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Pediatrics

SECOND EDITION

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Wolters Kluwer

Pediatrics

SECOND EDITION

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Contents

Cover image

Title page

Copyright

Dedication

Preface

Acknowledgments

Contributors

Contributors to the Previous Edition

Chapter 1 Pediatric Health Supervision

- I. Well-Child Care—General Concepts
- II. Growth
- III. Immunizations
- IV. Well-Child Screening
- V. Circumcision
- VI. Pediatric Dental Care
- VII. Developmental Screening
- VIII. Anticipatory Guidance
- Review Test
- Answers and Explanations

Chapter 2 Behavioral and Developmental Pediatrics

- I. Normal Developmental Milestones
- II. Disorders of Development
- III. Specific Sensory Impairments
- IV. Common Behavioral Concerns
- Review Test
- Answers and Explanations

Chapter 3 Adolescent Medicine

- I. Adolescent Growth and Development
- II. Adolescent Health Screening
- III. Depression and Suicide
- IV. Substance Abuse
- V. Obesity and Eating Disorders
- VI. Female Reproductive Health Issues

VII. Sexually Transmitted Infections (STIs)
VIII. Menstrual Disorders
IX. Reproductive Health Issues in Males
Review Test
Answers and Explanations

Chapter 4 Neonatology
I. Evaluation of the Newborn
II. Abnormalities of Maturity
III. Growth Abnormalities
IV. Cyanosis
V. Respiratory Distress
VI. Respiratory Distress Syndrome (RDS)
VII. Meconium Aspiration Syndrome (MAS)
VIII. Persistent Pulmonary Hypertension of the Newborn (PPHN)
IX. Apnea of Prematurity
X. Neonatal Jaundice
XI. Fetal Exposure to Drugs of Abuse
XII. Surgical Conditions of the Newborn
XIII. Hypoglycemia
XIV. Infants of Diabetic Mothers (IDMs)
XV. Polycythemia
Review Test
Answers and Explanations

Chapter 5 Genetic Disorders and Inborn Errors of Metabolism
I. Inheritance Patterns
II. Types of Genetic Tests
III. Fetal Evaluation and Prenatal Diagnosis
IV. Common Genetic Disorders
V. General Concepts of Inborn Errors of Metabolism (IEM)
VI. Defects in Amino Acid Metabolism
VII. Defects of Carbohydrate Metabolism
VIII. Fatty Acid Oxidation Disorders
IX. Lysosomal Storage Diseases
X. Mitochondrial Disorders
XI. Disorders of Metal Metabolism
Review Test
Answers and Explanations

Chapter 6 Endocrinology
I. Short Stature
II. Disorders of Puberty

III. Disorders of Sexual Differentiation (DSD or Formerly Known as Ambiguous Genitalia)
IV. Disorders of the Adrenal Gland
V. Diabetes Mellitus
VI. Type 1 Diabetes Mellitus (Type 1 DM)
VII. Type 2 Diabetes Mellitus (Type 2 DM)
VIII. Diabetic Ketoacidosis (DKA)
IX. Thyroid Disorders
X. Bone Mineral Disorders
XI. Diabetes Insipidus (DI)
XII. Hypoglycemia
Review Test
Answers and Explanations

Chapter 7 Infectious Diseases

I. General Approach to the Child With Possible Infection
II. Evaluation of the Child With Fever
III. Fever of Unknown Origin (FUO)
IV. Meningitis
V. Upper Respiratory Infections
VI. Middle and Lower Respiratory Infections
VII. Cervical Lymphadenitis
VIII. Parotitis
IX. Skin and Soft Tissue Infections
X. Bone and Joint Infections (see Chapter 17, section III.B)
XI. Diarrhea
XII. Urinary Tract Infections (see Chapter 11, section XIV)
XIII. Specific Viral Infections
XIV. Specific Fungal Infections
XV. Specific Parasitic Infections
XVI. Specific Helminth Infections
XVII. Miscellaneous Infections
Review Test
Answers and Explanations

Chapter 8 Cardiology

I. Congestive Heart Failure (CHF)
II. Innocent Cardiac Murmurs
III. Acyanotic Congenital Heart Disease
IV. Cyanotic Congenital Heart Disease
V. Acquired Heart Disease
VI. Dysrhythmias
VII. Chest Pain
Review Test

Answers and Explanations

Chapter 9 Pulmonology

I. Anatomy and Physiology of the Respiratory System

II. Clinical Assessment of Pulmonary Disease

III. Infectious Disorders of the Respiratory Tract

IV. Noninfectious Disorders of the Respiratory Tract

Review Test

Answers and Explanations

Chapter 10 Gastroenterology

I. Nutrition

II. Malabsorption

III. Gastroesophageal Reflux

IV. Intestinal Anatomic Obstructions That Result in Vomiting

V. Acute Abdominal Pain

VI. Chronic Abdominal Pain

VII. Constipation

VIII. Diarrhea

IX. Inflammatory Bowel Disease (IBD)

X. Gastrointestinal Bleeding

XI. Liver Abnormalities and Hepatitis

Review Test

Answers and Explanations

Chapter 11 Nephrology and Urology

I. Fluids, Electrolytes, and Dehydration

II. Hematuria

III. Proteinuria

IV. Hypertension

V. Glomerulonephritis

VI. Nephrotic Syndrome (NS)

VII. Hemolytic Uremic Syndrome (HUS)

VIII. Hereditary Renal Diseases

IX. Renal Tubular Acidosis (RTA)

X. Acute Kidney Injury

XI. Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD)

XII. Structural and Urologic Abnormalities

XIII. Urolithiasis

XIV. Urinary Tract Infection (UTI)

Review Test

Answers and Explanations

Chapter 12 Neurology

I. The Hypotonic Infant
II. Hydrocephalus
III. Spina Bifida
IV. Approach to the Comatose Patient
V. Seizure Disorders of Childhood
VI. Headaches in Childhood
VII. Approach to Unsteady Gait
VIII. Movement Disorders
IX. Duchenne and Becker Muscular Dystrophies (DMD, BMD)
X. Myasthenia Gravis
Review Test
Answers and Explanations

Chapter 13 Hematology
I. Anemia
II. Pancytopenia and Aplastic Anemia
III. Polycythemias
IV. Disorders of Hemostasis
V. Neutropenia
Review Test
Answers and Explanations

Chapter 14 Oncology
I. General Considerations
II. Leukemias
III. Lymphomas
IV. Brain Tumors
V. Renal and Suprarenal Tumors
VI. Soft Tissue Tumors
VII. Bone Tumors
VIII. Liver Tumors
IX. Retinoblastoma
X. Germ Cell Tumors (Germinomas)
XI. Langerhans Cell Histiocytosis (LCH)
Review Test
Answers and Explanations

Chapter 15 Allergy and Immunology
I. Anaphylaxis
II. Allergic Rhinitis
III. Atopic Dermatitis
IV. Food Allergy
V. Insect Venom Allergy

VI. Urticaria (Hives)
VII. Drug Allergy
VIII. Asthma
IX. Immunology Overview
X. Disorders of Lymphocytes (Figure 15-2)
XI. Disorders of Granulocytes (Figure 15-3)
XII. Disorders of the Complement System
Review Test
Answers and Explanations

Chapter 16 Rheumatology
I. Henoch–Schönlein Purpura (HSP)
II. Kawasaki Disease (KD)
III. Juvenile Idiopathic Arthritis (JIA)
IV. Systemic Lupus Erythematosus (SLE)
V. Juvenile Dermatomyositis (JDM)
VI. Rheumatic Fever
VII. Lyme Disease
VIII. Other Rheumatologic Conditions of Childhood
Review Test
Answers and Explanations

Chapter 17 Orthopedics
I. Upper Extremity
II. Spine
III. Hip
IV. Lower Extremity
V. Common Fractures
Review Test
Answers and Explanations

Chapter 18 Ophthalmology
I. Ocular Examination and Vision Screening
II. Normal Visual Development and Amblyopia
III. Conjunctivitis and Red Eye
IV. Abnormal Tearing
V. Ocular Trauma
VI. Congenital Glaucoma
VII. Retinopathy of Prematurity (ROP)
VIII. Leukocoria
IX. Strabismus
Review Test
Answers and Explanations

Chapter 19 Dermatology

I. General Concepts

II. Newborn Skin Diseases

III. Inflammatory Disorders

IV. Hypersensitivity Disorders

V. Infections of the Skin

VI. Pigmentary Disorders

VII. Disorders of the Hair

VIII. Acne Vulgaris

IX. Vascular Skin Lesions

Review Test

Answers and Explanations

Chapter 20 Emergency Medicine

I. Infant and Child Cardiopulmonary Resuscitation (CPR)

II. Shock

III. Trauma

IV. Burns

V. Drowning

VI. Child Abuse

VII. Sudden Infant Death Syndrome (SIDS)

VIII. Poisonings

IX. Mammalian Bites

X. Biologic Poisonings (Venoms)

Review Test

Answers and Explanations

Index

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Dedication

To Bobbie, for her love, support, and laughter and for being a truly wonderful mother to our son; to Danny, the sunshine and pure joy of my life; and to my family and friends for their ongoing love and friendship.

Lloyd Brown

To Karen, Olivia, and Penelope, for providing me with life's true education, day after day. To my parents, siblings, and close friends, for believing more in me than I ever could myself.

Ryan Coller

To Kai, the rest of my family, and my dear friends, for their unwavering support, encouragement, and love, and to my mother, who was excited and very proud of this project and others at her 90th birthday celebration, with much love from Lee.

Lee Miller

Preface

We created this text to provide medical students and physicians with a comprehensive, yet hopefully very manageable, overview of the basic principles of pediatric medicine.

It is our great hope that medical students on their core pediatric clerkships, senior students on pediatric subinternships and pediatric subspecialty rotations, and students or physicians studying for the USMLE Step 2 examination will gain a strong foundation in pediatrics, on which to build their subsequent learning in both primary care and subspecialty pediatrics.

We have created case-based review questions at the end of each chapter to emphasize key take-home points and to help the reader to assess his or her understanding of each chapter's contents. The review questions are followed by answers and detailed explanations for both the correct and incorrect choices. Cross-references to the text appear in square brackets.

There is also a comprehensive 150-question examination at the end of the text to provide the reader with a self-assessment tool and additional review of the primary care and subspecialty areas covered in this text. Similar to the chapter review tests, the comprehensive examination includes detailed explanations for both the correct and incorrect choices.

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We would like to recognize the individuals who have made tremendous impacts on our medical education and on our professional growth and development.

I have been so privileged to learn from outstanding teachers and mentors at UCLA School of Medicine, Cedars-Sinai Medical Center, and Stanford School of Medicine. Lee Miller, one of the coeditors of this book, has influenced my career immeasurably as one of the finest teachers I have known. I would not have discovered my love for teaching without his mentorship and encouragement. I am also immensely grateful to my colleagues and friends at the Palo Alto Medical Foundation who, for the past 14 years, have supported me and helped me to grow as a clinician, leader, and educator.

Lloyd J. Brown

In health and education fields, we are constantly striving to be idealized versions of ourselves—better than we truly are. From exposure to those who are genuinely better than me, I have received invaluable education, encouragement, and perpetual inspiration. A partial list of those to whom I am indebted includes Drs. Lee Miller, Kate Perkins, Paul Chung, Alice Kuo, Tom Klitzner, and Ellen Wald. I hope to live up to all of the support that they, and others, have given to me.

Ryan J. Coller

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Lee T. Miller

We also owe so much to our present and past pediatric and medicine–pediatric residents with whom we feel very close, and to the thousands of medical students from all across the country, but most especially to those from Stanford University, from the University of Wisconsin School of Medicine and Public Health, and from the David Geffen School of Medicine at UCLA, who have stimulated us, energized us, and taught us so much along the way.

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CHAPTER 1

Pediatric Health Supervision

Kathy L. Perkins, James Heaysung Lee

I. Well-Child Care—General Concepts

A. **The purpose of routine well-child care** is to address the longitudinal health care needs of children from birth through adolescence. This is ideally achieved through a family-centered medical home model where the pediatric care team works in partnership with the family to ensure that all health-related needs are met. Features of well-child care include the following:
   1. Age-specific health supervision according to recommended periodicity schedules
   2. Disease detection through surveillance and screening:
      a. Assessment of growth and development
      b. Screening tests to detect asymptomatic diseases (e.g., vision, hearing, newborn metabolic screening, anemia, and lead screening)
      c. Developmental screening
   3. Disease prevention
      a. Primary prevention
         1. Sudden infant death syndrome, or SIDS, prevention ("back to sleep"), for example
         2. Immunizations
      b. Secondary prevention (e.g., care coordination for children with special health care needs)

B. **The content of the well-child visit includes**
   1. Eliciting parental and patient concerns
   2. **History** provides an opportunity to obtain diagnostic information and to form a doctor–patient–family alliance. The interview is shaped by family and patient concerns and by **age-specific trigger questions** about common problems (e.g., sleep, nutrition, behavior).
   3. **Developmental surveillance** is gathered through age-specific questioning, developmental questionnaires, observations during the visit, screening tests, and a review of academic school performance.
   4. **Observation of parent–child interaction**
   5. **Physical examination** should be comprehensive and also should focus on **growth** (i.e., length/height, weight, head circumference, and body mass index).
   6. **Additional screening tests** depend on the age of the child and may include lead level, hemoglobin, lipid levels, blood pressure, and hearing and vision assessment.
   7. **Immunizations**
   8. **Anticipatory guidance** includes a discussion of safety issues and upcoming developmental issues.

II. Growth

A. **Normal growth**
   1. **Weight, height, head circumference** (until 2 years of age), **body mass index** (starting at 2 years of age), and **sexual maturity** are monitored routinely during well-child care to assess for adequacy of growth and development.
   2. **Standardized growth curves**, produced by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC), reflect average values for age for 95% of children and are used to plot weight, height, body mass index, and head circumference over time.
   3. **Tables 1-1, 1-2, and 1-3** detail general "rules of thumb" for expected gains in weight, height, and head circumference. **Sexual maturity rating scales are found in Chapter 3, Figures 3-1, 3-2, and 3-3.**

B. **Growth disturbances** are defined as growth outside of the usual pattern. Three common types of growth disturbance include **failure to thrive (FTT), short stature,** and **head growth abnormalities.** Short stature is discussed in Chapter 6, section I.
   1. **FTT**
      a. **Definition.** Although there are multiple definitions, FTT is a term most commonly used to describe a growth rate less than expected for a child, and is of particular concern when a child's weight crosses two major percentile isobars on a growth chart.
      b. FTT may involve all growth parameters, although **weight gain is generally the most affected.** FTT should be distinguished from isolated short stature, in which height is the most abnormal growth parameter (see Chapter 6, section I).
      c. In children with FTT, weight is typically affected before linear growth, which is usually affected before head circumference growth. **Head circumference is initially spared in FTT.**
      d. **Classification.** FTT was previously categorized as either nonorganic (due to psychosocial factors) or organic (due to underlying organ system pathology). This classification is no longer recommended because these categories coexist in many cases. A more appropriate categorization of FTT describes whether there is **inadequate caloric intake**, **inadequate caloric absorption, inadequate utilization of nutrients**, or **excessive metabolic demand.** The most common etiology of FTT is inadequate intake of calories, which may result from a disturbed parent–child bond. The differential diagnosis of FTT is outlined in Figure 1-1.
      e. **Evaluation** of FTT requires a careful history and physical examination, a complete dietary history, and observation of the parent–child interaction. **No laboratory tests are routinely indicated in the initial evaluation of FTT.** Laboratory tests should be reserved for cases where the history or physical examination suggests a specific etiology for which laboratory testing will be helpful or for the child who fails to respond to nutritional interventions.
   2. **Head growth abnormalities** include abnormalities in size (microcephaly/macrocephaly) or shape (deformational plagiocephaly/craniosynostosis).
      a. **General concepts. Almost all head growth occurs prenatally and during the first 2 years of life.**
         1. Head circumference at birth is 25% of the normal adult head size, and it increases to 75% of the normal adult head size by 1 year of age.
         2. Note that **caput succedaneum** (scalp edema) and **cephalohematoma** (subperiosteal hemorrhage of the newborn cranium after a traumatic delivery)

may interfere with accurate head circumference measurement in newborns.

b. **Microcephaly**
   1. **Definition.** Head circumference is 2–3 standard deviations below the mean for age.
   2. Incidence is **1–2/1000** children.
   3. **Etiologies** are classified as either **congenital** or **acquired** (**Table 1-4**).
      a. **Congenital microcephaly** is associated with abnormal induction and migration of the brain tissue.
      b. **Acquired microcephaly** is caused by a cerebral insult in the late third trimester, perinatal period, or first year of life. Affected children are born with a normal head circumference that does not grow after the cerebral insult.
   4. **Clinical features**
      a. Because head size generally reflects brain size, **microcephaly is always associated with a small brain.**
      b. Microcephaly is usually associated with **developmental delay** and **intellectual impairment.**
      c. Microcephaly may be associated with **cerebral palsy** or **seizures.**

c. **Macrocephaly**
   1. **Definition.** Head circumference > 95% for age.
   2. **Unlike in microcephaly, the size of the head in a patient with macrocephaly does not necessarily reflect brain size.**
   3. **Etiologies**
      a. Benign **familial macrocephaly,** associated with an otherwise normal physical examination and a family history of large heads
      b. **Overgrowth syndromes** (e.g., Sotos syndrome), in which all growth parameters are enlarged
      c. **Metabolic storage disorders** (e.g., Canavan syndrome, gangliosidoses)
      d. **Neurofibromatosis** (see Chapter 19, Table 19-3)
      e. **Achondroplasia** (see Chapter 5, section IV.H.1)
      f. **Hydrocephalus** (see Chapter 12, section II)
      g. **Space-occupying lesions** (e.g., cysts, tumors)
   4. **Evaluation** includes measurement of parental head circumferences, and a careful physical examination that includes observation for split cranial sutures, bulging anterior fontanelle, irritability, or vomiting, all of which may suggest **elevated intracranial pressure.** Head ultrasound or computed tomography (CT) scan is performed to rule out **hydrocephalus,** if suggested by physical examination. Genetic evaluation may be useful if a genetic syndrome is suspected.

d. **Craniosynostosis**
   1. **Definition.** Premature closure of one or more of the cranial sutures (Figure 1-2).
   2. **Etiology** is often unknown. **80–90% of cases are sporadic** and 10–20% are familial or part of a genetic syndrome (e.g., Crouzon and Apert syndromes). Known risk factors include intrauterine constraint or crowding, and metabolic abnormalities including hyperthyroidism and hypercalcemia.
   3. **Clinical features. Head shape in craniosynostosis is determined by which suture closes prematurely**, because bone growth perpendicular to the affected suture is arrested.
      a. Premature closure of the **sagittal suture** results in an **elongated skull**

(termed **dolichocephaly** or **scaphocephaly**) and is the **most common form of craniosynostosis** (Figure 1-3).

b. Premature closure of the **coronal suture** results in a **shortened skull** (termed **brachycephaly**). This is more common in boys and may be associated with **neurologic complications** such as optic nerve atrophy.

c. Premature closure of the metopic suture leads to a triangular-shaped head and prominent longitudinal central ridge on the forehead (termed **trigonocephaly**).

d. Premature closure of multiple sutures is rare, and is associated with severe neurologic compromise.

4. **Diagnosis** is made by physical examination of the head. Craniosynostosis is usually noted by 6 months of age. The diagnosis may be confirmed by skull radiographs and head CT scan.
5. **Management** is **surgical repair,** most often indicated when cosmetic concerns are significant.

e. **Plagiocephaly**

1. **Definition.** Asymmetry of the infant head shape **not associated with premature suture closure**
2. **Clinical features.** The **most common type of plagiocephaly is positional plagiocephaly (Figure 1-4)**, associated with flattening of the occiput and prominence of the ipsilateral frontal area. Viewed from above, the skull has a parallelogram shape with the back of the head, ear, and forehead of one side displaced anteriorly.

a. May be associated with **congenital muscular torticollis** (see Chapter 17, section II.A.1), in which fetal head constraint during the third trimester can result in both trauma to the sternocleidomastoid and deformations of the skull.

b. Incidence has increased as a result of recommendations that infants sleep on their backs to decrease the risk of SIDS.

c. **Management** may include range of motion exercises for associated torticollis, repositioning the head during sleep, and increased time in the prone position when awake ("tummy time"). Cranial remodeling helmet therapy was a common treatment, but the American Academy of Pediatrics (AAP) updated its position in 2011 stating that helmet therapy was unnecessary for most babies with plagiocephaly.

Table 1-1
Rules of Thumb for Expected Increase in Weight

Age	Expected Weight Increase
Birth–2 weeks (average birth weight is 3.5 kg)	Lose up to 10% of birth weight, usually in the first week of life
	Regain birth weight by 2 weeks of age
2 weeks–3 months	30 g/day
3–6 months	20 g/day
	Double birth weight by 4–6 months of age
6–12 months	10 g/day
	Triple birth weight by 12 months of age
1–2 years	250 g/month or 3 kg/year
	Quadruple birth weight by 2 years of age
2 years–puberty	2 kg/year

30 g = 1 oz body weight.

