (palm down) positioning of the hand. The elbow has excellent geometric stability, and the musculature around the elbow primarily produces flexion and extension.

**Radial Head Subluxation**
Radial head subluxation is more commonly known as nursemaid’s elbow. Because the radial head is not as bulbous in infants and young children, the annular ligament that passes around it can partially slip off the radial head with traction across the elbow (Fig. 203-1). The subluxation is usually caused by a quick pull on the extended elbow when a child is forcefully lifted by the hand or when the child falls while holding hands with an adult. After a subluxation, the child usually holds the hand in a pronated position and will refuse to use the hand or move the elbow. Moving the hand into the supinated position while applying pressure to the radial head will usually reduce the injury. Usually, radiographs are not necessary unless reduction cannot be obtained or there is concern for fracture (swelling and bruising). Once the injury is reduced, the child will begin using the arm again without complaint. Parents should be educated about the mechanism of injury and encouraged to avoid that position. There is a high rate of recurrence for this injury. The problem generally resolves with maturation, but some children with high recurrence rates may benefit from casting or, rarely, surgical intervention.

**Panner Disease**
Panner disease is an osteochondritis of the capitellum (lateral portion of distal humeral epiphysis) that occurs spontaneously in late childhood. Clinical features include elbow pain, decreased range of motion, and tenderness to palpation over the capitellum. Radiographs reveal fragmentation of the capitellum. Treatment is activity restriction and follow-up radiographs to demonstrate spontaneous reossification of the capitellum over several months. There is usually no need for further treatment or imaging studies. This is not to be confused with osteochondritis dissecans of the capitellum, which usually will occur in adolescents involved with throwing sports.

**Throwing Injuries**
The elbow is especially vulnerable to throwing injuries in the skeletally immature athlete. These occur from excessive and repetitive tension forces across the radial aspect of the elbow and compression forces across the lateral aspect of the elbow. These injuries are commonly known as Little Leaguer’s elbow.

Although this injury is most common in baseball players who throw frequently (pitcher, catcher, third base, and shortstop), it also occurs in football quarterbacks and tennis players. Patients will usually complain of pain over the medial elbow with throwing that may last for a few days afterward. There may be associated swelling and lateral or posterior elbow pain. Radiation of pain may be secondary to ulnar neuropathy. There is often a flexion contracture of the elbow when compared to the opposite side. Palpation of the medial epicondyle, radial head, capitellum, lateral epicondyle, and olecranon process often reveals tenderness. Ulnar (medial) collateral ligament stability should be assessed. Radiographs should include the contralateral elbow for comparison. Radiographic findings in Little Leaguer’s elbow can vary and may include normal anatomy, medial humeral epicondyloapophyseal avulsion fracture, osteochondritis dissecans of the capitellum, radial head abnormalities, and foreign bodies in the elbow. MRI may be helpful.

Treatment depends on the underlying diagnosis but always includes pain control and rest from activity. Classic Little Leaguer’s elbow refers to medial humeral epicondyle apophysitis. These athletes benefit from rest, ice, anti-inflammatory medication, and a physical therapy program aimed at upper body strengthening. Throwing mechanics and the pitching guidelines published by Little League Baseball/Softball
should be reviewed with these players. Switching players to a lower throwing position (e.g., first base) after rehabilitation, to avoid pitching for the remainder of the season, is often recommended.

**WRIST AND HAND**

Multiple small joints, a delicately balanced intrinsic muscle system, a powerful extrinsic muscle system, dense sensory innervation, and specialized skin combine to make the hand a highly mobile and sensitive yet powerful anatomic part. The extrinsic muscles originate in the forearm and the intrinsic muscles are located in the hand and coordinate small, delicate movements. The movements of opening the hand, extending and spreading the fingers, and then clenching the hand into a fist requires coordinated function of the intrinsic and extrinsic muscles. Tenderness of direct palpation of the bones raises the concern for fracture. Scaphoid fracture is the most common carpal bone fracture in the pediatric population. It requires immobilization in a thumb spica cast, whereas displaced fractures require surgical intervention. Salter-Harris fractures of the distal radius are also very common. In young gymnasts, there is increased risk for injury at the distal radial physis from repetitive impact and upper extremity weight bearing. This is commonly called gymnast’s wrist and requires absolute rest from impact and weight bearing to prevent premature closure of the growth plate.

Ganglion cysts are synovial fluid-filled cysts about the wrist. The most common location is the dorsum of the wrist near the radiocarpal joint, followed by the volar radial aspect of the wrist. The defect is in the joint capsule, which allows synovial fluid into the soft tissues with wrist use, where it can become walled off with fibrous tissue. Often, in skeletally immature patients, the process is benign and disappears over time. Large ganglion cysts or cysts that are painful and interfere with function may require more aggressive therapy. Aspiration and steroid injection into the cyst may be helpful, but many will recur. Surgical excision will remove the tract that attaches to the wrist joint, so it is usually curative.