Table 1-2
Rules of Thumb for Expected Increase in Height

Age	Expected Height Increase
0–12 months (average birth length is 50 cm)	25 cm/year
	Birth length increases by 50% at 12 months of age
13–24 months	12.5 cm/year
2 years–adolescence	6.25 cm/year
	Birth length doubles by age 4 years
	Birth length triples by age 13 years

Table 1-3
Rules of Thumb for Expected Increase in Head Circumference

Age	Expected Head Circumference Increase
0–2 months (average birth head circumference is 35 cm)	0.5 cm/week
2–6 months	0.25 cm/week
By 12 months	Total increase = 12 cm since birth

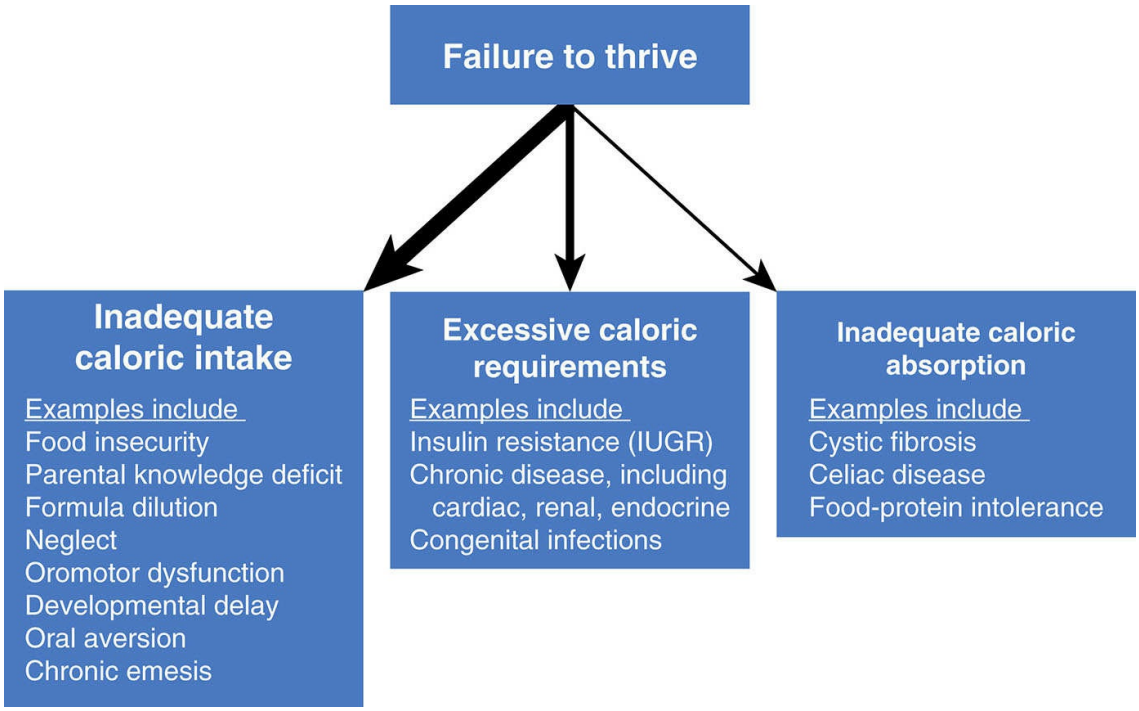

FIGURE 1.1 Differential diagnosis of failure to thrive (FTT). Inadequate caloric intake is the most common cause of FTT, followed by excessive caloric requirements. Inadequate caloric absorption is the least common cause of FTT. *IUGR* = intrauterine growth restriction.

Table 1-4
Causes of Microcephaly

Congenital
Early prenatal infection (e.g., HIV infection, TORCH)
Maternal exposure to drugs and toxins (e.g., fetal alcohol syndrome)
Chromosomal abnormality (e.g., trisomy 13, 18, or 21)
Familial microcephaly (autosomal dominant or autosomal recessive inheritance)
Maternal phenylketonuria
Acquired
Late third trimester or perinatal infections
Meningitis or meningoencephalitis during first year of life
Hypoxic or ischemic cerebral insult
Metabolic derangements (e.g., hypothyroidism, inborn errors of metabolism)

TORCH = *t*oxoplasmosis, *o*ther (syphilis), *r*ubella, *c*ytomegalovirus, *h*erpes simplex virus; *HIV* = human immunodeficiency virus.

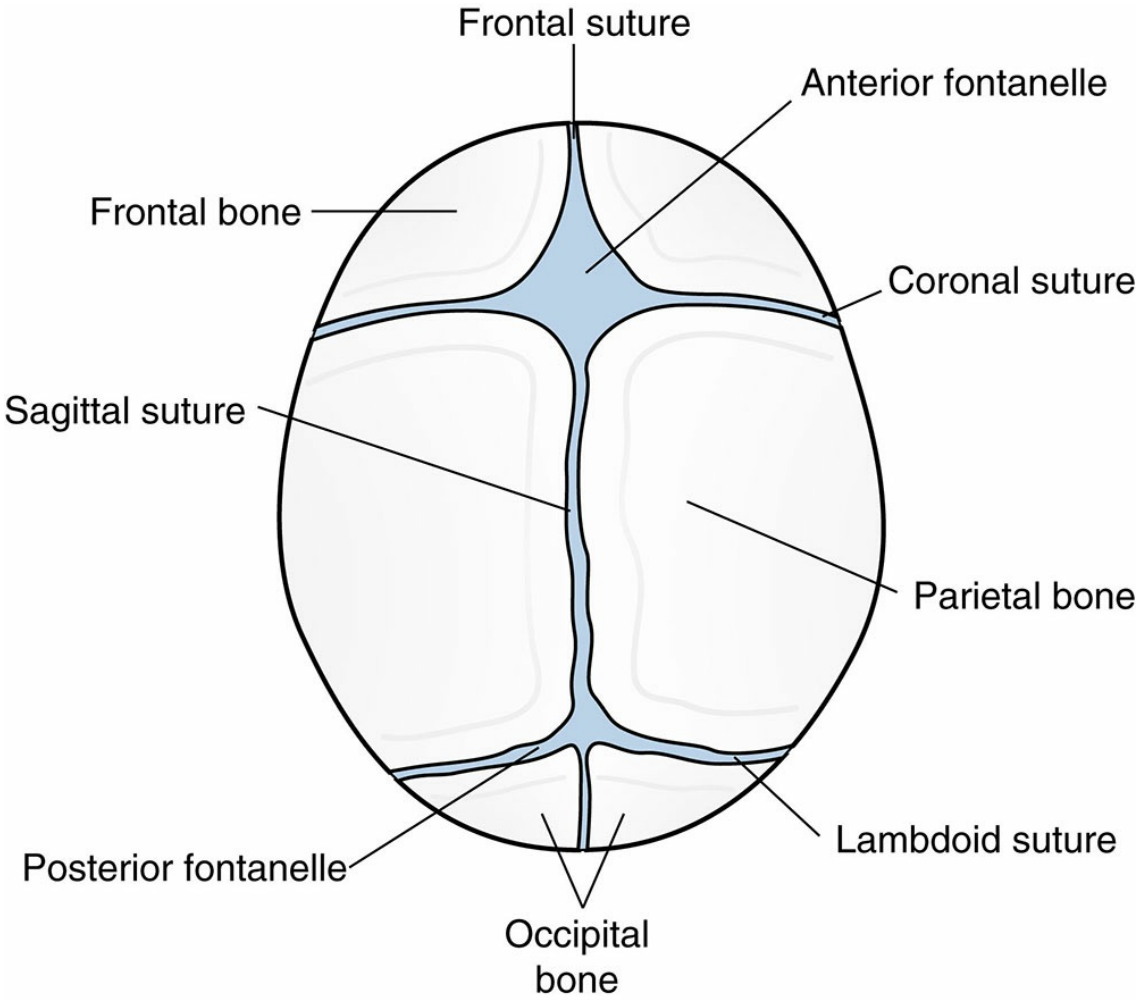

FIGURE 1.2 Cranial sutures in the neonatal skull.

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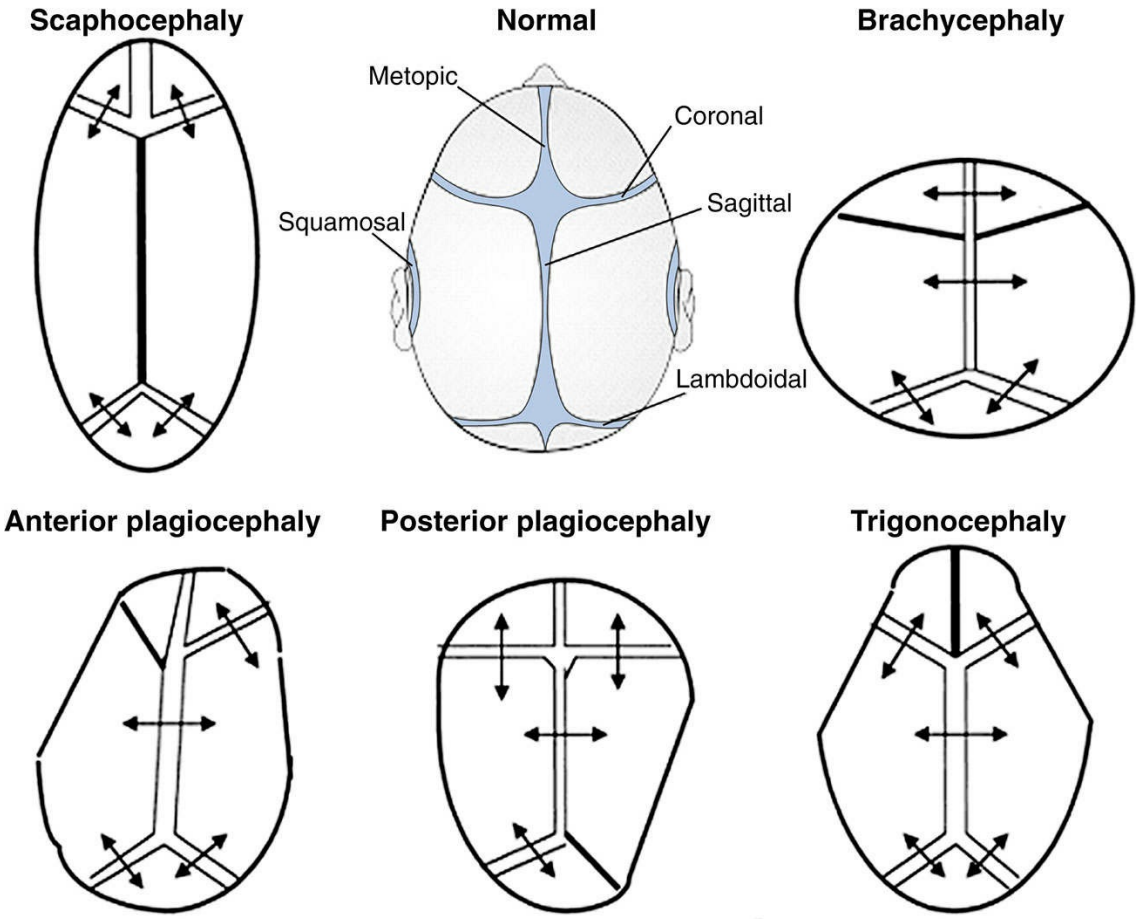

FIGURE 1.3 Types of craniosynostosis.

Reprinted with permission from Mongan P, Soriano SG, Sloan TB, Gravlee GP. Practical Approach to Neuroanesthesia. Philadelphia: Lippincott Williams & Wilkins, 2013.



FIGURE 1.4 Infant with positional plagiocephaly.

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III. Immunizations

A. **Immunizations are among the most important components of well-child care and disease prevention.** *Recommendations for routine immunizations are updated annually. For the most up-to-date recommendations on the childhood immunization schedule, please visit www.cdc.gov.*

B. **Types of immunizations**
   1. **Active immunization** involves induction of long-term immunity through exposure to live attenuated or killed (inactivated) infectious agents.
      a. **Live vaccines** are more likely to induce long-lasting immunity, but carry the risk of vaccine-associated disease in the recipient, or in a secondary host. As a result, **live vaccines should generally be avoided in patients with compromised immunity** (e.g., cancer, congenital or drug-induced immunodeficiencies, acquired immune deficiency syndrome). Examples of live vaccines include intranasal influenza; varicella; and measles, mumps, and rubella (MMR) vaccines.
      b. **Nonlive vaccines** are not infectious and tend to induce immunity for shorter periods, thus requiring booster immunizations. Examples include diphtheria, tetanus, and acellular pertussis (DTaP); hepatitis A (Hep A) vaccine and hepatitis B vaccine (HBV); inactivated polio vaccine (IPV); *Haemophilus influenzae* type b (HIB); inactivated influenza; pneumococcal and meningococcal vaccines.
   2. **Passive immunization** involves delivery of preformed antibodies to individuals who have no active immunity against a particular disease, but have either been exposed to or are at high risk for exposure to the infectious agent. Examples include the following:
      a. Varicella zoster immune globulin (VZIG) for immunocompromised patients who have been exposed to varicella and are at high risk for severe varicella infection, including newborns born to mothers who develop chicken pox between 5 days before and 2 days after delivery.
      b. Hepatitis B immune globulin, given to newborns born to hepatitis B–positive women
      c. Hepatitis A immune globulin, given as "predeparture" passive immunization to some visitors to high risk areas

C. **Specific immunizations**
   1. **Hepatitis B vaccine (HBV)**
      a. Rationale for vaccine: **90% of affected infants will develop chronic infection.** 240 million people are chronically infected worldwide, with up to 30 million new cases every year. More than 750,000 people die annually from hepatitis B and its complications.
      b. Type of vaccine: inactivated
      c. Timing of vaccination: HBV is given as a three-shot series within the first year of life.
   2. **DTaP**
      a. Rationale for vaccine: Diphtheria, tetanus, and pertussis all may cause serious disease, especially in young infants. Outbreaks of pertussis with significant mortality continue to occur in the United States.
      b. Type of vaccine
         1. Vaccine is inactivated.
         2. **DTP,** which contained **whole-cell,** killed *Bordetella pertussis*, had a high rate of side effects and was replaced with **DTaP** (1996)**,** a vaccine that contains purified components (**acellular**) of *B. pertussis,* with lower rates of vaccine-associated fever, seizures, and local reactions. DTaP is safer but has a waning

immunity to pertussis over time.

c. Timing of vaccination
    1. **DTaP** is recommended at 2, 4, and 6 months of age with boosters at 12–18 months and 4–6 years of age.
    2. **Tdap** (has less diphtheria component compared with DTaP) is a booster immunization, offering continued protection from these diseases in the adolescent and adult age group. Tdap is recommended at age 11–12. After receiving at least one Tdap, **the vaccine** should be given every 10 years thereafter for **continued protection.** Note that Tdap rather than DTaP is given to children 7–10 years of age if they did not complete their series of DTaP by their seventh birthday.

3. **Oral polio vaccine (OPV) and IPV**
    a. Rationale for vaccine: Poliovirus is an enterovirus with propensity for the central nervous system, which may cause transient or permanent paresis of the extremities and meningoencephalitis. Polio has been eradicated from the Western hemisphere and South Pacific, but remains in isolated pockets throughout the world.
    b. There are two types of vaccines.
        1. **Live attenuated (OPV),** administered orally
            a. **Advantages** include ease of administration and induction of both host immunity and secondary immunity, because it is excreted in the stool of the recipient and may infect, and thus immunize, close contacts.
            b. **Disadvantages** include the induction of vaccine-related polio, a rare complication. Because of the risk of vaccine-related polio, OPV is **no longer used in the United States.**
        2. **Nonlive or inactivated (IPV),** administered subcutaneously or intramuscularly, does not cause vaccine-related polio, but also does not confer secondary immunity.
    c. Timing of vaccination: In the United States, **only IPV is recommended** and is given at 2 and 4 months of age, with boosters at 6–18 months and 4–6 years of age.

4. **Rotavirus vaccines**
    a. Rationale for vaccine: Rotavirus infections are the most common cause of severe acute gastroenteritis worldwide. Worldwide, each year approximately **2 million children are hospitalized and 450,000 children die from disease caused by rotavirus.** Rotavirus is highly contagious and nearly every child is at risk of getting infected.
    b. Type of vaccine: oral, live vaccine
    c. Timing of vaccination: recommended at 2, 4, and 6 months of age

5. **HIB vaccine**
    a. Rationale for vaccine: HIB was a serious cause of invasive bacterial infection, including meningitis, epiglottitis, pneumonia, and sepsis, before vaccine licensure in 1985. Since licensure, HIB has become a rare cause of such infections.
    b. Type of vaccine: HIB vaccine is a **conjugate vaccine** (inactivated) with *H. influenzae* polysaccharide linked to various protein antigens, including diphtheria or tetanus toxoids, to augment immunogenicity.
    c. Timing of vaccination: HIB vaccine is recommended at ages 2, 4, and 6 months with a booster at ages 12–15 months. After 15 months of age, the vaccine confers lasting immunity. Therefore, children who receive the HIB vaccine at 15 months of age or older do not require additional doses, no matter how many doses were given before 15 months of age.

6. **MMR vaccine**

a. Rationale for vaccine: MMR immunizes against three viral diseases. Especially important in areas where misinformation regarding the vaccine has led to decreased vaccination rates and unfortunate outbreaks of the following:
    1. **Measles** is a severe illness with complications that include pneumonia associated with significant mortality. Classic signs include cough, coryza, conjunctivitis, and Koplik spots (an enanthem with white lesions on a reddened base on the inner cheek), followed by a classic rash (an exanthem described as morbilliform, starting on the face and moving caudally).
    2. **Mumps** is most commonly associated with parotitis but may also cause meningoencephalitis and orchitis.
    3. **Rubella** causes a mild viral syndrome in children, but may cause severe birth defects (commonly hearing loss and heart defects) in offspring of susceptible women who are infected during pregnancy.
b. Type of vaccine: **live attenuated vaccine**
c. Timing of vaccination: MMR vaccine is recommended at 12–15 months of age with a booster at 4–6 years of age. A special indication exists for infants 6–12 months of age traveling to countries where MMR is endemic. Because this dose is given before the recommended time of 12–15 months, it does not count toward the two-shot series and the child will subsequently need two additional doses at the appropriate times.

7. **Varicella vaccine**
    a. Rationale for vaccine: Varicella is the virus responsible for chicken pox and zoster. Varicella often causes uncomplicated illness, but may cause severe disease in very young and in older or immunosuppressed patients.
    b. Type of vaccine: **live attenuated vaccine**
    c. Timing of vaccination: Vaccine is recommended at 12–18 months of age with a booster at 4–6 years of age. It is commonly given in conjunction with MMR vaccine.
8. **Hep A vaccine**
    a. Rationale for vaccine: **Hep A is the most common viral cause of hepatitis worldwide,** although it is asymptomatic in up to 70% of infected children younger than 6 years. More severe disease is seen in older children and adults, although it is rarely associated with fulminant hepatitis.
    b. Type of vaccine: **inactivated**
    c. Timing of vaccination: Hep A vaccine is a two-dose vaccination series recommended for all children starting at 1 year of age. The booster should given at least 6 months later but ideally no later than 2 years of age. Children not fully vaccinated by 2 years of age should be vaccinated at subsequent visits.
9. **Pneumococcal vaccines (PCV-13 and PPSV-23)**
    a. Rationale for vaccine: Pneumococcal (*Streptococcus pneumoniae*) disease causes **more deaths in the United States each year than all other vaccine-preventable illnesses combined.** It is a common cause of acute otitis media, pneumonia, and invasive bacterial infections (bacteremia and meningitis) in the pediatric population.
    b. There are two types of vaccines. Both are inactivated.
        1. **PPSV23** is composed of polysaccharide capsular antigens from 23 pneumococcal serotypes.
            a. **Major advantage** is that the vaccine contains antigens from pneumococcal strains causing **almost all** cases of bacteremia and meningitis during childhood.
            b. **Major disadvantage** is that the vaccine has **<u>little</u> immunogenicity in children younger than 2 years.**

c. **Indications.** Vaccine is indicated in children with an immunocompromising condition and and for those with functional or anatomic asplenia. It is also indicated immunocompetent children with chronic heart disease, chronic lung disease, diabetes mellitus, cerebrospinal fluid (CSF) leak or cochlear implants.
d. Timing of vaccination: One dose should be given at 2 years of age and at least 8 weeks after the final dose of PCV13 (see below). Children with an immunocompromising condition or functional/anatomic asplenia should get a second dose 5 years after the first PPSV23.

2. **PCV13** is composed of 13 pneumococcal serotypes. PCV13 includes the 13 serotypes that account for most invasive pneumococcal diseases.
   a. **Major advantages** include **immunogenicity and efficacy** in preventing meningitis, pneumonia, bacteremia, and otitis media from the most common pneumococcal strains in children **younger than 2 years.**
   b. **Major disadvantage** is that it does not confer as broad coverage against as many pneumococcal strains as PPSV-23.
   c. Timing of vaccination: PCV-13 is recommended for all children at 2, 4, and 6 months of age, with a booster at 12–15 months of age. Healthy children who fall behind schedule should be caught up before their fifth birthday.

10. **Influenza vaccines**
    a. Rationale for vaccine: Influenza can be a very serious illness that may result in hospitalizations and even death, regardless of a child's medical history. About 20,000 children are hospitalized annually in the United States with influenza, and around 40% of children who die from influenza have no significant past medical history. Children **under 5 years of age and those with conditions that predispose to complications of influenza are considered to be at high risk.**
    b. There are two types of vaccines, with recommendations for administration updated annually.
       1. **Live attenuated influenza vaccine (LAIV)**, administered intranasally
          a. **Advantages:** no need for an injection.
          b. **Disadvantages:** it is only available for children 2 years of age or older without contraindications to the vaccine. It can cause nasal congestion and rhinorrhea for several days.
       2. **Inactivated influenza vaccine (IIV)**, administered intramuscularly
          a. **Advantages:** may be administered as early as at 6 months of age. There are no contraindications owing to underlying medical conditions, unless the child has a history of anaphylaxis to a previous influenza vaccination.
          b. **Disadvantages:** requires injection
          c. Timing of the vaccination: **Every child aged 6 months and older should receive the influenza vaccination annually.** Between 6 months and 8 years of age, first-time vaccine recipients need two doses of vaccine, spaced at least one month apart.

11. **Human Papilloma Virus (HPV) vaccines**
    a. Rationale for vaccine: HPV is the most common sexually transmitted disease in the United States, affecting the majority of sexually active adults. There are about 150 different types of HPV, some of which cause significant health problems such as genital warts and certain cancers (e.g., cervical, vaginal, anal, penile, and oropharyngeal). Thus, **HPV vaccine is one of the two cancer-preventive vaccinations**, the other being Hepatitis B vaccine.

b. Type of vaccine: inactivated vaccine
c. Timing of vaccine: All children aged 11–12 years should receive the two-dose series of HPV, with the second dose administered 6 months after the first. If the first dose is not started until age 15 or older, three doses of vaccine are required. Young men may be vaccinated up to 21 years of age, and women may be vaccinated up to 26 years of age. Ideally, the series is initiated during the preteen years, to facilitate development of an immune response before the initiation of sexual activity.

12. **Meningococcal vaccine (MCV)**
    a. Rationale for vaccine: Infection with *Neisseria meningitidis* can cause meningitis and sepsis, which is fatal in up to 15% of children. Up to 20% of survivors will develop permanent disabilities (e.g., loss of limbs, deafness, central nervous system damage). Rates of disease are highest in infants < 1 year of age, and in teens and young adults ages 16–23 years. Rates of meningococcal disease have been declining since 1990, which is thought to be a consequence of increased vaccination use.
    b. Type of vaccine: inactivated vaccine
    c. Timing of vaccine: All children aged 11–12 years should receive the quadrivalent vaccine to protect against serotypes A, C, W, and Y. A booster vaccination is given at 16–18 years of age. Children as young as 2 months old may receive the first dose of a four-dose meningococcal vaccine series if they are at high risk (e.g., anatomic or functional asplenia, complement deficiency, travel to hyperendemic or epidemic regions), with administration of doses recommended at 2, 4, 6, and 12–15 months of age. Vaccine for serotype B is recommended for children ≥ 10 years of age at increased risk of serotype B infection (e.g., community outbreak, functional/anatomic asplenia, and complement pathway abnormalities).

D. **Adverse effects of immunization**
1. Most vaccine side effects are mild to moderate in severity and occur within the first 24–48 hours after administration (e.g., local inflammation and low-grade fever).
2. Because **MMR** and **varicella** vaccines are live attenuated vaccines, fever and rash may occur **1–2 weeks after immunization** (i.e., after the incubation period of the virus).
3. Serious side effects, including those that are life-threatening or result in permanent disability, are rare (e.g., vaccine-related polio after OPV).
4. **While there is no evidence that neither vaccines nor preservatives such as thimerosal are linked to developmental disabilities,** as a precautionary measure the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) eliminated thimerosal from vaccines in 2001. Of the vaccines currently recommended for children younger than 6 years, only some forms of influenza vaccine contain small amounts of thimerosal.
5. **There is no evidence of a link between vaccines and autism.**

E. **Contraindications and precautions to immunization**
1. **Contraindications** to immunization include the following:
    a. **Anaphylaxis** to a vaccine or its constituents
    b. **Encephalopathy** within 7 days after **DTaP/Tdap** vaccine
    c. **Immunodeficient patients should not receive** live vaccines including **OPV, MMR, rotavirus, and varicella vaccines.** Household contacts of immunodeficient patients should not receive OPV vaccine, as it is shed in the stool.
    d. **Patients with a history of intussusception** should not receive **rotavirus** vaccine.
    e. Pregnant patients should not receive live vaccines, including OPV, MMR, and varicella.
2. **Precautions** (i.e., caution should be exercised) to immunization include the following:
    a. **For all vaccines**, **moderate to severe illness** (with or without fever). Note that mild

illnesses, including febrile illnesses, are **not** contraindications to immunization.

b. **DTaP vaccine**
    1. Temperature of 40.5°C within 48 hours after prior vaccination
    2. Collapse or shocklike state within 48 hours after prior vaccination
    3. Seizures within 3 days after prior vaccination
    4. Persistent, inconsolable crying lasting ≥3 hours occurring within 48 hours after prior vaccination
c. **MMR and varicella vaccines:** Intravenous Immunoglobulin (IVIG) administration within the preceding 11 months, which might interfere with the patient's immune response to these live vaccines

IV. Well-Child Screening

A. **The focus of each well-child visit is to identify undetected problems or the risks for such problems.**
B. **Screening assessments** include a complete history and physical examination, **growth measurements,** blood pressure measurements, strabismus and vision screening, hearing screening, tuberculosis risk assessment, and laboratory screening.
C. **Vision screening** for ophthalmologic disorders begins at birth and is detailed in Chapter 18.
D. **Hearing screening**
    1. **Universal newborn hearing screening** is recommended by 1 month of age, with confirmation of an abnormal screen by 3 months of age. Early intervention for hearing impairment is associated with better developmental language outcomes, and should be initiated no later than 6 months of age.
    2. Two types of audiometric tests are used for the newborn.
        a. **Otoacoustic emission (OAE)** measures sounds generated by normal cochlear hair cells that are detected by a microphone placed into the external auditory canal. This screening test is routinely performed in newborn nurseries before infant discharge. Administering the test takes only a few minutes and is painless, and the expenses for equipment and training are lower than for brainstem auditory-evoked response/auditory brainstem response (BAER/ABR) as below. OAE accuracy may be affected by debris or fluid within the external or middle ear.
        b. **BAER/ABR** measures electroencephalographic (EEG) waves generated in response to clicks via electrodes placed on the infant's scalp. Compared with OAE, BAER is a more accurate test, but it requires costly equipment, trained operators, and sometimes sedation. BAER is typically performed to confirm abnormalities found on OAE.
E. **Neonatal metabolic (state) screening**
    1. Many metabolic diseases can be diagnosed and treated in the newborn period.
    2. Although there is some variability among states as to which conditions are screened, **all states screen for congenital hypothyroidism**, **phenylketonuria (PKU),** and **galactosemia.** Each of these conditions is treatable, and if not detected early, each leads to irreversible brain injury.
    3. Most states screen for **sickle cell anemia** and other hemoglobinopathies, because early intervention in a comprehensive treatment program significantly decreases morbidity and mortality.
    4. Newborn screening tests for additional metabolic disorders (e.g., congenital adrenal hyperplasia) are performed in some states. The most extensive state screening panels screen for 50 disorders or more.
F. **Cholesterol and lipid screening**
    1. **Universal screening** for hypercholesterolemia, regardless of body mass index (BMI) or risk factors, has been recommended by the National Heart, Lung and, Blood Institute (NHLBI) and endorsed by the American Academy of Pediatrics (AAP). Obtaining a nonfasting non-HDL cholesterol level is recommended for all children between 9 and 11 years of age, and again between 17 and 21 years of age. For children with an abnormal result on the screen, a fasting lipid profile should be obtained.
    2. **Targeted screening** for hypercholesterolemia (consisting of fasting lipid profile performed twice within 2–12 weeks) **is recommended** for children between 2–8 years of age and 12–16 years of age with one of the following risk factors:
        a. History of diabetes, hypertension, BMI > 95th percentile (if 2–8 years old) or

BMI > 85th percentile (if 12–16 years old), or smoking
    b. History of one of the following moderate- or high-risk medical conditions: nephrotic syndrome, human immunodeficiency virus (HIV), Kawasaki disease with history of coronary aneurysms, and end-stage renal disease
    c. Parent with total cholesterol > 240 mg/dL or known dyslipidemia
    d. Parent, grandparent, aunt/uncle, or sibling with myocardial infarction, angina, stroke, or coronary artery bypass graft/stent/angioplasty at <55 years in males and <65 years in females
3. **Interventions for elevated cholesterol** should include dietary and behavioral modifications, and may include referral to a registered dietician for nutrition counseling for the family.

G. **Iron-deficiency anemia screening**
1. Iron-deficiency anemia occurs most commonly in children < 6 years of age, peaking between 9 and 15 months of age, but may occur throughout the entire pediatric age range. More than 10% of 1 year olds are iron deficient.
2. **Risk factors** for iron-deficiency anemia include:
    a. Prematurity
    b. Low birth weight
    c. Early introduction of cow's milk (before 12 months of age) or consumption of 24 oz or more of milk a day
    d. Insufficient dietary intake of iron
    e. Low socioeconomic status
3. **Universal screening** of hemoglobin levels is recommended at 12 months of age. Subsequently, selective screening should be based on annual risk assessment.

H. **Routine urinalysis screening** is not recommended. Analysis of urine samples are recommended only when clinically indicated.

I. **Tuberculosis screening**
1. Screening for latent tuberculosis infections is recommended for children at risk for tuberculosis. Tuberculosis screening may be performed through the use of tuberculin skin testing with intradermal injection of purified protein derivative (PPD, Mantoux skin test). Alternatively, interferon-gamma release assays (IGRAs), which are in vitro tests of cell-mediated immune response, may be used in children older than 5 years to screen for latent tuberculosis. They are useful in the evaluation of children who have received the Bacillus Calmette–Guérin (BCG) vaccine. Screening is indicated for children with one or more of the following risk factors:
    a. **Birth place in a high-risk country other than United States, Canada, Australia, New Zealand, or Western and Northern European countries**
    b. Travel to an endemic region (e.g., Africa, South America, Asia, Eastern Europe) for a **cumulative total of 1 week** or more
    c. **Exposure to anyone with tuberculosis**
    d. **Close contact with a person who has had a positive screen for latent tuberculosis**

J. **Lead screening**
1. **Lead intoxication (plumbism):** No safe blood lead level (BLL) in children has been identified, and lead intoxication remains a public health risk. While the incidence and severity of lead poisoning in the United States are decreasing, in large part owing to effective screening programs and increased public awareness, there is still a high number of affected children living in deteriorating housing built before the 1970s.
2. **Risk factors** for lead intoxication include the following:
    a. **Ingestion of lead-containing paint** from homes built before 1978
    b. Drinking water from **lead-containing pipes**

   c. Exposure to lead smelters, industrial manufacturing sites, or to adults with occupational exposures leading to contamination of clothes and hands
   d. Use of **lead-glazed pottery, imported toys, and imported candies** (Mexico, Malaysia, China, and India) that contain tamarind, chili powder, or salt
   e. Use of **lead-containing folk remedies**
   f. **Exposure to soil** with high lead levels due to **decades of burning leaded gasoline**
3. **Clinical features** of lead intoxication
   a. **Children < age 6 are most susceptible to the effects of lead** owing to a variety of mechanisms, including increased permeability of the blood–brain barrier to lead, higher rates of iron-deficiency anemia leading to increased lead absorption, and increased hand-to-mouth behaviors amongst infants and toddlers.
   b. **Acute lead intoxication** may lead to anorexia, apathy, lethargy, anemia, irritability, and vomiting. These symptoms may progress to encephalopathy (see also Chapter 20, section VIII.D.4).
   c. **Chronic lead intoxication** is most commonly **asymptomatic;** however, even patients with very low levels of lead (≥5 μg/dL) may suffer **neurologic sequelae,** including **developmental delay, learning problems, and intellectual disability.**
4. As the prevalence of childhood lead poisoning declines, there has been a movement to **focus on primary prevention, and to transition from universal screening to targeted screening.** AAP recommends that screening be performed in accordance with state laws when applicable. **If no state screening program is in place, then universal screening** at 1 and 2 years of age is recommended if the community has *any* of the following risk factors:
   a. ≥27% of the housing was built before 1950.
   b. ≥12% of children 12–36 months of age have BLLs ≥ 10 μg/dL.
   c. Information on the prevalence of elevated BLLs in the community is unavailable or inadequate.
5. **Intervention and management** of lead poisoning is based on serum lead levels after repeat testing, and generally includes education to decrease exposure and chelation for very high lead levels.

V. Circumcision

A. Approximately 60% of male infants in the United States are circumcised.
B. Though the existing evidence is not sufficient to recommend routine circumcision, **the AAP states that the health benefits of circumcision outweigh the risks,** and these benefits justify access for families interested in circumcision.
    1. Circumcision is associated with a significant reduction in risk of acquiring HIV and other sexually transmitted infections.
    2. Circumcised patients have a lower risk of penile cancer, although this type of cancer is very rare in all males.
    3. **Urinary tract infections** (UTIs) are 10 times more common in uncircumcised male infants, particularly in the first 3 months of life.
    4. Uncircumcised males may ultimately require circumcision for the following conditions:
        a. **Phimosis** is an inability to retract the foreskin. **Physiologic phimosis** usually resolves around 5–7 years of age but can be seen in older boys. Ballooning of the foreskin can be normal as long as the ballooning does not require manual compression by the patient. Signs of **pathologic phimosis** include dysuria, painful erection, bleeding from the preputial orifice, and recurrent balanoposthitis (inflammation of the glans penis and foreskin) and necessitate a referral for urologic evaluation.
        b. **Paraphimosis** occurs when the retracted foreskin cannot be returned to its normal position and acts as a tourniquet, leading to edema from obstruction of venous and lymphatic flow. **This is a urologic emergency** because ischemia distal to the obstruction may occur. Surgery is required if attempts at manual reduction fail.
        c. **Balanitis** is inflammation of the glans of the penis. It may be associated with *Candida* spp. or Gram-negative infections in infants, and with sexually transmitted infections.
C. **Pharmacologic analgesia** is strongly recommended during circumcision.
D. **Complications from circumcision include** bleeding, infection, poor cosmesis, phimosis (secondary to insufficient foreskin removal), urinary retention, and injury to the glans or urethra.
E. **Contraindications to circumcision** include **anatomic penile abnormalities** (e.g., hypospadias, penile torsion), because the foreskin may be required for the reconstruction, as well as medical concerns (e.g., prematurity, bleeding diatheses) associated with higher complication rates.

VI. Pediatric Dental Care

A. **Counseling about dental care is an important component of anticipatory guidance.**
B. **Tooth eruption**
    1. **Range for initial tooth eruption is between 3 and 16 months of age, with an average age of 6 months.**
    2. The first tooth is generally a **lower central incisor.**
    3. **Primary teeth** (20 teeth in total) are generally established by 2–3 years of age.
    4. **Secondary (permanent) tooth eruption** also begins with the lower central incisor, between 5 and 7 years of age, and generally finishes by 13–14 years of age. There are 32 secondary teeth.
    5. **Tooth eruption may be early or delayed.**
        a. **Early dental eruption** is defined as primary eruption **before 3 months of age.** Causes include **familial** causes**, hyperthyroidism,** precocious puberty, and growth hormone excess.
        b. **Delayed dental eruption** is defined as primary eruption that has not occurred by **18 months of age.** Causes include **familial** delayed eruption, **hypothyroidism,** hypopituitarism, **vitamin D deficiency,** and genetic syndromes such as **Down syndrome** and **ectodermal dysplasia** (associated with conical-shaped teeth, dysmorphic facial features, decreased numbers of sweat glands, and alopecia).
C. **Dental hygiene**
    1. **Tooth brushing** should begin **as soon as teeth erupt.** A moist washcloth or gauze pad may be used initially, and a soft toothbrush may be used as early as tolerated. Parents should initially do the brushing to ensure that the teeth are actually being cleaned. A rice-sized amount of fluoride toothpaste should be used after tooth eruption. At age 3 years, a pea-sized amount of fluoride toothpaste should be used.
    2. **Dental floss** to remove plaque from between teeth should be initiated when tight contact exists between teeth.
    3. **Fluoride**
        a. Children who consume optimal amounts of fluoride from birth until adolescence have 50–75% less dental decay than expected. **Fluoride protects against demineralization, promotes remineralization, and decreases the negative effects of cariogenic bacteria in the mouth.**
        b. **Sources of fluoride** include food, tap water, some bottled waters, fluoride varnish, and fluoride toothpaste. Fluoride varnish, applied every 3–6 months starting at tooth emergence through age 5, has been shown to prevent early childhood cavities.
        c. **Excess fluoride** can lead to **fluorosis.**
            1. **Fluorosis affects permanent teeth** and leads to abnormalities in dental enamel and dentin. Most cases of fluorosis are mild; moderate and severe forms are uncommon in the United States.
            2. **Effects are usually cosmetic** and include white streaks, pitting, or brown-gray staining. Structural abnormalities associated with fluorosis are extremely rare.
            3. Children are most **vulnerable to fluorosis between 15 and 30 months of age.** After 8 years of age, children are no longer at risk for fluorosis because permanent tooth enamel is fully mineralized.
        d. Although care must be taken to prevent fluorosis, *oral fluoride supplementation* remains important starting at 6 months of age for children whose water supply is deficient in fluoride (<0.3 ppm).
D. **Dental abnormalities**

1. **Early dental eruption.** Occasionally infants are born with teeth or have teeth that erupt within the first month of life.
    a. **Definitions**
        1. **Natal teeth** are those that are present at birth.
        2. **Neonatal teeth** are those that emerge during the first month of life.
    b. Among early erupting teeth, **mandibular central incisors** are the most common. More than 90% of early erupting teeth are primary teeth and 10% are supernumerary teeth (teeth in excess of usual number).
    c. **Management.** Extraction is indicated if the teeth are **hypermobile, are at risk for aspiration,** cause breastfeeding difficulty, or cause trauma to the infant's lip or tongue.
2. **Dental caries**
    a. **Epidemiology. Early childhood caries is the most common chronic infection in children <6 years of age.** Up to 60% of 12–19 year olds have at least one documented cavity. Caries disproportionately affect poor and minority populations.
    b. **Etiology.** Development of dental caries requires four components: **teeth, carbohydrate exposure, bacteria, and time.**
        1. Once teeth have erupted, they can be colonized by cariogenic bacteria. Children can acquire these bacteria from colonized parents and siblings. *Streptococcus mutans* and *Lactobacillus* species are the most common bacterial agents.
        2. **Carbohydrates** that are retained around the teeth may serve as a substrate for bacteria capable of causing caries. Severe tooth decay among infants with excessive exposure to sugar from milk, formula, or juice are sometimes called "baby bottle" or "early childhood" caries.
        3. The bacteria metabolize the carbohydrates and create acidic by-products. Over time, the acid leads to demineralization of the enamel. Multiple insults can cause collapse of the enamel's surface, leading to cavities.
    c. **Clinical features.** Caries commonly involve the **maxillary incisors, canines, and grooved surfaces of the molars.** Cavities are initially chalky white or yellow, signifying loss of enamel. After further demineralization, the lesion will become brown and irreversible.
    d. **Management** of dental caries involves a combination of restorative therapy (e.g., fillings) and preventive measures (e.g., limited sugar intake, fluoridated water, toothpaste, varnishes, etc.). Severe cases may require surgical interventions, such as placement of dental crowns or extraction.

E. **Dental trauma**

1. **A permanent tooth** that has been traumatically avulsed **may be reimplanted** if the avulsed tooth is placed into the socket rapidly.
    a. **Extraoral time** is the **most important factor** affecting the prognosis for successfully reimplanting a tooth. The tooth should be held by the crown and washed in water for 10 seconds and then reimplanted.
    b. If the tooth cannot be reimplanted at home, **prognosis is highest if the avulsed tooth is stored in liquids such as cold milk,** which extends viability time for the tooth when compared with that for a tooth stored in water.
    c. After 30 minutes or longer, a **dry stored tooth** is unlikely to be successfully reimplanted.
2. **Management**. After referral to a dentist, radiographs should be obtained to rule out fractures if there is a history of trauma. Even if the avulsed tooth is a primary tooth,

radiographs are indicated to assess the status of other unerupted permanent teeth.

3. Avulsed primary teeth do not require reimplantation.

VII. Developmental Screening

One of the most important surveillance measures of well-child care is assessment of developmental milestones, which occurs during each visit from infancy through school age. School performance substitutes for formal developmental assessment in typically developing children older than 5–6 years. Development is discussed in depth in Chapter 2.

VIII. Anticipatory Guidance

A. **Anticipatory guidance** includes both **patient and parent education,** and is provided during each well-child visit. Guidance is tailored to the child's developmental level and to anticipated changes in the child's development before the next scheduled well-child visit. **It is one of the most important aspects of the well-child visit.**

B. **Topics covered by anticipatory guidance include**
   1. **Family support**
   2. **Child development**
   3. **Mental health**
   4. **Healthy weight and nutrition**
   5. **Physical activity**
   6. **Oral health**
   7. **Healthy sexual development and sexuality**
   8. **Safety and injury prevention**
   9. **Community relationships and resources**

C. **Age-appropriate anticipatory guidance** topics for children from birth to 5 years of age are detailed in **Table 1-5**.

Table 1-5
Age-Appropriate Anticipatory Guidance Topics for Discussion for Children From Birth to Age 5

Age	Child Development/Healthy Habits	Safety and Illness Prevention	Healthy Weight and Nutrition	Family Support
Newborn	Cord care Circumcision care Skin and nail care Normal vaginal discharge and bleeding Normal sneezing and hiccups Stools change from meconium to transitional Amount of clothing needed and temperature regulation	Rear-facing car seat until 2 years of age Sleep on back Hot water heater <120°F Never leave alone Early signs of illness: fever, failure to eat, vomiting, diarrhea, dehydration, irritability or lethargy, jaundice, or rash Use of thermometer	Breastfeeding Feeding schedule for breastfeeding or formula feeding on demand (8–12 times/day) for 4–6 weeks of age Supplement with vitamin D (400 IU) in the first year of life to prevent rickets for both breastfeeders and infants taking in less than 1 L/day of formula If formula feeding, ensure proper preparation of formula	Talk, read, and sing to baby Approach to crying Burping and spitting up Thumb sucking and pacifiers Normal sleep patterns and sleeping arrangements Never shake a baby Screen for maternal depression
1 month	Sleeping 18–20 hours/day, 3–4 hours at a stretch Stooling decreasing in frequency and changes to brown and more formed	Same as newborn	Same as newborn No cereal No solids No honey until age 1 Relief bottle for breastfeeding moms	Colic may begin at 3–4 weeks of age and last till 3–4 months of age

	Some infants strain with stool			
2 months	Sleep 4–8 hours at a stretch Feed every 3–4 hours Stooling qod to 3–4 times/day	Risk of aspiration of small objects	Same as 1 month old	Establish bedtime routine Encourage vocalizations Most working mothers return to work by 2–4 months
4 months	Feeding every 4–5 hours Sleeping 6–8 hours at a stretch	Aspiration risk No infant walkers	Breastmilk/formula continues to be primary source of nutrition through 1 year of age. Maintenance amounts of iron should be added to the vitamin D supplementation. Iron-fortified infant cereal and solids can be introduced	Continue encouraging vocalizations—talking, singing, and reading to infant Introduce transitional object (e.g., toy, stuffed animal, blanket)
6 months	Feedings spaced out Sleeping through night for many	Baby-proof home Pool and water safety Weapons and pet safety Child gates on stairs Aspiration risk Sunscreen use No infant walker	More solids introduced Continue breast- or bottle-feeds plus solids Avoid foods with aspiration risk or choking risk (e.g., peanuts, popcorn, hot dogs, carrots, celery sticks, whole grapes, raisins, corn)	Provide opportunities for exploration Establish nighttime routine Transitional object To discipline, use distraction and routines Discuss separation anxiety Encourage reading, and give infant the first book
9 months	Drinks from cup Eats appropriate finger foods	Same as 6 months	Same as 6 months	Observe increasing independence and autonomy Anticipate separation anxiety and sleep disturbances