**Finger Abnormalities**

Polydactyly (extra digits) occurs in simple and complex varieties (see Table 201-2). Skin tags and digit remnants that occur near the metacarpophalangeal joint of the fifth digit and thumb that do not have palpable bones or possess voluntary motion are simple varieties. These may be excised or ligated in the nursery. Complex deformities should be referred to a pediatric orthopedist for amputation. Syndactyly (fused digits) are concerning because of the possibility of shared structures and the tethering effects on bone growth (see Table 201-2). All patients with syndactyly should be referred for treatment options.

Trigger thumb and trigger finger are secondary to isolated thickening of the flexor tendons. As the thickened nodule enlarges, it may catch in a bent position, then snap or trigger straight as it passes through the first pulley that anchors the tendon. Ultimately, as it enlarges, it cannot pass through at all and produces a flexion deformity at the interphalangeal joints. The nodule may be palpable near the metacarpophalangeal joint. These children should be referred for surgical correction.

**Table 204-1 Benign Bone Tumors and Cysts**

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CHARACTERISTICS</th>
<th>RADIOGRAPHIC FINDINGS</th>
<th>TREATMENT</th>
<th>PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteochondroma (osteoarticular exostosis)</td>
<td>Common; distal metaphysis of femur, proximal humerus, proximal tibia; painless, hard, nontender mass</td>
<td>Bony outgrowth, sessile or pedunculated</td>
<td>Excision, if symptomatic</td>
<td>Excellent; malignant transformation rare</td>
</tr>
<tr>
<td>Multiple hereditary exostoses</td>
<td>Osteochondroma of long bones; bone growth disturbances</td>
<td>As above</td>
<td>As above</td>
<td>Recurrences</td>
</tr>
<tr>
<td>Osteoid osteoma</td>
<td>Pain relieved by aspirin; femur and tibia; found predominantly in boys</td>
<td>Dense sclerosis surrounds small radiolucent nidus, &lt;1cm</td>
<td>As above</td>
<td>Excellent</td>
</tr>
<tr>
<td>Osteoblastoma (giant osteoid osteoma)</td>
<td>As above, but more destructive</td>
<td>Osteolytic component; size &gt;1cm</td>
<td>As above</td>
<td>Excellent</td>
</tr>
<tr>
<td>Enchondroma</td>
<td>Tubular bones of hands and feet; pathologic fractures, swollen bone; Ollier disease if multiple lesions are present</td>
<td>Radiolucent diaphyseal or metaphyseal lesion; may calcify</td>
<td>Excision or curettage</td>
<td>Excellent; malignant transformation rare</td>
</tr>
</tbody>
</table>

Benign bone tumors and cystic lesions are common in childhood. Some represent fibrous dysplasia. Others are benign bone cysts (unicameral) or benign bone tumors (osteoid osteoma). Subacute osteomyelitis (Brodie abscess) and eosinophilic granulomas are lesions not associated with abnormal bone or cartilage growth. Some of these lesions can produce pain, limp, and pathologic fractures. Others can be incidental findings on radiographs. The prognosis is usually excellent. A brief differential diagnosis of bone tumors and their management is listed in Table 204-1. Malignant bone tumors are discussed in Section 21.
### Table 204-1 Benign Bone Tumors and Cysts—cont’d

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>CHARACTERISTICS</th>
<th>RADIOGRAPHIC FINDINGS</th>
<th>TREATMENT</th>
<th>PROGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonossifying fibroma</td>
<td>Silent; rare pathologic fracture; late childhood, adolescence</td>
<td>Incidental radiographic finding; thin sclerotic border, radiolucent lesion</td>
<td>None or curettage with fractures</td>
<td>Excellent; heals spontaneously</td>
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<tr>
<td>Eosinophilic granuloma</td>
<td>Age 5–10 years; skull, jaw, long bones; pathologic fracture; pain</td>
<td>Small, radiolucent without reactive bone; punched-out lytic lesion</td>
<td>Biopsy, excision rare; irradiation</td>
<td>Excellent; may heal spontaneously</td>
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<tr>
<td>Brodie abscess</td>
<td>Insidious local pain; limp; suspected as malignancy</td>
<td>Circumscribed metaphyseal osteomyelitis; lytic lesions with sclerotic rim</td>
<td>Biopsy; antibiotics</td>
<td>Excellent</td>
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<tr>
<td>Unicameral bone cyst (simple bone cyst)</td>
<td>Metaphysis of long bone (femur, humerus); pain, pathologic fracture</td>
<td>Cyst in medullary canal, expands cortex; fluid-filled unilocular or multilocular cavity</td>
<td>Curettage; steroid injection into lesion</td>
<td>Excellent; some heal spontaneously</td>
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<tr>
<td>Aneurysmal bone cyst</td>
<td>As above; contains blood, fibrous tissue</td>
<td>Expands beyond metaphyseal cartilage</td>
<td>Curettage, bone graft</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

### Suggested Reading