12 months	Feeding 3 times/day plus 2–3 snacks Establish sleep hygiene—transitional objects, bedtime routine, sleeping through night Begin weaning from bottle	Child-proof house	Switch to whole milk Drink from cup Table food—watch aspiration risk Weight gain slows down, intake decreases, do not force foods	Praise good behavior Encourage language development—read to toddler Encourage exploration and initiative Discipline with distraction, gentle restraint, "time out" No "screen time" (television, phones, tablets)
15 months	Feeds self Naps 1–2 times/day	Same as 12 months	Same as 12 months	Begin discussion of toilet training readiness; do not push; be patient
18 months	Feeds self May begin toilet training Naps 1–2 times/day	Same as 12 months	Avoid cookies and sweets as bribe to eat Whole milk < 24 oz/day	View negativism as budding independence Encourage language development by reading, singing, and talking Make discipline brief and specific Anticipate night terrors, nightmares, night fears Do not expect toddler to share
2 years	Change to bed from crib Initiate toilet training if not prior	Same as above, plus the following: Can make car seat forward facing Will not transition to booster seat until at least 4′9″ (8–12 years old).	Food struggles are common Change to 2% milk Never force child to eat Offer nutritious foods	Anticipate new fears, indecision—provide reassurance Anticipate parallel play, sibling rivalry if new baby expected Acknowledge conflict but

				do not allow behavior; biting and hitting are common No more than 2 hours of "screen time"
3 years	90% bowel trained 85% bladder trained (day) 65% bladder trained (night)	Bicycle helmets Street safety Stranger danger Firearm safety Tricycle safety Pet and water safety	Continue healthy food choices	Use correct terms for genitalia Introduce notion that some areas of the body are private Anticipate preschool Observe beginning of sharing during play
4 years	95% bowel trained 90% bladder trained (day) 75% bladder trained (night)	Swimming lessons Scissor and pencil use Firearm safety Bicycle helmets	Continue healthy food choices Anticipate imitating peers in eating choices	Provide opportunities for socialization with other children Establish and enforce consistent, explicit rules for safe behavior Observe beginning of imaginative play Observe discovery of sexual identity
5 years	Sleeps 10–12 hours/night Teach personal care and hygiene	Bicycle helmets Stranger danger Firearm safety Phone number memorized	Continue healthy food choices, including school lunch	Library cards, learning to read Rules for bedtime, TV watching Age-appropriate chores School participation encouraged

Review Test

1. A 6-month-old girl has been noted to fall off her growth curve, and her weight is now <5% for her age. You suspect failure to thrive (FTT) and consider the most common causes. Which one of the following is the most common cause of FTT?
   A. A disturbed parent–child bond that results in inadequate caloric intake or retention
   B. Prenatal onset of inadequate weight gain that persists in the postnatal period
   C. A skeletal abnormality resulting in short stature with associated poor weight gain
   D. Malabsorption or the inability to completely absorb ingested calories and nutrients
   E. Endocrinologic abnormalities, such as growth hormone deficiency or hypothyroidism
2. A 2-month-old male infant is seen for routine well-child evaluation. At birth, his head circumference was <5% for age. His head circumference has increased 1 cm in size since birth. Which one of the following is the most likely cause of the infant's condition?
   A. Intraventricular hemorrhage
   B. Perinatal asphyxia
   C. Third trimester infection with cytomegalovirus
   D. Craniosynostosis
   E. First trimester infection with toxoplasmosis
3. A 4-week-old boy is evaluated for macrocephaly. In addition to a head circumference >95%, his coronal and sagittal sutures are split 1 cm and his fontanelle is bulging. Both of his parents' head circumferences are >95%. Which one of the following is the most likely explanation for the infant's macrocephaly?
   A. Familial
   B. Achondroplasia
   C. Hydrocephalus
   D. Metabolic storage disorder
   E. Neurofibromatosis
4. A 9-month-old girl is diagnosed with iron deficiency anemia. Her past medical history includes an uncomplicated delivery at 38 weeks. The infant was fed with formula until 6 months of age, at which time she was switched to baby foods and whole milk. Which one of the following is correct regarding her iron-deficiency anemia?
   A. Her age is atypical for the presentation of iron deficiency anemia.
   B. Her early birth at 38 weeks gestation has led to the anemia.
   C. Early introduction of cow's milk is the likely cause of her anemia.
   D. Insufficient dietary intake of iron is the likely cause of her anemia.
   E. The patient's early introduction of solids is the likely cause of her anemia.
5. An asymptomatic 12-month-old girl is screened for lead exposure. Which one of the following is correct regarding lead screening and lead intoxication?
   A. Most patients exposed to lead are asymptomatic.
   B. Children between 5 and 10 years of age are at highest risk for lead effects.
   C. Low lead levels on screening indicate that a child is at no risk for the neurologic sequelae of lead exposure.
   D. Chelation has not been shown to be effective for patients with high lead levels.
   E. Ingestion of paint from a home built in 1990 would place a child at risk for lead poisoning.
6. At a prenatal visit, the expectant parents of a first-born male child ask you to summarize the benefits, risks, and contraindications to performing a circumcision on their son. Which one of the following statements is correct?
   A. Circumcision has not been shown to decrease the risk of urinary tract infection.

B. Because of the young age at which circumcision is performed, analgesia is generally not required, thus decreasing the risks of the procedure when performed in the newborn period.
C. If their child is not circumcised in the newborn period, he may require circumcision at 9 months of age if he is subsequently diagnosed with phimosis.
D. The American Academy of Pediatrics recommends routine circumcision for medical benefit.
E. Hypospadias is a contraindication to circumcision.

7. A 20-month-old boy is seen for routine well-child care. Physical examination reveals caries involving the maxillary incisors. Which one of the following is most likely to have contributed to this condition?
   A. The use of both fluoride drops and fluoride toothpaste simultaneously, which has caused fluorosis
   B. Falling asleep with a water-filled bottle in the mouth
   C. Falling asleep while breastfeeding
   D. Oral colonization with *Staphylococcus aureus*
   E. Living in an area in which tap water contains no fluoride
8. A 1-year-old child living in an apartment with old chipping paint is suspected of being at high risk for lead intoxication. Which of the following findings on a routine health maintenance visit would support this diagnosis?
   A. Failure to thrive
   B. Anemia
   C. Fluorosis
   D. Microcephaly
   E. Impaired hearing
9. On a routine health maintenance visit, a 4-month-old infant is noted to have normal growth and development and an unremarkable physical examination. Which of the following should be included in your counseling of the parents at this time?
   A. Vitamin D supplementation with iron should be initiated, especially if the child is breastfed.
   B. The patient should be encouraged to begin using a walker to stimulate gross motor development.
   C. The infant should now be placed in a forward-facing car seat.
   D. Toilet training should be initiated.
   E. Honey may now be introduced into the infant's diet.
10. You receive a telephone call from the parents of a 10-month-old infant, who are concerned that their baby does not yet have any teeth. A review of the infant's growth chart reveals that the patient's weight, length, and head circumference are at the 50th, 25th, and 25th percentiles, respectively. The infant's developmental milestones are normal. Which of the following would be the most appropriate course of action?
    A. Refer the patient to a pediatric dentist.
    B. Refer the patient to a geneticist.
    C. Reassure the parents that their infant's pattern of dental eruption is within the normal range.
    D. Order radiographs to assess the patient's bone age.
    E. Order radiographs of the patient's oral cavity.

Answers and Explanations

1. **The answer is A** [II.B.1.d]. The most common etiology of failure to thrive (FTT) is inadequate intake of calories. Conditions that lead to malabsorption, increased metabolic demand, or decreased utilization of nutrients should also be in the differential diagnosis but are much less common causes. Short stature should be distinguished from FTT. Those with FTT have primary failure of weight gain (and subsequent poor linear growth and poor head circumference growth), whereas those with short stature have primary failure of linear growth.
2. **The answer is E** [Table 1-4, II.B.2.b]. Given his small head circumference at birth, this patient's microcephaly is congenital. Causes of congenital microcephaly include TORCH (**t**oxoplasmosis, **o**ther-syphilis, **r**ubella, **c**ytomegalovirus, **h**erpes simplex virus) infections during the first trimester, in utero exposure to drugs and toxins, and chromosomal abnormalities. In addition, congenital microcephaly may be familial. Perinatal asphyxia, intraventricular hemorrhage, craniosynostosis, and late prenatal and perinatal infections may all cause acquired microcephaly. Patients with acquired microcephaly are usually born with a normal head circumference.
3. **The answer is C** [II.B.2.c]. This patient has signs of increased intracranial pressure, which include split sutures and a bulging fontanelle. Other symptoms of intracranial pressure include irritability and vomiting. Hydrocephalus is the only option that is associated with increased intracranial pressure. Metabolic storage disorders, neurofibromatosis, achondroplasia, and familial macrocephaly are associated with enlarged head circumference but are not associated with increased intracranial pressure in a patient of this age.
4. **The answer is C** [IV.G.2.c]. The introduction of cow's milk should occur only after 12 months of age, as its early introduction (in this case at 6 months) is a known risk factor for iron deficiency anemia and is the likely cause in this case. This is because whole cow's milk offers less bioavailable iron and may also result in stool blood loss. Although insufficient dietary intake of iron is a possible cause, this patient received iron-fortified formula for at least 6 months, making this cause less likely. Prematurity (defined as <37 weeks) may result in lower iron stores with resultant anemia. Pediatricians start screening for iron-deficiency anemia at 12 months of age. The prevalence of iron-deficiency anemia in the United States is estimated to be more than 10% at 1 year of age. Finally, solids were introduced at an appropriate time in this patient (6 months) and this is not a risk factor for anemia.
5. **The answer is A** [IV.J]. Most patients with elevated lead levels are asymptomatic. Children younger than 6 years of age are at highest risk for the effects of lead. Risk factors include a history of ingestion of lead-containing paint or soil from homes, drinking water from lead pipes, use of lead-glazed pottery in food preparation, use of lead-containing folk remedies, and eating high-risk imported candies. Even patients with very low lead levels may suffer from developmental delay and learning problems. Chelation is required for very high lead levels.
6. **The answer is E** [V.B–E]. Contraindications to circumcision can be broken down into two main groups: anatomic and medical. Anatomic contraindications include hypospadias, ambiguous genitalia, and penile torsion. Medical contraindications include bleeding diathesis, connective tissue disorders that impair normal healing, and prematurity. Although phimosis is an indication for circumcision in some patients, it is considered normal unless they have signs of pathologic phimosis (e.g., dysuria, painful erection, bleeding from the preputial orifice, recurrent balanoposthitis). Other indications for circumcision include recurrent balanitis and unreducible paraphimosis. The American Academy of Pediatrics states that the medical benefits of circumcision outweigh the risks, but the benefits are not great enough to

recommend universal circumcision. No matter the patient's age, circumcision should be performed with analgesia/anesthesia.

7. **The answer is E** [VI.C.3.c, VI.D.2] This patient has dental caries. Those who live in areas with low fluoride levels in their water are at increased risk for caries. Water fluoridation has been named one of the 10 greatest public health achievements in the 20th century by the Centers for Disease Control and Prevention because of its effect on decreasing the risk of developing dental caries. In addition to decreasing the negative effects of cariogenic bacteria, fluoride decreases demineralization and promotes remineralization of enamel. Excess fluoride may cause cosmetic abnormalities to the enamel, but the risk of caries is not increased. Any exposure to carbohydrates (e.g., juice, milk) can serve as a substrate for infection. The evidence suggesting that breastfeeding can also increase the risk of caries is mixed. *Streptococcus mutans* and *Lactobacillus* are the most common bacterial agents.
8. **The answer is B** [IV.J.3]. Lead intoxication may cause a variety of clinical manifestations, including neurocognitive impairment, lethargy, microcytic anemia, constipation, and irritability. Most patients exposed to lead, however, are asymptomatic. Fluorosis is not associated with lead exposure, and lead exposure has not been known to result in microcephaly, failure to thrive, or hearing impairment.
9. **The answer is A** [Table 1-5]. Oral vitamin D supplementation is recommended to prevent the development of rickets in all children. The addition of iron to vitamin D supplementation is recommended at 4 months of age for exclusively breastfed infants and in formula-fed babies who are taking less than 1 L of formula/day. Infant walkers are not recommended because of the risk of injury associated with their use. Infants should be placed in a rear-facing car seat until they are 24 months of age. Toilet training is generally initiated between 2 and 3 years of age. Because of the risk of botulism, honey should be avoided until at least 1 year of age. After this time, honey is acceptable and is recommended for management of cough for children with upper respiratory infections.
10. **The answer is C** [VI.B]. Although the average age of initial tooth eruption is 6 months of age, there is a wide range of normal variability, ranging from 3 to 16 months of age. Delayed dental eruption is defined as primary eruption after 18 months of age and may be related to endocrine disorders (hypothyroidism and hypopituitarism), vitamin D deficiency, genetic syndromes (Down syndrome and ectodermal dysplasia), or may be familial.

CHAPTER 2

Behavioral and Developmental Pediatrics

Brian G. Tang

I. Normal Developmental Milestones

A. **General principles**
   1. **Developmental assessment and surveillance** are central components of health maintenance.
   2. **Developmental domains include motor, language, cognitive, and social–emotional skills.**
   3. **It is essential to understand normal development** and acceptable developmental variations in young children to recognize pathologic patterns. In addition, it is **important to monitor the attainment of developmental milestones in each domain to accurately identify children with developmental delays** who may benefit from early intervention.
   4. **Development typically occurs in an orderly, predictable, intrinsic manner.**
      a. Development proceeds from **head to toe** in a **proximal to distal fashion.**
      b. **Generalized reactions to stimuli develop into more specific, goal-directed reactions** that become increasingly precise.
   5. **Normal development is an uneven process with wide variation in the attainment of milestones.**
   6. **Development may be influenced by both intrinsic factors** (e.g., child's physical characteristics, state of health, temperament, and genetic attributes) and **extrinsic factors** (e.g., temperament of family members, economic status, caregiver mental health, availability of learning experiences in the environment, and the cultural setting into which the child is born).

B. **Developmental assessment**
   1. **Understanding developmental milestones** provides a **systematic way to assess an infant's progress.**
      a. **Attainment of a particular skill depends on the achievement of earlier skills** (only rarely are skills skipped).
      b. **Delays in one developmental domain may impair development in another domain** (e.g., deficits caused by neuromuscular disorders may affect a child's ability to explore the environment, which in turn affects cognitive development).
      c. **A deficit in one developmental domain may compromise the assessment of skills in another domain** (e.g., it may be difficult to assess problem-solving skills in the child with cerebral palsy who understands the concept of matching geometric forms, but lacks the physical ability to demonstrate that knowledge).
   2. **Developmental screening is crucial during the first 3 years of life and is an essential component of the well-child visit. Standardized screening tests provide structured methods of assessing developmental progress; however, parental concern should not be disregarded,** even if the initial screen is normal. Identifying young children with delays allows them to benefit from early intervention when brain growth is most rapid and plastic.
   3. **Developmental quotients (DQs)** are used to determine whether a child's development is delayed and to measure the extent of delay. The quotient may be calculated as follows:
      a. DQ > 85: normal
      b. DQ < 70: abnormal
      c. DQ 70–85: borderline delay
   4. Further **developmental testing** and assessment is needed if a child "fails" a screen. These children are typically referred to a clinical psychologist or developmental–behavioral pediatrician. In addition, these children benefit from an evaluation through their state's Part C early intervention programs.

C. **Developmental domains** include **motor development, language skills, cognitive development, and social–emotional skills.**
   1. **Motor development.** Information about motor milestones should be obtained from the history as well as from the physical examination.
      a. **Gross motor development evaluation** includes an assessment of milestones and neuromaturational markers. **Milestones of gross motor development** are listed in Table 2-1. **Neuromaturational markers** should also be assessed; these include **primitive reflexes and postural reactions, as described in** Table 2-2.
         1. **Primitive reflexes,** such as the **Moro reflex,** develop during gestation and are **present at birth.** They usually disappear between 3 and 6 months of age. Each primitive reflex requires a specific sensory stimulus to generate the stereotypical motor response**. Infants with central nervous system (CNS) injuries show stronger and more sustained primitive reflexes** (i.e., they may persist and not disappear as expected).
         2. **Postural reactions,** such as the **parachute reaction,** are **not present at birth (i.e., they are acquired).** These reactions, which help facilitate the orientation of the body in space, require a complex interplay of cerebral and cerebellar cortical adjustments to proprioceptive, visual, and vestibular input. **Infants with CNS damage may have delayed development of postural reactions.**
      b. **Fine motor skills** involve the use of the small muscles of the hands. An infant's fine motor skills progress from control over proximal muscles to control over distal muscles. **Fine motor milestones** are listed in Table 2-3.
         1. During the first year of life, as balance in sitting improves, the hands become more available for the manipulation of objects. As control over distal muscles improves, reaching and manipulative skills are enhanced.
         2. During the second year of life, the infant learns to use objects as tools (e.g., building blocks).
      c. **Red flags in motor development**
         1. **Persistent hand fisting beyond 3 months of age is often the earliest sign of neuromotor problems.**
         2. **Lack of steady head control beyond 2 months.**
         3. **Early rolling over, early pulling to a stand instead of sitting, and persistent toe walking may all indicate spasticity.**
         4. **Spontaneous postures, such as scissoring** in a child with spasticity or a frog-leg position in a hypotonic infant, are important visual clues to motor abnormalities.
         5. **Early hand dominance (before 18 months of age)** may be a sign of weakness of the opposite upper extremity associated with a hemiparesis. Hand preference generally develops between 4 and 5 years of age.
         6. **Any asymmetries to movement**
      d. **Differential diagnosis of motor delay** includes CNS injury, spinal cord dysfunction, peripheral nerve pathology, motor end plate dysfunction, muscular disorders, metabolic disorders, and neurodegenerative conditions.
   2. **Language skills**
      a. **General principles**
         1. **Delays in language development are more common than delays in other domains.**
         2. **Receptive language is always more advanced than expressive language** (i.e., a child can usually understand 10 times as many words as he or she can speak).

3. **Language and speech are not synonymous. Language** refers to the ability to communicate with symbols (i.e., in addition to speech, this includes sign language, gestures, writing, and "body language"). **Speech** is the vocal expression of language.
4. **A window of opportunity for optimal language acquisition occurs during the first 2 years of life.**
5. **Basic speech and language milestones are listed in Table 2-4.**

b. **Periods of speech development**
1. **Prespeech period (0–10 months of age):** Expressive language consists of musical-like vowel sounds (**cooing**) and then adding consonant sounds (**babbling**). Receptive language is characterized by an increasing ability to localize sounds.
2. **Naming period (10–18 months of age)** is characterized by the infant's understanding that people have names and objects have labels.
3. **Word combination period (18–24 months of age):** Early word combinations are "telegraphic" (e.g., without prepositions, pronouns, and articles). Typically, children begin to combine words 6–8 months after they say their first word.

c. **Differential diagnosis of speech or language delay**
1. **Global developmental delay**
2. **Hearing impairment**
3. **Environmental deprivation**
4. **Autism spectrum disorders**
5. **Intellectual disability**

3. **Cognitive development** involves skills in thinking, memory, learning, and problem-solving.

a. **General principles**
1. **Intellectual development depends on attention, information processing, and memory.**
2. **Infant intelligence** can be estimated by evaluating problem-solving and language milestones. **Language is the single best indicator of intellectual potential.** Gross motor skills correlate poorly with cognitive potential.
3. **In the school-age child, standardized intelligence tests measure both verbal skills and performance (nonverbal) skills. Significant discrepancies between verbal and nonverbal abilities suggest possible learning disabilities.**

b. **Stages in cognitive development**
1. The **sensorimotor period** (birth to 2 years of age) is a time during which the infant explores the environment through **physical manipulation of objects.** At first, the infant brings objects to the mouth for oral exploration. As peripheral motor skills improve, the infant's ability for precise manual–visual manipulation improves, leading to true inspection of objects. **The infant therefore progresses from "learning to manipulate" to "manipulating to learn."**
2. The **stage of functional play begins at about 1 year of age when the child recognizes objects and associates them with their function** (e.g., a 15-month-old puts a toy telephone to their ear and vocalizes).
3. The **stage of imaginative play begins when the child is able to use symbols** (24–30 months of age; e.g., a young child uses blocks to build forts, or uses sticks as eating utensils or trains).

4. **Concrete thinking** (i.e., interpreting things literally) evolves during the preschool and early elementary school years.
5. **Abstract thinking** (i.e., manipulating concepts and contingencies) evolves during the adolescent years.

c. **Cognitive concepts that evolve over time**
1. **Object permanence,** developing at about **9 months,** is the concept that people and objects continue to exist even when an infant cannot see them. As a result of this ability to maintain an image of a person, **separation anxiety (common at 6–18 months of age)** develops when a loved one leaves the room.
2. **Cause and effect** is understanding which actions cause certain results (e.g., learning that dropping toys over the high chair tray makes them fall to the floor). Infants typically explore this concept **at 9–15 months of age.**
3. **Magical thinking** is a normal state of mind during the **preschool toddler years** when a child assumes that inanimate objects are alive and have feelings.

d. **Red flags in cognitive development.** Language development estimates verbal intelligence, whereas problem-solving skills estimate nonverbal intelligence.
1. If skills are delayed significantly in both language and problem-solving domains, **intellectual disability** should be considered.
2. If only language skills are delayed, a **hearing impairment or a communication disorder** should be considered.
3. If only problem-solving skills are delayed, **visual or fine motor problems** that interfere with manipulative tasks may be present.
4. If there is a significant discrepancy between language and problem-solving skills, the child is at high risk for a **learning disability.**

4. **Social–emotional skills** are the ability to interact and empathize with other people. Development of social skills depends on cultural and environmental factors. Several important milestones develop in the first 3 years of life.

a. **Attachment.** Bonding with a primary caregiver begins at birth. Developing empathy is critical during the first 3 years of life.

b. **Shared (joint) attention.** Emerges between 8 and 10 months of age when the infant follows the caregiver's gaze. By 14 months of age, children begin pointing to request something, or show something spontaneously to a caregiver or social partner, to share awareness of an object or event. By 18 months of age, most children can point at, bring or share something with another person to indicate interest.

c. **A sense of self and independence.** The process of separation and individuation begins at about 15 months of age.

d. **Social play.** Toddlers exhibit parallel play during the first 2 years of life. They learn to play together, share, and cooperate at about 3 years of age. Fantasy and more complex types of interactive play emerge by 5 years of age.

e. Red flags in social–emotional development
1. Lack of smiling or joyful expressions at 6 months of age
2. Rarely responding to name when called at 12 months of age
3. Not demonstrating the ability to initiate or understand joint attention by 18 months of age
4. No emergence of pretend play by 3 years of age

Table 2-1
Gross Motor Milestones*

Age	Milestone

Birth	Turns the head side to side
2 months	Lifts the head when lying prone
	Head lag when pulled from the supine position
4 months	Rolls over
	No head lag when pulled from the supine position
	Pushes the chest up with the arms when lying prone
6 months	Sits alone
	Leads with the head when pulled from the supine position
8–10 months	Crawls
9 months	Pulls to stand
	Cruises
12 months	Walks

*Normal infants show significant variation in the attainment of these milestones.

Table 2-2

Primitive Reflexes and Postural Reactions

Description of Reflex/Reaction	Appears	Disappears
Primitive Reflexes		
Moro reflex: Symmetric abduction and extension of arms with trunk extension, followed by adduction of upper extremities	Birth	4 months of age
Hand grasp: Reflex grasp of any object placed in the palm	Birth	1–3 months of age
Atonic neck reflex: If the head is turned to one side, arms and legs extend on the same side and flex on the opposite side ("fencer position")	2–4 weeks of age	6 months of age
Rooting reflex: Turning of the head toward the same side as stimulus when a corner of the infant's mouth is stimulated	Birth	6 months of age
Postural Reactions		
Head righting: The ability to keep the head vertical despite the body being tilted	4–6 months of age	Persists
Parachute: Outstretched arms and legs when the body is abruptly moved head first in a downward direction	8–9 months of age	Persists

Table 2-3

Fine Motor Milestones*

Age	Milestone
Birth	Keeps hands tightly fisted
3–4 months	Brings hands together to midline and then to the mouth
4–5 months	Reaches for objects
6–7 months	Rakes objects with the whole hand. Transfers the object from hand to hand
9 months	Uses immature pincer (the ability to hold small objects between the thumb and index finger)
12 months	Uses mature pincer (the ability to hold small objects between the thumb and tip of the index finger)

*Normal infants show significant variation in the attainment of these milestones.

Table 2-4

Basic Language Milestones*

Age	Milestone
Birth	Attunes to human voice
	Develops differential recognition of parents' voices
2–3 months	Cooing (runs of vowels), musical sounds (e.g., *ooh-ooh, aah-aah*)
6 months	Babbling (mixing vowels and consonants together) [e.g., *ba-ba-ba, da-da-da*]
9–12 months	Jargoning (e.g., babbling with mixed consonants, inflection, and cadence)
	Begins using *mama, dada* (nonspecific)
12 months	1–3 words, *mama and dada* (specific)
18 months	4–20 words
2 years	Over 50 words
	Two-word telegraphic sentences (e.g., *mommy come*)
	25–50% of child's speech should be intelligible
3 years	Three-word sentences
	More than 75% of the child's speech should be intelligible

*Normal infants show significant variation in the attainment of these milestones.

II. Disorders of Development

A. **Motor deficits**
   1. **Cerebral palsy**
      a. **Definition. Cerebral palsy** is a diverse group of **static (i.e., nonprogressive) encephalopathies** caused by injury to the developing brain in which **motor function is primarily affected. Intelligence may be normal, but injuries to the brain that cause cerebral palsy often lead to other neurologic effects, including seizures, cognitive deficits, intellectual disability, learning disabilities, sensory loss, and visual and auditory deficits.**
      b. **Epidemiology and etiology. Risk factors** for cerebral palsy are listed in **Table 2-5**. The **timing of the injury** may be prenatal or perinatal, or it may occur during the first few years of life. **The incidence of cerebral palsy in the world is 2 in 1000 children. Low birth weight and preterm birth are the biggest risk factors.** Ten to fifteen percent of surviving infants with birth weight < 1500 g have cerebral palsy.
      c. **Diagnosis.** Diagnosis is based on **repeated neurodevelopmental examinations** showing increasing tone or spasticity, hypotonia, asymmetric reflexes or movement disorder, persistence of primitive reflexes, or emergence of postural responses.
      d. **Classification of cerebral palsy**
         1. **Spastic cerebral palsy.** Affected patients have increased tone. This type of cerebral palsy may be subclassified into three groups.
            a. **Spastic diplegia** involves the lower extremities more than the upper extremities or face.
            b. **Spastic hemiplegia** is characterized by unilateral spastic motor weakness.
            c. **Spastic quadriplegia** is characterized by motor involvement of the head, neck, and all four limbs.
         2. **Extrapyramidal cerebral palsy** (commonly referred to as **athetoid cerebral palsy**). These patients have problems modulating the control of the face, trunk, and extremities, often writhing. Significant oral motor involvement often occurs.
      e. **Management of cerebral palsy. The primary goal is to optimize functionality of adaptive skills.** This includes mobility, self-care, communication, educational attainment and social participation. Treatment programs should be individualized and are typically interdisciplinary (e.g., physical therapy, special education, orthopedics, and neurology).
   2. Other causes of motor deficits include **metabolic abnormalities** (see Chapter 5, section V), **chromosomal abnormalities** (see Chapter 5, section IV), **motor neuron diseases, degenerative diseases, spinal cord injury, congenital myopathies, leukodystrophies, and CNS structural defects.**

B. **Cognitive deficits include intellectual disability and learning disabilities.**
   1. **Intellectual disability** is defined as **significant limitations in both intellectual functioning *and* adaptive behavior** (e.g., self-care, social skills, work, and leisure). It is **manifested before 18 years of age, typically in early childhood.**
      a. **Etiology. Causes** are listed in **Table 2-6**.
      b. **Classification and diagnosis.** Using an appropriate psychometric measure of **intelligence (intelligence quotient [IQ]) and measures of adaptive behavior,** the degree of intellectual disability can be classified as
         1. **Mild** (IQ = 50–70)

2. **Moderate** (IQ = 35–50)
3. **Severe** (IQ = 25–35)
4. **Profound** (IQ < 25)

c. **Management**
1. Early intervention programs promote optimal development.
2. Behavior therapy is used to teach activities of daily living and manage behavior problems.
3. Special education to optimize learning of academic and self-help skills
4. Community resources and parent support groups are helpful.
5. Medication is used to treat comorbid behavioral and emotional disorders.
6. There is a trend away from institutionalization of individuals with intellectual disability. Many with mild to moderate intellectual disability live in group homes and work in sheltered or supported environments.

2. **Learning disabilities** are defined as a heterogeneous group of disorders manifested by a significant discrepancy between a child's academic achievement and the level expected on the basis of age and intelligence.
a. **Etiology.** Causes include **CNS injuries** (e.g., prematurity, closed head injury, lead poisoning, fetal alcohol syndrome), **genetic disorders** (e.g., fragile X syndrome), and **metabolic disorders** (e.g., galactosemia). The **most common cause is idiopathic.**
b. **Types of learning disabilities** include **deficiencies in specific academic subjects** (e.g., developmental disorders of reading, mathematics, or written expression). **Dyslexia** is the most common specific learning disability, accounting for ~80% of learning disabilities, presenting initially as early delays in language development.
c. **Management. A psychoeducational evaluation (typically includes IQ and academic achievement testing) is needed to establish a diagnosis.** Classroom accommodations, special education, individualized instruction, and bypass strategies (e.g., presenting information verbally for the child with a specific reading disorder) may be used to help compensate for the learning disability.

C. **Autism spectrum disorder.** This **developmental disability is characterized by persistent deficits in social communication and repetitive/restrictive patterns of behavior, interests, or activities.**

1. **Epidemiology**
a. Incidence is **1 in 68.** Incidence has increased as incidence was 1 in 150 in 2000.
b. Increased incidence is related in a large part to **early screening/detection and broader diagnostic criteria.**
c. Autism is **more common in boys** (**4:1 ratio**).

2. **Etiology**
a. Multifactorial. **Genetics explains 10–20%** (many genes implicated). The extent to which environmental, epigenetic, and medical risk factors contribute has yet to be determined.
b. Strong evidence has shown that **vaccinations do not cause autism.**

3. **Clinical features**
a. **Qualitative impairment in social communication (all three of the following are present on evaluation or by history)**
1. Deficits in social–emotional reciprocity (back and forth interactions)
2. Deficits in nonverbal communicative behaviors used for social interaction
3. Deficits in developing, maintaining, and understanding relationships

b. **Repetitive, restricted, and stereotyped patterns of behavior, activities, and interests (two of the following criteria present on evaluation or by history)**

1. Stereotyped or repetitive motor movements, use of objects, or speech
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior
    a. Highly restricted, fixated interests with abnormal intensity or focus
    b. Hyper- or hyporeactivity to sensory input; unusual interest in sensory aspects of the environment

c. **Symptoms are present in early childhood.**
d. **Symptoms cause significant functional impairment** (e.g., learning, adaptive behavior, peer/family relationships).
e. **Spectrum is wide** (high functioning vs. low functioning) with many individual differences in presentation.

4. **Associated conditions** may include intellectual disability, learning disabilities, epilepsy, tic disorders, sleep disorders, feeding disorders, attention deficit/hyperactivity disorder (ADHD), other psychiatric conditions, and genetic syndromes (e.g., Fragile X).
5. **Management.** There are many interventions to treat "core" symptoms of autism, but none are curative.
    a. Primary treatments include behavioral interventions (ABA [applied behavioral analysis]), special education, speech–language therapy, occupational therapy and social skills training. ABA is a set of principles used to understand and modify behavior in the context of the child's environment. **ABA has the best evidence in treating the core symptoms of autism in young children.**
    b. Medication may be needed to manage comorbid psychiatric conditions or maladaptive behaviors unresponsive to other approaches.

D. **ADHD.** *This disorder is characterized by poor selective attention, difficulty focusing, distractibility, hyperactivity, impulsivity, disinhibition, and social immaturity.*
1. **Epidemiology and etiology**
    a. **Occurs in about 5% of the pediatric population**
    b. ADHD is **more common in boys (2:1 ratio).**
    c. The **cause of ADHD is unknown.**
        1. **Genetic factors play a large role.** Up to 30–50% of affected children have a first-degree relative with ADHD.
        2. Abnormalities in neurotransmitter function, especially dopamine and norepinephrine, are associated with symptoms.
        3. Several risk factors have been implicated (e.g., preterm birth, fetal alcohol spectrum disorder).
2. **Differential diagnosis** (Table 2-7)
3. **Clinical features.** Specific criteria must be present, including the following:
    a. Onset of symptoms **before 12 years** of age
    b. Symptoms in **more than one setting** (e.g., school and home)
    c. **Impairment in functioning** (e.g., academic performance, personal relationships)
    d. Symptoms of **inattention,** including not being able to focus during classroom instruction, difficulty with organization, and forgetfulness
    e. Symptoms of **hyperactivity–impulsivity,** which may include fidgeting, acting as if driven by a motor, excessive talking, blurting out answers before a question is completed, and difficulty remaining seated in the classroom
4. Potential consequences of ADHD on a child
    a. **Difficulty conforming to a routine**
    b. **Social adjustment problems**
    c. **Damage to self-esteem**
    d. **Impaired relationships with parents and peers**

e. **Difficulty learning**
f. **Comorbidities** (two-thirds of patients have a comorbidity) include anxiety, tic disorder, oppositional-defiant disorder, and obsessive–compulsive disorder

5. **Assessment and diagnosis of ADHD**
   a. **Assessment** includes parent and teacher behavior rating scales, psychoeducational testing, direct observation, a complete history and physical examination, and hearing and vision testing.
   b. Most valid, reliable assessments use **several sources** (teachers, parents, and counselors) and combine several methods. Direct and specific observations using validated questionnaires are most useful.
   c. **A key focus** of assessments should be to **identify the child's strengths and coping strategies.**
6. **Management.** Therapy is multifaceted and includes the following:
   a. **Demystification.** Explaining ADHD to the child and family, correcting myths and misconceptions, is critical.
   b. **Classroom modifications.** Preferential seating and elimination of distractions may be useful.
   c. **Educational assistance.** Help should be tailored to the individual needs of the student. Strategies include placement in small groups or one-on-one teaching, help with organizational skills, and strategies to bypass weak areas (e.g., keyboarding if handwriting is a problem).
   d. **Behavior management/therapy is the first-line treatment for preschool children.** This involves parent and teacher training and includes consistent rewards and consequences.
7. **Medications**
   a. **Stimulants** are the **first-line pharmacologic treatment for grade school children and adolescents.** These drugs may **improve attention, impulsivity, and hyperactivity.**
      1. **Mechanism of action. Stimulants appear to enhance catecholamine transmission** in the CNS. Higher levels of dopamine and norepinephrine improve ADHD symptoms.
      2. **Dosage. The dosage needed to control symptoms varies among patients and is not weight based.**
      3. **Adverse drug reactions (Table 2-8). Medication effects should be monitored** using side effect diaries and behavior rating scales.
      4. **Stimulant options** include **methylphenidate** and **dexamphetamine derivatives. More than 80% of children with ADHD will clinically improve with either a methylphenidate or dexamphetamine derivative.**
   b. **Nonstimulant medications** may be considered as **second-line** therapy. These drugs most commonly include atomoxetine and alpha-2 agonists (e.g., clonidine and guanfacine). Alpha-2 agonists may be especially useful at bedtime to counter stimulant effects or in combination with a stimulant for patients who have comorbid aggression or tic disorders. Atomoxetine may be useful in patients with comorbid anxiety.

Table 2-5
Risk Factors for Cerebral Palsy

Risk Category	Specific Risk Factor
Maternal	Multiple gestation
	Preterm labor

Prenatal	Intrauterine growth retardation
	Congenital malformations
	Congenital infections (e.g., TORCH infections)
Perinatal	Prolonged, precipitous, or traumatic delivery
	Apgar score < 3 at 15 minutes
	Prematurity (<37 weeks) or postdates (>42 weeks) birth
Postnatal factors	Hypoxic–ischemic encephalopathy
	Intraventricular hemorrhage
	Trauma
	Kernicterus

TORCH = *t*oxoplasmosis, *o*ther infections (syphilis), *r*ubella, *c*ytomegalovirus, *h*erpes simplex.

Table 2-6

Causes of Intellectual Disability

Etiologic Category	Specific Etiologic Factor
Idiopathic	
Genetic causes	Chromosome abnormalities (e.g., Down syndrome, Fragile X syndrome) Inborn errors of metabolism (e.g., Hurler syndrome) Single gene abnormalities (e.g., tuberous sclerosis)
Prenatal and perinatal problems	Fetal malnutrition Placental insufficiency Maternal drug and alcohol use Brain malformations (e.g., hydrocephalus) Perinatal hypoxia or asphyxia Infection (e.g., herpes simplex, rubella, cytomegalovirus, toxoplasmosis)
Environmental problems	Psychosocial deprivation Parental mental illness
Postnatal acquired insults	Infection (e.g., meningitis, encephalitis) Head trauma Nonfatal drowning

Table 2-7

Differential Diagnosis of Attention Deficit/Hyperactivity Disorder

Hearing or vision deficits
Sleep disorders, including obstructive sleep apnea
Autism
Thyroid disease
Anemia
Toxins or heavy metal exposure (e.g., lead poisoning)
Anxiety
Depression
Bipolar disorder
Intellectual disability
Specific learning disabilities
Medication side effects (e.g., albuterol, steroids, anticonvulsants, decongestants, antihistamines)
Family dysfunction
Normal child, but parents have unreasonable expectations for age or developmental stage

Table 2-8

Adverse Drug Reactions of Stimulants

Anorexia
Weight loss is the most common adverse drug reaction
Insomnia
More common with long-acting stimulants

Gastrointestinal
Nausea and abdominal pain
Headache
Irritability
Common as the stimulant is wearing off
Cardiovascular
Palpitations and hypertension
Effect on stature
Methylphenidate may decrease growth velocity, but ultimately stature is not affected significantly
Tics
Tourette syndrome and attention deficit/hyperactivity disorder may be genetically related
Transient tics occur in almost 10% of children treated with stimulants

III. Specific Sensory Impairments

A. **Hearing impairment**

1. **Epidemiology. This affects 2–4 per 1000 live births in developed countries and upward of 6 per 1000 in developing countries.** More than half of these infants are normal newborns who have no obvious evidence of suspected hearing impairment.
2. **Early identification** of the hearing-impaired child is vital because language and communication **outcomes** are demonstrably better if intervention occurs before 6 months of age. **Sequelae of late identification include delayed speech and language skills and academic and behavior problems.**
3. **Etiology**
    a. **Type of hearing loss relates to the anatomical section of the ear in which the abnormality occurs.**
        1. **Conductive hearing loss: external and/or middle ear**
        2. **Sensorineural hearing loss: inner ear of the cochlea, nerve transmission of the vestibulocochlear nerve**
        3. **Central hearing loss: auditory pathways from the brainstem to cerebral cortex**
        4. **Mixed: a combination of the above**
    b. **Genetic factors** account for at least **50%** of sensorineural hearing loss; 80% of genetic transmission occurs by **autosomal recessive** inheritance of the **connexin gene.**
    c. **About 20% of childhood hearing loss is caused by perinatal, prenatal, or postnatal factors (e.g., congenital infections, prematurity, bacterial meningitis, middle ear anomalies).**
4. **Prognostic factors. The variables that influence the impact** of hearing loss on function and development include
    a. **Degree of loss**
    b. **Etiology.** Children with acquired deafness are at higher risk for other neurologic impairment.
    c. **Family atmosphere.** Family willingness and ability to use sign language have a major impact on the child.
    d. **Age at onset** of acquired deafness. Children who become deaf before 2 years of age are at a disadvantage compared with those who are able to incorporate language structure before deafness.
    e. **Timing of amplification and educational interventions.** The earlier this occurs, the better.
    f. **Cochlear implants.** Although these may lead to dramatic improvements in hearing, their use is controversial in some deaf communities.
5. **Medical evaluation for hearing loss**
    a. **Complete history**, including history of perinatal infections and antibiotic exposure
    b. **Complete physical examination**, focused on a thorough ear examination and identifying findings suggestive of a genetic syndrome (e.g., cleft lip/palate, ear pits)
    c. **Genetics evaluation** and chromosome studies if there are suspicious clinical findings or family history
    d. **Creatinine level,** because of the association between kidney disease and ear abnormalities (Alport syndrome; see Chapter 11, section VIII.B)
    e. **Viral serologies** if clinically indicated, looking for toxoplasmosis, rubella, cytomegalovirus, herpes, and other viruses that can cause deafness (i.e., TORCH

infections)

f. Consider magnetic resonance imaging (MRI) of the inner ear if etiology is undetermined.

6. **Hearing screening recommendations** are given in Chapter 1, section IV.D.

B. **Visual impairment**

1. **Incidence** is 1.5 per 1000 children (almost 90% are from developing countries)
2. **Leading causes** of blindness in children:
   a. ***Chlamydia trachomatis* infection** is common in developing nations and is the **primary cause of blindness worldwide.**
   b. **Retinopathy of prematurity** (see Chapter 18, section VII)
   c. **Congenital cataracts** (see Chapter 18, section VIII.A)
3. **Effects of blindness on development** include delayed locomotion, decreased fine motor skills, and difficulties with attachment.
4. **Adaptive skills**
   a. **Developing auditory perception skills**
   b. **Using haptic perception** (e.g., feeling someone's face to form a mental image of them by combining kinesthetic spatial feedback and input from tactile sensation)
5. **Vision screening** is described in Chapter 18, section I.

IV. Common Behavioral Concerns

A. **Colic.** *Colic is significant because it has the potential to disrupt attachment* between infant and parents, and it can be a **source of family stress.**
   1. **Definition. Colic is crying that lasts >3 hours/day and occurs >3 days/week.** (Normal crying usually lasts up to 2 hours/day at 2 weeks of age and increases to 3 hours/day at 3 months of age.)
   2. **Epidemiology.** Colic occurs in approximately **10% of newborns.**
   3. **Etiology. Colic has an unknown basis and may have many causes.**
   4. **Characteristic features**
      a. **Occurs in healthy, well-fed infants**
      b. **Begins at 2–4 weeks of age and resolves by 3–4 months of age**
      c. **Involves periods of irritability,** which typically begin in the late afternoon or early evening
   5. **Differential diagnosis.** Sources of pain and discomfort that may be confused with colic include intestinal gas, milk protein intolerance, gastroesophageal reflux disease, food allergy, corneal abrasion, otitis media, testicular torsion, inguinal hernia, and digital ligature (i.e., hair wrapped around finger or toe).
   6. **Management**
      a. **Treat any identified conditions.**
      b. **Reassure parents** that their infant is healthy and that the colic is not the parents' fault.
      c. **Recommend comfort measures,** which may include decreased sensory stimulation (e.g., placing the infant in front of a blank wall), increased sensory stimulation by movement or vibration (e.g., automobile rides, rocking, stroller rides), or positioning (e.g., swaddling or placing infant on his or her side or stomach while awake).

B. **Enuresis**
   1. **Definition.** Enuresis is urinary incontinence beyond the age when the child is developmentally capable of continence (>4 years of age for daytime continence and >5 years of age for nocturnal continence).
   2. **Classification** is based on the timing and history.
      a. **Timing: Continuous incontinence** refers to continuous wetting and is usually associated with congenital malformations of the urinary tract system, in contrast to **intermittent incontinence** that may be nocturnal or daytime only.
      b. **History: Primary incontinence** describes a patient who has never been consistently dry. In **secondary incontinence** a patient has a history of at least 6 months of prior consecutive dryness.
   3. **Epidemiology**
      a. **Incidence is based on age.** Bed-wetting occurs at least monthly in
         1. 30% of 4 year olds
         2. 15–20% of 5 year olds
         3. 10% of 6 year olds
         4. 3% of 12 year olds
      b. Fifteen to twenty percent of those with nocturnal enuresis also have diurnal or daytime incontinence.
   4. **Etiology.** The causes of enuresis are typically unknown but may include the following:
      a. **Genetics.** There is about a 45% chance that a child will have enuresis if one parent had enuresis, and about a 75% chance if both parents had it. Several genes have

been identified.

b. **Psychosocial. Secondary enuresis** is often associated with stressful situations, such as the birth of a sibling, death of a family member, or the separation of parents.
c. **Chaotic social situation** at home may contribute to poor voiding habits and daytime incontinence.
d. **Sleep–arousal mechanisms** play an elusive role. Although not proven, parents frequently report that children with nocturnal incontinence have deeper sleep and are more difficult to arouse than dry siblings. **Obstructive sleep apnea** is a risk factor for nocturnal incontinence.
e. **Urine volume.** Some patients may produce **large volumes of dilute urine,** which may be caused by lack of normal diurnal variation in **vasopressin release.**
f. **Bladder capacity.** Some children may have a small bladder capacity.
g. **Organic causes** of secondary enuresis include urinary tract infections, child abuse, and diabetes mellitus.
h. **Constipation is a comorbid or etiologic factor** in some patients. Hard stool can impinge on the bladder. **Symptoms of encopresis** may be present.

5. **Evaluation**
   a. **History** should include questions about family history, pattern of enuresis, associated symptoms, time of onset, and parental interventions or attempts at therapy.
   b. **Physical examination** should be complete and include an evaluation of the abdomen, genitals, perineal sensation, anal wink reflex, and lower spine. A neurologic examination should also be performed.
   c. **Laboratory evaluation**
      1. **Urinalysis and urine culture**
      2. **Additional laboratory or imaging studies** should be tailored to the history and physical examination. Imaging of the kidney and bladder, MRI of the spine, or other studies may be appropriate.
6. **Management of uncomplicated nocturnal enuresis**
   a. **Education.** It may help to uncover misconceptions, **remove blame from the child,** and explain anatomy and physiology.
   b. **Conditioning alarms.** An alarm sounds every time urination occurs, and the child learns to respond in anticipation. This technique is successful in two-thirds of cases, but it **requires patient motivation and parental support.** This therapy must be used for a minimum of 3–5 months.
   c. **Pharmacotherapy. Medications, if used alone, result in frequent relapses.** Best efficacy uses a combination of alarms, medications, and behavioral modification as outlined below.
      1. **Desmopressin acetate (DDAVP),** which decreases urine volume, is used because the child with enuresis may have an abnormal circadian rhythm for release of arginine vasopressin. Although a child may achieve complete dryness with DDAVP, relapse after termination of medication is common. Hyponatremia is a possible side effect of DDAVP.
      2. **Tricyclic antidepressants** have limited efficacy to decrease the frequency of nighttime wetting. **Imipramine is the most widely used of these agents.** Patients often relapse after medication is discontinued, and there is a **danger of fatal cardiac dysrhythmias with an overdose.**
   d. **Other management options. Behavioral modification** (e.g., star charts, praise for dry nights, limited fluids before bed, voiding before bed), hypnotherapy, and treating coexisting constipation may be useful.

7. **Management of diurnal enuresis.** Effective interventions may include bladder stretching exercises (if small bladder capacity is suggested), scheduling timed voiding every 90–120 minutes, and treatment of coexisting constipation if present.

C. **Encopresis** (see Chapter 10, section VII.A.2)

D. **Sleep problems**
   1. **Epidemiology.** It is estimated that more than half of infants experience sleep problems as perceived by parents.
   2. **Normal sleep patterns**
      a. **Day–night reversals are common** in the first weeks of life. The normal pattern is random sleep for 4 weeks, after which clustering of sleep time occurs.
      b. **Sleeping through the night** is defined as sleeping more than 5 hours after midnight for a 4-week period. Fifty percent of infants sleep through the night at 3 months of age.
   3. **Abnormal sleep patterns**
      a. **Trained night waking** occurs between 4 and 8 months of age when the infant **does not resettle without parental intervention** (e.g., feedings, rocking, attention) during normal night stirrings and awakenings. **Management** includes establishing routines and placing the infant in bed while drowsy but awake.
      b. **Trained night feeding** occurs when the infant continues to wake to eat because the parents keep responding to the wakening with a feeding. **Management** includes lengthening intervals of daytime feeding and teaching parents not to respond with a feeding every time the infant stirs.
   4. **Common sleep problems**
      a. **Nightmares** are common after 3 years of age, although they may occur as early as 6 months of age. These frightening dreams tend to have themes of threats to security, separation, self-esteem, or survival. They occur during **rapid eye movement (REM) sleep.**
         1. **History. The child is able to give a detailed recall** of extended and frightening dreams. The child rapidly becomes alert and oriented after awakening.
         2. **Management.** Reassurance by the parents and comforting measures are helpful. It is important to address the child's needs for security and to promote regular sleep patterns and good sleep habits. Any inciting causes (e.g., frightening movies) should be identified and eliminated. Nightmares are usually transient and not very disruptive.
      b. **Night terrors** are common at 3–5 years of age but have a pattern distinct from ordinary nightmares. Night terrors occur 90–120 minutes after sleep onset during **non-REM stage 4 sleep.**
         1. **History.** Parents describe a child who suddenly arouses screaming and thrashing with signs of autonomic arousal such as tachypnea, tachycardia, and diaphoresis. The child does not respond to visual or verbal cues, and parents report the child stares "glassy-eyed" without seeing. **The child does not remember the incident the next day.**
         2. **Management.** Reassuring parents and telling them that the episodes usually terminate spontaneously and will resolve over time is helpful.

E. **Selective eating**
   1. **Epidemiology. Selective eating (i.e., picky eating) is common in preschoolers** with approximately 50% affected. Parents may report problems such as food refusal, food gorging, and food jags (when a child will only eat a single food item or a very small group of food items, meal after meal, and a perception that the toddler does not eat

enough).

2. **Characteristics**
    a. Appetite normally decreases after 1 year of age.
    b. **Control is the major issue in toddler feeding problems.** Autonomy is more important than hunger to children at this stage.
    c. Children also reject food because they **dislike the flavor, texture, or appearance.**
3. **Management.** Successful management includes **avoiding power struggles,** offering food without comment, shared responsibility in what to eat, offering a variety of foods, making meals fun and enjoyable, and establishing a set meal schedule. Parents should be counseled to avoid bribes, pressuring, or forcing the child to eat. Feeding provides physical and social contact with caregivers and forms the foundation for healthy parent–child relationships.
4. **Associated conditions. Severe selective eating** is associated with several conditions, including autism spectrum disorder, anxiety disorders, failure to thrive, and preterm birth.

F. **Anxiety**

1. **Developmentally appropriate anxiety**
    a. **Fears and worries are part of normal child development.** Developmentally appropriate anxiety includes the emergence of stranger anxiety during the first 1–2 years of life, fears about monsters and the dark during the preschool years, fears about injury and natural events during school-age years, and academic performance and social competence fears during adolescence.
    b. **Management typically includes parent and child reassurance, guidance, and education.**
2. **Anxiety disorders. Anxiety disorders** are characterized by **excessive and developmentally inappropriate worry that significantly impairs a child's functioning.**
    a. **Epidemiology.** Anxiety disorders are common among children and adolescents. They are typically **more frequent in girls than in boys** (2–3:1 ratio). **More than 70% of adults diagnosed with an anxiety disorder had symptoms in childhood. Childhood anxiety disorders are highly predictive of major depression during adulthood.**
    b. **Symptoms.** Children frequently present with **somatic complaints** (stomach ache, headache), anger, irritability, and crying. Anxiety interferes with the child's normal functioning in multiple settings, and affects peer and family relationships.
    c. **Types. Triggers** are wide ranging and can include excessive worry in a number of areas (**generalized anxiety disorder**), excessive and developmentally inappropriate distress when the child is separated from home or major attachment figures (**separation anxiety disorder**), feelings of fear or discomfort in social and performance situations (**social phobia**), and the presence of obsessions or compulsions that cause marked distress and are time-consuming (**obsessive compulsive disorder**).
    d. **Selective mutism** is an anxiety-related condition in which the child is **unable to speak in certain social settings** where speaking is expected (e.g., school, daycare), **despite speaking in other typically more familiar settings** (e.g., home). Children are typically extremely shy. Onset of symptoms usually occurs before 5 years of age and lasts for greater than 1 month. Between 10 and 30% of children have a history of speech–language delay. **Selective mutism is highly correlated with social phobia.**
    e. **Management.** Cognitive-behavioral therapy (CBT) is typically the first-line treatment, as there is substantial evidence supporting its use in treating childhood

anxiety disorders. Medication with a selective serotonin reuptake inhibitor (e.g., fluoxetine) is used for patients with CBT-resistant anxiety, or for severely impairing and unremitting anxiety.

G. **Temper tantrums.** These are expressions of emotions (usually anger) that are beyond the child's ability to control.
   1. **Epidemiology.** Temper tantrums are **common** between **1 and 3 years of age.**
   2. **Etiology. Frustration, hunger, or fatigue** may cause tantrums. Children with poor fine motor skills or expressive language delays are likely to have more tantrums because of frustration. **Tantrums are not necessarily manipulative or willful and may be related to individual differences in temperament.**
   3. **Management**
      a. **Tantrums that demand something should be ignored.**
      b. **Children should be encouraged to verbalize their feelings** (learned by 3 years of age). This helps to **decrease tantrums.**
      c. **Developmentally appropriate behavior management** helps (see section IV.K).

H. **Breath-holding spells**
   1. **Definition.** Breath-holding spells are benign episodes in which children hold their breath long enough to cause parental concern. **The spells are involuntary in nature, harmless, and always stop by themselves.**
   2. **Epidemiology.** Breath-holding spells occur in 4% of young children, usually starting between 6 and 18 months of age and disappearing by 5 years of age. Equal male/female prevalence.
   3. **Types**
      a. **Cyanotic breath-holding spells** are most common and are usually precipitated by an event that makes the child frustrated or angry. The child cries and becomes cyanotic, and in some cases becomes apneic and unconscious, or may have a seizure.
      b. **Pallid breath-holding spells** are often provoked by an unexpected event that frightens the child, resulting in a hypervasovagal response, in which the child becomes pale and limp.
   4. **Management**
      a. **Reassure** the parents that the episodes will resolve without harm.
      b. **Counsel parents** not to undertake potentially harmful resuscitation efforts.
      c. **Iron** supplementation has been reported to help some patients, but the mechanism of benefit is not clear.
      d. If the spells are precipitated by exercise or excitement rather than by frustration or fright, an **electrocardiogram** may be indicated to rule out a dysrhythmia (e.g., prolonged QT syndrome or supraventricular tachycardia).

I. **Sibling rivalry**
   1. **Manifestations** include bids for attention, regressive symptoms (e.g., wanting a bottle or going back to diapers), and aggression toward a new sibling. **The arrival of a newborn** is especially stressful for children younger than 3 years of age. Jealousy is frequently demonstrated up to 5 years of age.
   2. **Management**
      a. **Before arrival of a newborn.** Methods for prevention include talking about the arrival of the new baby and praising the child for mature behavior. Mastery of new skills (e.g., toilet training) should not be demanded during this stressful time.
      b. **In older children.** Children should be encouraged to settle their own arguments without hitting, name calling, or property damage. Parents should try to keep out of arguments, teach children how to listen to one another, protect each child's

personal possessions, and praise children for good behavior.

J. **Toilet training**
   1. **Age normals. The age at which young children achieve urinary and bowel continence around the world is highly variable, ranging from as early as 18 months of age up to 3–4 years of age.** This variability is due to differences in cultural expectations, parenting practices, and training methods, as well as definitions of urinary/bowel continence. It is unlikely that physiologic differences explain such wide variation in the achievement of continence.
   2. **Prerequisites**
      a. The child must understand the meaning of words such as *wet, dry, pee, poop, clean, messy,* and *potty.*
      b. The child prefers being dry to being wet or soiled.
      c. The child recognizes the sensation of bladder fullness and the urge to defecate, is able to hold urine and stool, and has the communicative ability to inform a caregiver.
      d. The child has the motor skills and coordination to sit on the toilet seat.
   3. **Management. Stress encouragement, praise, and patience.** Avoid shaming or blaming the child.
      a. Parents should allow multiple practice tries with praise for cooperation. It may be necessary to give small rewards or use sticker charts, but social reinforcement is best.
      b. Parents should **avoid pressure or force,** which tends to make the child uncooperative. **Resistance to toilet training** symbolizes a **power struggle** between child and parents. This is a sign to take a break and resume when the child shows interest in toileting again.
      c. **Point out to parents that autonomy issues are important** in toilet training, which proceeds optimally when parents appreciate the child's need for mastery.

K. **Discipline issues**
   1. The basic premise of discipline is teaching the child limits. Parents must teach the child to respect the rights of others and control his or her behavior. Parents must provide external controls over the child's behavior, beginning at about 6 months of age. **Children should start developing internal controls (self-control) between 3 and 4 years of age.**
   2. **Discipline techniques** are **most effective** when they are **based on the developmental needs and stages of the child.**
      a. Before 6 months of age, **no discipline is indicated.**
      b. As the infant becomes more mobile, **distraction and redirection** can be used to ensure the child's safety.
      c. From 18 months to 3 years of age, **ignoring, time-out, and disapproval** (both verbal and nonverbal) may be effective.
      d. In preschool children, **logical consequences** (e.g., taking away a toy that is used to hurt another child) may be effective.
      e. After 5 years of age, **negotiation and restriction of privileges** are used.
   3. **Rules must be clear, concrete, and consistent.** Parents should state explicitly what the desired behaviors are and ignore unimportant misbehavior.
   4. **Guidelines for using punishment.** Apply consequences and make the punishment brief and immediate. Follow the consequence with love and trust. **Direct the punishment toward the behavior, not the person.**
   5. **Time-out is a highly effective** form of discipline when used appropriately and consistently, but it is **frequently used inappropriately and inconsistently by parents.**
      a. **Definition.** The caregiver interrupts misbehavior by isolating the child from social

interactions for a brief period of time.

b. **Purpose.** The child has time to think about the misbehavior and what acceptable behavior could be.
c. **Length. There are no steadfast guidelines for the duration of** time-outs, but the general rule of thumb is that they should last no longer than 5 minutes. The key is that the duration of time-outs should be established ahead of time to avoid ambiguity.
d. **Time-out is ineffective without time-in.** Time-in refers to brief, nonverbal affection or verbal praise when the child displays appropriate or acceptable behavior. The goal of time-in is to reinforce positive behaviors.

Review Test

1. The parents bring a 13-month-old child to the office for a routine health maintenance visit. The child has been well since the last health maintenance visit, and the parents have no concerns today. The parents report he is sleeping through the night in his own crib and has a balanced diet and normal elimination patterns. During your physical examination, you perform a screening developmental evaluation. Which of the following findings on your developmental assessment would be most likely to merit a referral for a more thorough developmental evaluation?
   A. The child cruises but is not walking independently.
   B. The child's only words are *mama, dada, dog,* and *ball.*
   C. The child is afraid of strangers.
   D. The child neither eats with a spoon nor drinks from a cup.
   E. The child appears to be left-handed.
2. You are seeing a 1-month-old male infant in your office for a routine health maintenance visit. He was born at 32 weeks' gestation and had Apgar scores of 3 at 1 minute and 8 at 5 minutes. His hospital course was unremarkable, and he has been feeding and growing well since going home. His mother is now concerned that he is at a higher risk for cerebral palsy because of his prematurity. It would be most appropriate to make which of the following comments?
   A. It is unlikely that the child has cerebral palsy because his growth and development so far are normal.
   B. If cerebral palsy does develop, it will cause loss of developmental milestones.
   C. The child is at very high risk for cerebral palsy because of his prematurity.
   D. Repeated examinations will be necessary to assess for cerebral palsy.
   E. Laboratory testing can determine whether the child has cerebral palsy.
3. At a routine health maintenance visit, the parents of a 1-year-old child would like to learn more about toilet training. Which of the following information is most appropriate to give the parents?
   A. It is important that toilet training begin now.
   B. Toileting is a skill to be learned just like any other and depends on the interests and readiness of the child.
   C. It is important that the parents establish control over toileting now or the pattern will be set for losing power struggles later.
   D. Toilet training should be finished as soon as possible for the good of caregivers and the environment.
   E. Whatever the parents and grandparents agree on is appropriate.
4. Parents in your practice are concerned about the increased incidence of autism that they have been reading about in the press. Which of the following histories would be most reassuring for parents worried that their child may be diagnosed with autism spectrum disorder?
   A. The parents report that their child does not enjoy playing with other children and prefers to play alone.
   B. The parents report that their child is clumsy.
   C. The parents describe that their child engages in repetitive lining up of objects.
   D. The parents report that their child has a fascination with letters and numbers.
   E. The parents report that their child has significant language delay.
5. The parents of a 7-year-old boy bring him to see you because of secondary enuresis. He achieved daytime dryness when he was 2.5 years of age and was dry at night by 3 years of age. Recently, he has developed dribbling incontinence, which embarrasses him at school. The parents do not report any recent psychosocial stress, but they are concerned that he trips often

when he walks quickly or runs. His physical examination is normal, except you cannot elicit an anal wink reflex. Urinalysis and urine culture are both normal. Which of the following would be the most appropriate next management step?

A. Neuroimaging studies of the brain and spine
B. Bladder stretching exercises
C. Trial of desmopressin (DDAVP)
D. Trial of imipramine
E. Psychological counseling

6. You are evaluating a toddler during a routine health maintenance visit, which includes a thorough developmental assessment. The parents report that their son is able to point to three to five body parts, uses approximately 60 words that his parents understand, and says two-word telegraphic phrases. 50% of his words are understandable. Assuming his language skills are normal for age, how old is this child?

A. 13 months
B. 15 months
C. 18 months
D. 24 months
E. 30 months

7. On screening in the newborn nursery, an infant has an abnormal hearing screen. His examination is otherwise normal. Which of the following etiologic factors most likely explains the hearing loss in this infant?

A. Prenatal factors, such as maternal substance abuse
B. Perinatal factors associated with a preterm or traumatic delivery
C. Postnatal infection, such as meningitis
D. An autosomal recessive genetic defect
E. An autosomal dominant genetic defect

8. The mother of a 9-year-old boy brings him to the pediatrician because her son is exhibiting hyperactivity and inattention in school. Before this year, the boy has performed well in school and has shown no signs of hyperactivity or inattention. His teacher reports that the boy is restless in the classroom and frequently leaves his seat. His mind seems to wander during the teacher's lectures. On questionnaires, the teacher confirms the inattention and hyperactivity. The boy shows no symptoms at home, and he does well at church school and at camp. Which of the following would be the most appropriate first step in managing this patient?

A. Explaining to the parents that he meets criteria for attention deficit/hyperactivity disorder and what that diagnosis means.
B. Looking for other causes of the hyperactivity and inattention in the differential diagnosis.
C. Beginning an empiric trial of stimulant medication to see whether his symptoms improve with pharmacologic intervention.
D. Working with the school to modify the boy's assignments and the classroom setting.
E. Referring to a counselor for self-esteem enhancement, social skills training, and behavior modification.

9. The parents of a 3.5-year-old boy are concerned that their son has been experiencing nightmares. On further questioning, you make the diagnosis of night terrors. Which of the following factors would most support your diagnosis of night terrors and not nightmares?

A. This child's events occur approximately 30 minutes after sleep onset.
B. This child's events are likely to decrease in frequency after age 3 years
C. The child responds to the parent's attempts to comfort him during the events.
D. The child becomes alert and oriented immediately after the event.
E. The child does not remember the event the next day.

10. A 2-month-old male infant is brought to your office with concerns about excessive crying.

Based on the history, you suspect colic. Which of the following findings on your evaluation best supports this diagnosis?

A. The crying spells usually occur in the morning hours, lasting 2 hours every day, 5 days every week.
B. The infant's weight has decreased and crossed two growth isobars since birth.
C. The parents have noticed an intermittent bulge in the infant's right inguinal region associated with crying spells lasting anywhere from 2 to 6 hours.
D. The infant has been growing at the 10th percentile consistently since birth, with 3–4 hours/day of crying, 4 days every week.
E. The infant appears to be thriving but cries for 2 hours every day of the week, more commonly in the early afternoon or evening hours.

11. The parents of an 18-month-old boy are very concerned because he has had several episodes in which he became frustrated and angry, held his breath, and turned blue. Which of the following is appropriate information for parents about breath-holding spells?

A. The spells are voluntary, and the boy is very likely deliberately trying to gain attention from the parents.
B. The age of onset for these spells is unusual.
C. The boy is unlikely to lose consciousness during a spell.
D. An electrocardiogram is indicated if the spells are associated with physical activity.
E. The spells may eventually cause learning disabilities and poor attention if they are allowed to continue.

12. A child is still in the sensorimotor stage of development. He is beginning to look over the high chair to see where a dropped object has gone and is starting to use a brush and comb on his hair. He has not yet started building forts with blocks. Assuming he is normal cognitively, which of the following is most likely his age?

A. 6–9 months
B. 10–14 months
C. 15–18 months
D. 18–24 months
E. 24–27 months

The response options for statements 13–14 are the same. Please select one answer for each statement in the following set.

A. 4 months
B. 6 months
C. 8 months
D. 10 months
E. 12 months

For each of the following infants, select the most likely age of the infant based on the infant's developmental milestones.

1. While playing with blocks with an infant, the infant becomes upset when you hide the blocks out of view. The infant is only able to say *mama* and becomes upset when his mother leaves the room. He is able to hold a small object between his thumb and his index finger.
2. An infant is able to transfer objects from hand to hand and to sit alone. He is also able to mix both vowel and consonant sounds, although he is not yet saying *mama* and *dada.* You are not able to elicit a parachute reaction.

Answers and Explanations

1. **The answer is E** [I.C.1.c]. An early hand preference may indicate weakness or spasticity of the contralateral upper extremity. It is unusual to see a hand preference in an infant younger than 18 months. Hand preference typically emerges between 4 and 5 years of age. Infants walk at a mean age of 12 months, and the range of normal (2 standard deviations) is 9–15 months of age. Using two words in addition to *mama* and *dada* is appropriate for a 13-month-old child. Stranger anxiety is both common and normal between 6 and 18 months of age. A 13-month-old child may play with utensils but may not use them appropriately in meals until 15–18 months of age.
2. **The answer is D** [II.A.1.c]. Periodic developmental evaluations and physical examinations are necessary to monitor for signs of cerebral palsy. Although it is important to evaluate this infant's tone and reflexes, abnormalities of the motor examination are frequently not appreciated until the infant is older than 6 months. Cerebral palsy is a nonprogressive or static encephalopathy and should not lead to loss of milestones. Only a minority of low birth weight premature infants <1500 g develop cerebral palsy (10–15% incidence). No specific laboratory testing is available to diagnose or predict the course of the disease.
3. **The answer is B** [IV.J]. The age of toilet training coincides with the psychological stage of developing autonomy and mastering new skills. The basic principles of rewarding appropriate behaviors apply to toileting as well as to the achievement of other new skills. One year of age is too early to begin toilet training and is likely to lead to frustration and power struggles. Although environmental issues and caregiver convenience are important considerations, they are not paramount issues. Harmony between generations is desirable, but overly coercive training by controlling parents is associated with later encopresis and anxiety.
4. **The answer is B** [II.C.2]. Children with autism spectrum disorder have evidence of impairments in social communication and repetitive/restrictive behaviors. Difficulty using language to communicate with others is the hallmark of autism spectrum disorder, although the spectrum ranges from no verbal language to subtle deviations. People with autism may have difficulty "reading" facial expressions and hand gestures. The repetitive/restrictive behaviors are also wide ranging in its presentation and can be associated with sensory processing challenges and stereotyped mannerisms (e.g., hand flapping, sensitivity to sounds, and scripted speech) but not increased clumsiness.
5. **The answer is A** [IV.B.5]. This child's history is concerning for a potential neurologic abnormality because of the reported tripping. The abnormal anal wink reflex on examination may suggest spinal cord compression or spinal nerve entrapment and the need for neuroimaging studies. Bladder stretching exercises may be appropriate for the child who wets when his functional bladder capacity is exceeded, but the history here does not suggest that small bladder capacity is the problem. Conditioning alarms, desmopressin (DDAVP), and imipramine have all been used for nocturnal incontinence, whereas this child has daytime incontinence. Secondary enuresis is usually associated with an identified stress such as the birth of a sibling, divorce in the family, or a recent move. Psychological counseling can sometimes be useful in such situations.
6. **The answer is D** [Table 2-4]. The language milestones described are usually achieved around the age of 24 months. At 13 months of age, most children use about three words that the parents understand and they are also able to play peek-a-boo and patty-cake. At 18 months of age, children may speak 20 words or more. At 24 months of age, children should be using multiple telegraphic two-word sentences and speak over 50 words, of which 25–50% should be understandable. At 36 months of age, children begin to use pronouns, adjectives, and adverbs; ask questions; and use sentences longer than two words.

7. **The answer is D** [III.A.3]. **Genetic factors** account for at least **50%** of sensorineural hearing loss. Of these, a great majority (80%) of genetic transmission of hearing impairment is caused by inheritance of the connexin gene, an autosomal recessive trait. Maternal substance abuse, traumatic deliveries, and prematurity are less frequent causes of isolated hearing impairments. Although meningitis and prenatal congenital infections are also potential causes of hearing impairment, they are among the nongenetic factors that account for a much smaller percentage of hearing loss in infants.
8. **The answer is B** [II.D.3]. It is important to establish the correct diagnosis before beginning therapeutic interventions. This child does not meet the criteria for the diagnosis of attention deficit/hyperactivity disorder (ADHD) because his symptoms appeared after 7 years of age and are present in only one setting (school). It would be important to assess whether factors such as the teacher's expectations, classroom dynamics, or peer issues are affecting his classroom behavior and performance. If a child meets the criteria for ADHD, all of the other management options become reasonable parts of a therapeutic plan.
9. **The answer is E** [IV.D.4]. Children with night terrors do not respond to their parents' attempts to comfort them, do not become oriented during their arousals from sleep, and do not remember the event the next day. In contrast, children with nightmares rapidly become alert and oriented, recall details of the frightening dreams on awakening, and often recall the next day that they had a bad dream during the night. Nightmares occur in REM (rapid eye movement) sleep, whereas night terrors occur in stage 4 non-REM sleep, 90–120 minutes after sleep onset. The peak incidence for night terrors is between 3 and 5 years of age; nightmares are common after 3 years of age.
10. **The answer is D** [IV.A]. To qualify for a diagnosis of colic, the infant must be between the ages of 2 weeks and 4 months, be healthy and well-fed, and cry for more than 3 hours a day more than 3 days a week. Periods of crying with colic typically increase in the late afternoon or early evening hours. Known causes of pain must be excluded to make the diagnosis of colic, including corneal abrasion, hair tourniquet wrapped around a digit, and inguinal hernia that may be intermittently incarcerated. Infants who have concurrent failure to thrive must be evaluated for other etiologic factors.
11. **The answer is D** [IV.H]. Breath-holding spells are common, occurring in as many as 5% of children. These spells generally begin in children at 6–18 months of age and may continue up until 5 years of age. They are harmless and involuntary in nature. Even if they produce a loss of consciousness, which may occur in some children, learning problems or other long-term sequelae do not result. Spells that are associated with exercise or physical activity should be evaluated with an electrocardiogram to look for an underlying dysrhythmia.
12. **The answer is B** [I.C]. Knowing that this child is still in the sensorimotor stage places his age at less than 2 years. This child is old enough to start using tools for their function, which would not be seen in a typical infant who is 6–9 months of age. He is not using symbolic play, which begins at about 24–30 months of age. He is beginning to process the concept of cause and effect; infants usually start looking over the high chair for dropped objects at about 9 months of age. This developmental clue places him at the early stage of functional play, making an age of 10–14 months more likely than ages older than 15 months.
13. **The answers are D** [I.C.3.c; Tables 2-3 and 2-4] **and B** [Tables 2-2, 2-3, and 2-4], **respectively.** Infants develop "object permanence," an understanding that objects continue to exist even when the infant cannot see them, at about 9 months of age. Infants usually begin saying *mama* and *dada* between 9 and 12 months of age and usually have between one and three additional words in their vocabulary by 12 months of age (1 year). Separation anxiety may develop anytime between 6 and 18 months of age when a loved one leaves the infant's vision. An immature pincer, or the ability to hold a small object between the thumb and the index finger, usually develops about 9 months of age. Based on the choices provided, this infant in question

13 is most likely to be 10 months of age.

14. Infants are able to transfer objects and to sit alone at about 6 months of age. In addition, a 6-month-old infant would be expected to mix vowel and consonant sounds but will not begin saying *mama* or *dada* until 9–12 months of age. The parachute reaction is one of the postural reactions that help facilitate the orientation of the body in space and usually develops at approximately 8 months of age. Based on the choices provided, the infant in question 14 is most likely 6 months of age.

CHAPTER 3

Adolescent Medicine

Monica Sifuentes, Lloyd J. Brown

I. Adolescent Growth and Development

A. **Growth.** Adolescence is a time of substantial physical growth and pubertal maturation.
   1. **Changes in physical growth**
      a. **The average duration of the growth spurt is 2–4 years.**
      b. **Growth** is predominantly controlled by **growth hormone,** although insulin, thyroid hormone, and sex steroids also influence growth.
      c. **Nearly 50%** of ideal adult body weight and **25%** of final adult height are gained during the pubertal growth spurt.
      d. **The growth spurt** occurs **18–24 months earlier** in females than in males (Tanner 2–3 for girls vs. Tanner 4 for boys).
   2. **Development of genitalia and secondary sexual characteristics**
      a. **The average duration of puberty is 3–4 years.**
      b. **Endocrinologic changes during puberty**. The precise factor responsible for the initiation of puberty is unknown.
         1. **Adrenarche,** the onset of adrenal androgen steroidogenesis, occurs 2 years before the maturation of the hypothalamic–pituitary–gonadal axis.
         2. **True puberty** is said to occur when gonadotropins, such as luteinizing hormone (LH), follicle-stimulating hormone (FSH), and gonadal sex steroids (e.g., estrogen and testosterone) increase.
         3. Table 3-1 lists the actions of hormones in males and females.
      c. **Physical changes during puberty**
         1. **Males.** Puberty begins later in males than in females.
            a. **Testicular enlargement and thinning of the scrotum** often begins between ages 11 and 12 years and is the **first sign of puberty**.
            b. **Facial and axillary hair** growth begins approximately 2 years after the growth of pubic hair begins.
            c. Figure 3-1 shows the five stages of development of male genitalia and pubic hair as described by Tanner **(Tanner staging or sexual maturity rating [SMR])**.
         2. **Females.** Puberty begins with the development of breast buds **(thelarche)** at a mean age of **9.5 years**.
            a. **Pubic hair** generally follows thelarche.
            b. **Menarche**, the onset of the first menstrual cycle, occurs at a mean age of **12.5 years** and occurs **2–3 years after thelarche**.
            c. Figures 3-2 and 3-3 show the development of breasts and pubic hair, respectively, as described by Tanner.

B. **Psychosocial development.** Adolescent development may be classified into three stages: **early**, **middle**, and **late**. As an adolescent passes through the stages of psychosocial development, he or she develops a sense of self, achieves increasing independence from his or her parents, increases his or her involvement with peer groups, and develops a healthy body image as well as more defined goals for the future.
   1. **Early adolescence** (10–13 years of age)
      a. **Early shift to independence** from parents, with declining interest in family activities, beginnings of conflicts with parents, and the presence of mood and behavior changes
      b. **Preoccupation with pubertal body changes** and the need for privacy
      c. **Same-sex peer relationships**
      d. **Concrete cognition.** Beginnings of abstract thinking and **lack of impulse control**,

with **risk-taking** behaviors

2. **Middle adolescence** (14–17 years of age)
    a. **Increased conflicts** with parents and heightened demands for privacy and autonomy
    b. **Diminished preoccupation** with pubertal changes but increased preoccupation with methods to improve one's own physical attractiveness
    c. **Intense peer group involvement** and initiation *of romantic relationships*
    d. **Increasing abstract reasoning** and **risk-taking**
    e. Introspective, long-term thinking but **questionable decision-making skills**
3. **Late adolescence** (18–21 years of age)
    a. **Development of self as distinct** from parents. Adolescents are better able to take and more likely to seek advice from parents. **Peers are less influential.**
    b. **Being comfortable with own body image**
    c. **A shared intimate relationship** with at least one partner
    d. Well-developed **abstract thought processes,** with **fewer risk-taking** behaviors. Adolescents are able to articulate future educational and vocational goals.

Table 3-1
Actions of Sex Hormones in Both Males and Females

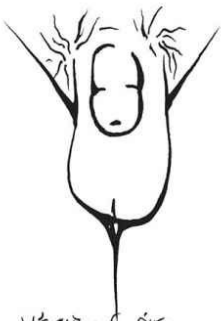
Hormone	Action in Males	Action in Females
Follicle-stimulating hormone	Induces spermatogenesis	Stimulates development of ovarian follicles Stimulates ovarian granulosa cells to produce estrogen
Luteinizing hormone	Induces testicular Leydig cells to produce testosterone	Stimulates ovarian theca cells to produce androgens Stimulates corpus luteum to produce progesterone Midcycle surge results in ovulation
Testosterone	Increases linear growth and muscle mass Induces development of penis, scrotum, prostate, and seminal vesicles Induces growth of pubic, axillary, and facial hair Deepens voice Increases libido	Stimulates linear growth Stimulates growth of pubic and axillary hair
Estradiol	Increases rate of epiphyseal fusion	Stimulates breast development Triggers midcycle luteinizing hormone surge Stimulates labial, vaginal, and uterine development Stimulates growth of a proliferative endometrium Low level stimulates linear growth High level increases rate of epiphyseal fusion
Progesterone		Converts endometrium to a secretory endometrium
Adrenal androgens	Stimulates growth of pubic hair Stimulates linear growth	Stimulates growth of pubic hair Stimulates linear growth

Adapted from Neinstein LS. Adolescent Health Care, A Practical Guide. 3rd Ed. Baltimore: Williams & Wilkins, 1996.

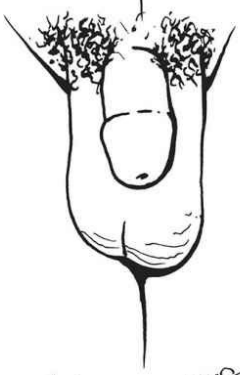
Stage 1 Preadolescent
No pubic hair
Prepubertal testes



Stage 2 Testes larger
Sparse, long, downy hair



Stage 3 Testes further enlarged
Penis length enlarged
Darker, coarser, and curlier hair



Stage 4 Darkening of scrotal skin
Penis length and width increased; glans develops
Coarse and curly pubic hair extending over symphysis pubis



Stage 5 Testes and penis adult in size and shape
Adult-type pubic hair that spreads to medial surface of thighs

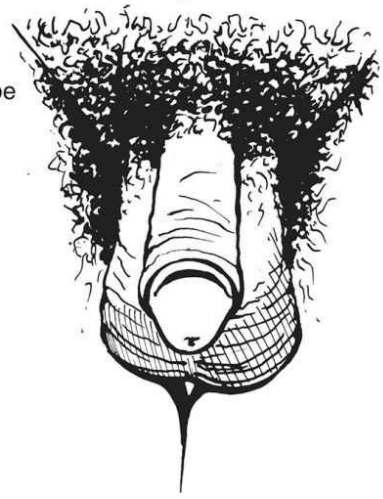
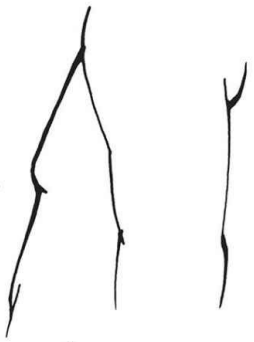
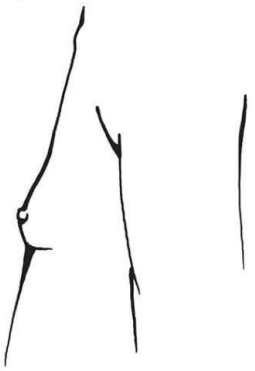


FIGURE 3.1 Sexual maturity ratings for male genitalia and pubic hair development.

Stage 1 Preadolescent



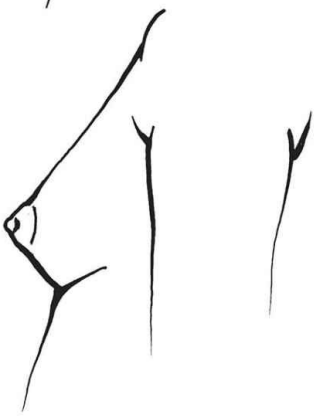
Stage 2 Elevation of breast and nipple as small projections



Stage 3 Enlargement of breast
No separation of areola and breast
Areola enlarges



Stage 4 Areola and nipple project to form secondary mound above level of breast



Stage 5 Only nipple projects
Areola usually recedes to contour of breast
Adult breast size

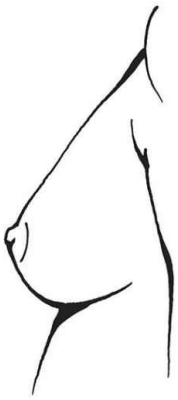
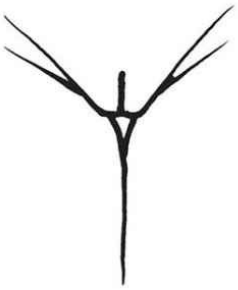


FIGURE 3.2 Sexual maturity ratings for female breast development.

Stage 1 Preadolescent
No pubic hair



Stage 2 Sparse, long, downy hair along labia



Stage 3 Darker, coarser, and curlier hair



Stage 4 Coarse and curly adult-type hair covering symphysis pubis



Stage 5 Adult-type hair spread onto medial surface of thighs



FIGURE 3.3 Sexual maturity ratings for female pubic hair development.

II. Adolescent Health Screening

A. **Goals** are to promote optimal physical and psychosocial growth and development.

B. **History. Information should be obtained directly from the adolescent alone.** However, the family can also be an important source of additional information. Practitioners may choose to interview the family together with the adolescent, either before or after interviewing the adolescent alone.

1. **Confidentiality, trust, and rapport** are important to establish to provide effective care to adolescents. Confidentiality encourages adolescents to seek care and protects them from embarrassment and discrimination.
    a. **Rapport** can be best established by beginning the history with nonthreatening subjects such as favorite hobbies, interests, or activities.
    b. **Information** provided by the adolescent should remain confidential, although **sexual or physical abuse** and **suicidal or homicidal intention must be reported to the appropriate authorities**.
    c. **Most state laws allow** adolescents to consent without parent approval for pregnancy-related care, prevention, diagnosis and treatment of sexually transmitted infections (STIs), reproductive health care, sexual assault services, counseling and treatment of drug or alcohol problems, and mental health treatment.
2. **Components of the history** include present illness or concerns, medical and family histories, and a psychosocial history using the **HEADDSSS** assessment (home, education/employment, activities, diet, drugs, sexual activity, suicide and depression, safety; **Table 3-2**).

C. **Physical examination.** The physician should pay special attention to physical growth and pubertal development, detection of disease, and specific adolescent concerns.

1. **Height and weight** should be measured and plotted on age-appropriate growth charts. Body mass index (BMI) should be calculated.
2. **Blood pressure, pulse, and vision and hearing** assessments should be performed.
3. **Skin** should be examined for acne and fungal infections or any other rashes. Tattoos and body piercings should be noted.
4. **Teeth** should be examined for malocclusion and hygiene.
5. **Thyroid** should be palpated for enlargement or nodules.
6. **Back** should be evaluated for scoliosis or kyphosis.
7. **Pubertal development** should be assessed, and an SMR (Tanner rating) should be assigned (**see Figures 3-1, 3-2, and 3-3**).
8. **Male genitalia** should be examined for scrotal masses and inguinal hernias. Instruction should be given on the performance of a proper **testicular self-examination**.
9. **Female genitalia** should be examined at least once during puberty to document SMR. A **complete pelvic examination** should be performed (1) **if the patient is sexually active** ***and*** *has a history of* **pelvic pain, vaginal discharge, or abnormal bleeding** or (2) if she is **21 years or older** to perform cervical cancer screening, if indicated. In addition, instruction should be given on the performance of proper **breast self-examination** for future health maintenance examinations.

D. **Immunizations**

1. **Tetanus, diphtheria, and acellular pertussis booster (Tdap)** should be given between 11 and 12 years of age, and Td every 10 years thereafter.
2. **Measles, mumps, and rubella booster (MMR)** and the **hepatitis B vaccine series** should be given if not given before adolescence.
3. **Hepatitis A vaccine** should be given to those adolescents who reside in endemic areas

and who have not previously received the hepatitis A vaccine series.

4. **Varicella vaccine** should be administered if the adolescent has not had chickenpox and has not received the appropriate vaccination series against the disease.
5. **Meningococcal vaccine** should be given between 11 and 12 years of age and at 16 years.
6. **Human papillomavirus (HPV) vaccine series** should begin routinely at 11 or 12 years of age, and it can be administered starting at 9 years.
7. **Annual influenza vaccination**

E. **Laboratory studies**

1. **Hemoglobin or hematocrit** to screen for anemia
2. **Urinalysis** screening is no longer recommended.
3. **Cholesterol level or fasting lipid panel** (see Chapter 1, section IV.F for guidelines)
4. **Human immunodeficiency virus (HIV) testing** is recommended annually for all sexually active teens.
5. **Mantoux skin test (purified protein derivative [PPD])** for tuberculosis (TB) should be administered at least once during adolescence. PPD may be necessary more often if the adolescent is at high risk of exposure to TB. The interferon-gamma release assay (e.g., QuantiFERON-TB Gold) may be indicated for greater specificity in lieu of the PPD skin test.
6. **Sexually active adolescent females** should be screened annually for the following STIs:
    a. **Nucleic acid amplification test (NAAT) of urine or vaginal swab for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.**
    b. **Serologic test for syphilis** for high-risk teens, including pregnant adolescents
    c. *HIV testing*
    d. Routine screening for *Trichomonas vaginalis*, bacterial vaginosis (BV), herpes simplex virus (HSV), HPV, and hepatitis A and B virus is generally **not** recommended for adolescents who are asymptomatic.
7. **Sexually active adolescent males** should have annual HIV screening and syphilis serology (for young men who have sex with men [YMSM] and routinely for all young men in communities with higher prevalence), routine urinalysis for pyuria, and a NAAT for *C. trachomatis* and *N. gonorrhoeae.*

F. **Health guidance.** Counseling should be provided annually regarding:

1. **Injury prevention.** Education should include counseling about alcohol, tobacco and drug avoidance, firearm safety, violence management, the use of seat belts and motorcycle and bicycle helmets, and dangers of driving while intoxicated or riding with a driver who has been drinking alcohol.
2. **Benefits of a healthy diet and physical exercise**
3. **Education regarding responsible sexual behaviors and healthy relationships**

Table 3-2
HEADDSSS Questionnaire Used in Psychosocial Assessment of Adolescents

Home	Where, and with whom, does the teen live? Does the teen feel like he or she has his or her own "space"? Has the teen ever run away or been arrested? How does the teen interact with parents? Is there a firearm at home?
Education and employment	Is the teen in school? What is the teen's academic performance? What classes does the teen enjoy? Dislike? Has the teen ever been truant or suspended? Dropped out? What are the teen's career goals? Does the teen have a job? If so, does the job contribute to the overall household budget?

Activities	What are the teen's hobbies? What does the teen enjoy doing after school? On weekends? With whom does the teen spend free time?
Diet	What is a typical meal? Does the teen have any food restrictions? Is the teen comfortable with current weight? What does the teen do to maintain weight?
Drugs	Has the teen tried any drugs? If yes, which drugs and how much? How often? Has the teen used tobacco? Alcohol? Steroids? Do the teen's friends use drugs, tobacco, or alcohol?
Sexual activity	Does the teen currently have a romantic interest or attraction to someone? What is the teen's sexual orientation? Is the teen currently sexually active? If yes, what type of contraception is used? Does the teen use condoms? How many sexual partners? Any STIs? Does the teen have any history of sexual or physical abuse?
Suicide and depression	Is the teen ever sad or depressed? Any cutting behavior?
Safety	Has the teen ever considered or attempted suicide? Does the teen wear a helmet when riding a bike? Use seatbelts when driving? Drive with someone who has been drinking alcohol?

STI = sexually transmitted infection.

III. Depression and Suicide

A. **Epidemiology**
   1. **Suicide** is the **third leading cause of death** in adolescents 15–19 years of age, after unintentional injuries and homicide.
   2. **Episodes of sadness or depressed mood** occur monthly in the majority of adolescents, and **10%** *of teens are clinically depressed.*
   3. **Females** are depressed two times as often as males.
   4. **Risk factors** for suicide or depression
      a. **Family or peer conflicts**
      b. **Substance abuse**
      c. **Significant loss,** including death of a loved one
      d. **Divorce or separation** of parents
      e. **Poor school performance or learning disability**
      f. **Physical or sexual abuse**
      g. **Family history of depression or suicide**
      h. **Previous suicide attempt**
      i. **Physical illness or chronic disease**

B. **Clinical features** *ofdepression*
   1. **Teens with depression** can have a wide range of behavioral, physical, and psychological symptoms.
      a. **Behavioral signs of depression** include missing school, change in school performance, acting out (e.g., arguing with family and friends, stealing, destruction of property), lack of interest in activities that previously were pleasurable, desire to be alone or being withdrawn, and substance abuse.
      b. **Physical signs of depression** include abdominal pain, headaches, weight loss, overeating, insomnia, anxiousness, diminished appetite, and fatigue.
      c. **Psychological signs of depression** include sadness, feelings of hopelessness, low self- esteem, excessive self-criticism, and feeling worthless.
   2. **The following are the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) criteria for major depression: Five or more of nine** symptoms must be present **almost every day for at least 2 weeks** and must **impair ability to function normally**.
      a. **Depressed or irritable mood**
      b. **Diminished interest or pleasure in activities**
      c. **Significant weight gain or loss**
      d. **Insomnia or hypersomnia**
      e. **Psychomotor agitation or retardation**
      f. **Fatigue or energy loss**
      g. **Feelings of worthlessness or excessive or inappropriate guilt**
      h. **Diminished ability to think or concentrate**
      i. **Recurrent thoughts of death or suicide, a suicide attempt, or a specific plan**

C. **Clinical features** of **dysthymic disorder**. Dysthymia is a more chronic mood disturbance that lasts at least 1 year. The symptoms of dysthymia are milder than those of depression. The following are the DSM-5 criteria for dysthymia:
   1. **While depressed, two of six** of the following symptoms must be present:
      a. **Poor appetite or overeating**
      b. **Insomnia or hypersomnia**
      c. **Diminished energy or fatigue**

   d. **Low self-esteem**
   e. **Difficulty concentrating or making decisions**
   f. **Feelings of hopelessness**
2. **Symptoms must last for at least 1 year.**
3. **Symptoms are not attributable to physical effects of a substance, medication, or another medical condition.**

IV. Substance Abuse

A. **Epidemiology.** Of high school seniors, 75% have tried alcohol, 50% have tried an illicit drug, and 50% have tried cigarettes.
B. **Etiology. Use by family or peers, experimentation, stress relief, poor self-esteem, boredom, social acceptance, enhancement of ability to act socially, and acting-out behavior against authority figures** are all reasons why adolescents may use illicit drugs, alcohol, or tobacco.
C. **Diagnosis. Substance abuse should be considered** if the following factors are present: mood or sleep disturbances, truancy, decline in school performance, changes in friends and family relationships, absent or hostile communication, diminished appetite or weight loss, depression, and diminished participation in school or household responsibilities.
D. **Risk factors** for the development of substance abuse
    1. **Household use**
    2. **Depression**
    3. **Anxiety**
    4. **Impulse control problems**
    5. **Attention deficit disorders, including attention deficit/hyperactivity disorder**
E. **Most commonly used substances: alcohol, tobacco, and marijuana**
    1. **Alcohol is the most commonly used substance.**
        a. **Problem drinking** is defined as having been intoxicated six or more times within 1 year or having problems in areas attributable to drinking, such as missing classes at school; arguing with teachers, classmates, or friends; or driving intoxicated.
        b. **Binge drinking** is defined as five or more consecutive drinks at one sitting. As many as 50% of all college students report binge drinking, and binge drinkers are more likely to become involved in physical altercations, to drive drunk, and to have unplanned sexual intercourse.
        c. **Alcoholism** is defined as a preoccupation with and impaired control over drinking, despite adverse consequences.
        d. The **CAGE questionnaire** may be used to screen for alcoholism, but is generally a more appropriate screening tool for adults.
            1. Have you ever felt you had to **cut** down on drinking?
            2. Have people **annoyed** you by criticizing your drinking?
            3. Have you ever felt **guilty** about drinking?
            4. Have you ever had a drink first thing in the morning (**eye opener**)?
        e. The **CRAFFT screening tool** is a validated behavioral health screening tool developed for use with patients younger than 21 years to screen for high-risk alcohol and other drug use disorders simultaneously. (If the answer to one or more questions in Part A is "yes," continue with Part B.)
            1. **Part A.** During the past 12 months, did you
                a. Drink any alcohol (more than a few sips)?
                b. Smoke any marijuana or hashish?
                c. Use anything else to get high?
            2. *Part B*
                a. Have you ever ridden in a **CAR** driven by someone (including yourself) who was "high" or had been using alcohol or drugs?
                b. Do you ever use alcohol or drugs to **RELAX**, feel better about yourself, or fit in?
                c. Do you ever use alcohol or drugs while you are by yourself or **ALONE**?
                d. Do you ever **FORGET** things you did while using alcohol or drugs?

e. Do your **FAMILY** or **FRIENDS** ever tell you that you should cut down on your drinking or drug use?
f. Have you ever gotten into **TROUBLE** while you are using alcohol or drugs?

2. **Tobacco**
   a. **Teens who smoke tobacco** are more likely to try other drugs and have lower academic performance.
   b. **Nicotine is highly addictive.** Most adult smokers began smoking in their teenage years.
   c. **Health risks of smoking**
      1. **Coronary artery disease and stroke**
      2. **Cancers** of the lungs, mouth, esophagus, stomach, larynx, and urinary tract
      3. **Chronic lung disease and asthma**
      4. **Peptic ulcer disease**
      5. **Pregnancy complications,** such as stillbirth, low birth weight, and higher-than- average infant mortality
   d. More than 3 million teens chew **smokeless tobacco**. Smokeless tobacco is associated with oral cancers, gingival recession, and low birth weight and premature delivery in mothers who use it during pregnancy.
   e. **Alternative tobacco products such as electronic cigarettes (e-cigs)** are battery-powered devices that heat and vaporize a liquid nicotine solution. The user inhales the vapor created and ingests the nicotine ("vaping"). E-cigs are sold in many colors, shapes, flavors, and sizes. The amount of nicotine and other harmful ingredients in each cartridge is variable. These products are not regulated or approved by any government agencies, and in some states, there is no age limit to purchase e-cigs.
3. **Marijuana is the most widely used illicit drug.** It is derived from the plant *Cannabis sativa.* The **active ingredient** is tetrahydrocannabinol (THC).
   a. **Physical effects** typically include tachycardia, mydriasis, sleepiness, conjunctival erythema, dry mouth, auditory and visual hallucinations, increased appetite, and impaired cognition.
   b. **Long-term consequences** of heavy marijuana use may include asthma, impaired memory and learning, truancy, diminished interpersonal interactions, and depression.

V. Obesity and Eating Disorders

A. **Obesity** is one of the most common chronic illnesses among adolescents.
   1. **Definitions**
      a. **Body weight 20% greater than ideal body weight**
      b. **BMI** (body weight in kilograms divided by height in meters squared) **greater than 95% for age and sex**
      c. **Body fat** content may also be determined by measuring skinfold thickness at the triceps and subscapular areas.
   2. **Etiology.** Often multifactorial. Obesity is commonly the result of the interaction of genetic factors, increased caloric intake, diminished energy expenditure, and poor eating behaviors. Underlying endocrinologic or genetic causes (e.g., hypothyroidism, Cushing disease, hypogonadism, Prader–Willi syndrome) are found in only 5% of patients.
   3. **Health effects associated with obesity**
      a. **Earlier pubertal development**
      b. **Hypertension and cardiovascular disease**
      c. **Hypercholesterolemia and elevated triglycerides**
      d. **Type 2 diabetes mellitus**
      e. **Gallbladder disease**
      f. **Orthopedic problems** such as back pain and tibia vara (bowlegs)
      g. **Poor body image, depression, and low self-esteem**
   4. **Management.** Treatment is challenging and must be multifaceted. Therapies include modification of eating behaviors, promotion of healthy nutrition, a balanced weight reduction program, exercise, and psychological support.

B. **Anorexia nervosa and bulimia nervosa** typically occur in females 13–18 years of age.
   1. **Epidemiology. Anorexia nervosa** occurs in approximately 0.5–1% of adolescents, and **bulimia nervosa** occurs in approximately 1–5% of adolescents.
   2. **Diagnostic criteria for anorexia nervosa**
      a. **Caloric intake is insufficient** to maintain weight or growth.
      b. **Adolescent** has a **delusion of being fat** and an **obsession to become thin**.
      c. **Specific criteria (DSM-5)**
         1. **Refusal to maintain body weight** at normal weight for age and height. Body weight is **below a minimally normal level for age, sex, developmental growth, and physical health**.
         2. **Intense fear of weight gain or becoming fat** with **persistent behavior that interferes with weight gain**
         3. **Disturbed body image (weight or shape)**
      d. **Excessive exercise, fluctuating emotions, withdrawal from peers and family, and a preoccupation with food** are often present.
      e. **Patients often do not recognize the serious medical implications of their malnourished state.**
   3. **Diagnostic criteria for bulimia nervosa**
      a. **Eating pattern** includes **binge eating,** in which a large volume of food is consumed in a short period.
      b. **Specific criteria (DSM-5)**
         1. **Recurrent episodes of binge eating at least once a week for 3 months with inappropriate compensatory behaviors to prevent weight gain.**
         2. **Lack of control over eating** during binging. **Anxiety, guilt, or sadness** often occurs after each binge.

3. **Purging** using self-induced vomiting, laxatives, diuretics, or other medications, including enemas **to prevent weight gain**. **Fasting, rigorous exercise, or diet pills** also may be used to prevent weight gain.
4. **Disturbed body image**

4. **Physical examination and laboratory findings** are described in **Table 3-3**.
5. **Management.** Treatment of an adolescent with anorexia nervosa or bulimia nervosa is challenging and long term, and requires a multidisciplinary team approach, including **involvement of the family**.
   a. **Normal nutrition** must be established, anorexic or bulimic behaviors must be relinquished, and the adolescent must gain insight into the reasons behind the disorder. Nutritional guidance and psychological counseling are often required.
   b. **Hospitalization** is necessary if the adolescent has evidence of severe weight loss, electrolyte abnormalities, dehydration, abnormal vital signs, suicidal thoughts, out-of-control behavior, medical complications (such as seizures, cardiac arrhythmias, or pancreatitis), or failure of outpatient medical management (including food refusal).

Table 3-3
Physical Examination and Laboratory Abnormalities in Anorexia Nervosa and Bulimia Nervosa

Eating Disorder	Examination Findings	Laboratory Findings
Anorexia nervosa	Weight ≥ 15% below ideal level Hypothermia Hypotension Bradycardia Delayed growth and puberty Amenorrhea Malnourished (wasted, hypoactive bowel sounds, dependent edema, fine lanugo hair) Evidence of dehydration	Anemia Leukopenia Low thyroxine Low glucose Low calcium Low magnesium Low phosphorus Low zinc Low sex steroids High blood urea nitrogen High liver transaminases High cholesterol Prolongation of QTc on electrocardiogram
Bulimia nervosa	Less ill-appearing Normal weight (usually) Hypothermia, hypotension, and bradycardia if excessive purging Sequelae of vomiting (trauma to palate and hands, loss of dental enamel, parotid swelling)	Low chloride, low potassium, low sodium, and high blood urea nitrogen and high bicarbonate if excessive vomiting

VI. Female Reproductive Health Issues

One-half of adolescents are sexually active by the end of high school.

A. **Pregnancy**
   1. **Epidemiology.** One million adolescent females (one of every nine) become pregnant every year in the United States.
      a. **One-fifth** of adolescent pregnancies occur within the first month after the teen first commences sexual intercourse.
      b. **Most (80%)** adolescent pregnancies are **unintentional**.
      c. **One-half** of adolescent pregnancies result in delivery, **one-third** result in abortion, and **one-sixth** result in miscarriage.
   2. **Associated conditions. Adolescent pregnancy** is a **high-risk pregnancy** associated with increased incidence of the following:
      a. **Infant health problems,** including **low birth weight** and **increased infant mortality**
      b. **Maternal health problems,** including **anemia, hypertension, and preterm labor**
      c. **Dropping out of school**
      d. **Unemployment and the need for public assistance**

B. **Contraception**
   1. **One-half of all sexually active adolescents do not use any contraception** for one or more of the following reasons:
      a. **Ignorance** of the contraceptive methods available
      b. **Denial** of the risk of pregnancy
      c. **Barriers** toward obtaining contraception, including issues of confidentiality and cost
      d. **Refusal** by partner to use contraception
      e. **Religious beliefs**
      f. **Ambivalence about, or desire for, pregnancy**
   2. **Contraceptive methods**
      a. **Abstinence** offers the greatest protection and should always be discussed as a reasonable option to sexual intercourse.
      b. **Barrier methods** include the male condom, female condom, vaginal diaphragm, and cervical cap. The vaginal diaphragm and cervical cap are not recommended for most teenagers.
         1. **Male condom.** This sheath is placed onto the erect penis to prevent passage of sperm into the vagina.
            a. **Condoms are very important as a barrier against STIs.** Only condoms made of **latex** protect against transmission of the HIV virus.
            b. **Advantages** include low cost and safety.
            c. **Disadvantages** include availability, interference with spontaneity, and rare allergic reactions.
         2. **Female condom.** This polyurethane sheath is placed **into the vagina** to prevent the passage of sperm.
            a. **Advantages** include **protection against STIs**.
            b. **Disadvantages** include vaginal irritation or allergy and awkwardness of placement.
      c. **Intrauterine devices (IUDs)** can be safe, effective methods of birth control for most adolescents. Two types of IUDs, the T38A copper-bearing and the progesterone-releasing IUD, are available.

1. **Mechanisms of action** include interference with sperm transport and motility (copper IUD) and induction of endometrial atrophy (progesterone IUD).
2. **Advantages** include a single act of motivation for long-term use, no further office visits required once inserted, long term cost-effectiveness, reversibility, rapid return to fertility, convenience, and privacy.
3. **Disadvantages** include lack of protection against STIs, uterine bleeding and cramping, need for insertion by a health care professional, and initial higher cost. Risk of pelvic inflammatory disease (PID) with IUDs is only during insertion.

d. **Etonogestrel implant.** This single-rod, progestin-only subdermal radiopaque implant is placed at the inner side of the nondominant upper arm. It is effective for up to 3 years and must be removed by the end of the third year.
   1. **Mechanism of action** includes suppression of ovulation, increased viscosity of the cervical mucus, and alterations in the endometrium.
   2. **Advantages** include a single act of motivation required for insertion, no further health care visits needed, reversibility, rapid return to fertility, convenience, and privacy.
   3. **Disadvantages** include changes in menstrual cycle, lack of protection against STIs, need for insertion and removal by a certified professional, and initial higher cost.

e. **Vaginal ring.** This flexible polymeric ring releases estrogen and progesterone continuously through the vaginal wall into the systemic circulation. It is self-inserted into the vagina and worn for 3 out of 4 consecutive weeks.
   1. **Mechanism of action** includes inhibition of ovulation, alteration of the cervical mucus to prevent sperm entry, and promotion of endometrial changes to reduce the likelihood of implantation.
   2. **Advantages** include safety; high effectiveness; monthly method, which promotes adherence; and easy reversibility.
   3. **Disadvantages** include local irritation, vaginal discomfort and discharge, sensation of foreign body, and coital expulsion. In addition, the teen must be comfortable touching the genitalia for insertion and removal.

f. **Oral contraceptives** are either a combination of estrogen and progesterone or progesterone only.
   1. **Mechanisms of action** include inhibition of ovulation and thickening of cervical mucus, which interferes with passage of sperm.
   2. **Advantages** include decreased dysmenorrhea, regulation of menstrual bleeding, possible protection against endometrial and ovarian cancer, improved acne, and spontaneity.
   3. **Disadvantages** include headache, weight gain, amenorrhea, breakthrough bleeding, mood changes, nausea, lack of protection against STIs, and the need to remember to take the pill daily.
   4. **Absolute contraindications** to taking oral contraceptives include pregnancy, history of thromboembolic events, breast cancer, stroke, coronary artery disease, and liver disease. **Relative contraindications** include hypertension, migraine headaches, sickle cell anemia, elevated lipids, and smoking. However, the advantages of combined oral contraceptives generally outweigh the risks in those who are younger than 35 years and smoke.

g. **Contraceptive injections** involve the slow release of the progestin **depomedroxyprogesterone acetate (Depo-Provera)**.
   1. **Advantages** include contraceptive protection for **3 months** after each injection

and confidentiality.

2. **Disadvantages** include need for an intramuscular injection every 3 months, irregular bleeding, possible weight gain, reversible osteopenia, and lack of protection against STIs.

h. **Table 3-4** lists the failure rate for each of the contraceptive methods.

Table 3-4
Contraceptive Effectiveness

Method	Failure Rate (%)
Chance	85
Female condom	21–26
Spermicide alone	21
Withdrawal	19
Male condom	12–15
Oral contraceptives	3–10
Vaginal ring	0.65–1
Intrauterine device	0.1–0.6
Depo-Provera	<0.3
Implantable rod	<0.05

Adapted from Neinstein LS. Adolescent Health Care, A Practical Guide. 5th Ed. Baltimore: Lippincott Williams & Wilkins, 2007:586.

*Failure rate is percent accidental pregnancy during the first year of typical use.

VII. Sexually Transmitted Infections (STIs)

HSV, HPV, and *C. trachomatis* are the three most common STIs in the United States.

A. **Epidemiology**
   1. **STIs** occur most commonly in adolescents and young adults. **Diagnosis of one STI** is **strongly associated** with the likelihood of having another STI.
   2. **Risk factors** for STIs
      a. **Lack of barrier contraception**
      b. **Young age** at initiation of sexual intercourse
      c. **Spontaneous** sexual encounters
      d. **Multiple sequential sexual partners**
      e. **Concurrent substance abuse**
      f. **Perceived lack of risk**
      g. **Incarceration**
      h. **Teen pregnancy**
      i. **Teens who are homosexual or bisexual**
      j. **Cervical ectopy in adolescent females.** In general, these individuals are at a higher risk because of the presence of cervical ectopy (the presence of cervical columnar epithelium) to which *C. trachomatis* and *N. gonorrhoeae* preferentially attach.
      k. **Minority youth**

B. **Clinical features**
   1. **Vaginitis.** This disorder may be sexually transmitted, in the case of *T. vaginalis*, or may be caused by Bacterial Vaginosis (BV) or candidal infection, diseases not necessarily associated with sexual transmission.
      a. ***T. vaginalis,*** a protozoan, accounts for **15–20%** of cases of adolescent vaginitis.
         1. **Clinical findings**
            a. **Malodorous, profuse, yellow-green discharge**
            b. **Cervix may be friable and covered with petechiae (strawberry cervix)**
            c. **Vulvar inflammation and itching**
            d. **Dyspareunia** (pain during sexual intercourse)
            e. *T. vaginalis* is **asymptomatic or mild** in 70–85% of males and females.
         2. **Diagnosis**
            a. **NAAT** on endocervical, vaginal, or urethral swab or urine specimen
            b. **Wet-mount saline microscopy** may demonstrate motile flagellated protozoa but has low sensitivity.
            c. **Positive culture** for *T. vaginalis*
            d. **Vaginal pH > 4.5**
         3. **Management** includes oral metronidazole or tinidazole. Alcohol ingestion while taking these medications may result in an Antabuse-type reaction with severe vomiting. **Partners should also be treated.**
         4. **Complications include increased risk for HIV acquisition, preterm delivery, and adverse pregnancy outcomes**
      b. **BV** is a **common cause** of vaginitis in adolescents, and is caused by a change in the vaginal flora because of a reduction of lactobacilli, which are normally present. Fewer lactobacilli result in increased concentration of *Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealyticum,* and anaerobic Gram-negative rods.
         1. **Clinical findings**
            a. **Gray-white thin vaginal discharge** that may adhere to the vaginal wall
            b. **Pungent "fishy" odor**

c. **Little vaginal or vulvar inflammation**

2. **Diagnosis**
    a. **Positive "whiff test"** in which the "fishy" odor is enhanced on addition of 10% potassium hydroxide solution to vaginal secretions
    b. **Presence of "clue cells"** on wet-mount saline microscopy (vaginal epithelial cells covered with adherent bacteria, which results in a hazy, granular appearance to the cell borders)
    c. **Typical vaginal discharge**
    d. **Vaginal pH > 4.5**
3. **Management** includes oral metronidazole or topical intravaginal therapy with 2% clindamycin or 0.75% metronidazole gel. **Partners do not require treatment.**
4. **BV infection increases the risk of acquisition of other STIs** (including HIV, gonorrhea, chlamydia, and HSV-2), **complications after gynecologic surgery, pregnancy-related complications, and recurrence of BV**. **BV also increases the risk of transmission of HIV to male sex partners**.

c. **Candidal vulvovaginitis** is usually caused by *Candida albicans*.
1. **Clinical findings**
    a. **Severe itching** and a **thick white, curdlike vaginal discharge**
    b. **Vulvar and vaginal inflammation**: edema, erythema, fissures, excoriations
2. **Diagnosis**
    a. **Clinical signs and symptoms**
    b. **Fungal hyphae** seen on wet-mount saline or potassium hydroxide microscopy or Gram stain of vaginal discharge
    c. **Normal vaginal pH (<4.5)**
    d. **Positive culture** for yeast
3. **Management** includes oral fluconazole or topical intravaginal antiyeast therapies. **Partners do not require treatment. Teens should be aware that oil-based intravaginal anti-yeast creams and suppositories may weaken latex condoms.**

2. **Cervicitis.** This inflammation of the mucous membranes of the endocervix is most commonly caused by *C. trachomatis* or *N. gonorrhoeae.* Other causes include HSV (especially primary HSV-2 infection) and *T. vaginalis.*
a. ***C. trachomatis*** is an intracellular bacterium that infects the cervical columnar epithelium.
1. **Clinical findings**
    a. **Purulent or mucopurulent endocervical discharge**
    b. **Friable, edematous, erythematous cervix**
    c. **Dysuria and urinary frequency**
    d. **Fifty percent of males and as many as seventy-five percent of females are asymptomatic.**
2. **Diagnosis**
    a. **NAATs are the most sensitive tests and can be performed on urine, vaginal, and endocervical specimens.**
    b. **Rapid antigen detection by direct fluorescent antibody staining** or **enzyme immunoassay** is very sensitive but has high false-positive rates.
3. **Complications** include PID, tubo-ovarian abscess (TOA), infertility, ectopic pregnancy, chronic pelvic pain, Fitz-Hugh–Curtis syndrome (perihepatitis), and neonatal conjunctivitis and pneumonia.

4. **Management of uncomplicated *C. trachomatis* cervicitis** includes oral azithromycin in a single dose (preferred method for teens) or doxycycline, erythromycin, levofloxacin, or ofloxacin for 1 week. **Partners should also be treated.**

b. ***N. gonorrhoeae*** is a Gram-negative intracellular diplococcus that infects the cervical columnar epithelium.

1. **Clinical findings**
   a. **Mucopurulent endocervical discharge,** sometimes with vaginal bleeding
   b. **Dysuria and urinary frequency**
   c. **Dyspareunia**
   d. **Asymptomatic infection** is common in females. Males may also be asymptomatic but often have symptoms.
2. **Diagnosis**
   a. **NAATs on urine, vaginal, or endocervical specimens**
   b. **Culture** of endocervical discharge inoculated immediately onto modified Thayer–Martin media
   c. **Gram stain** demonstrating intracellular Gram-negative diplococci may be considered evidence of infection in symptomatic patients.
3. **Complications** include PID, TOA, chronic pelvic pain, neonatal conjunctivitis, Fitz-Hugh–Curtis syndrome, and infertility. Disseminated infection may occur in up to 3% of patients and is characterized by asymmetric polyarthritis, papular and pustular skin lesions, and, rarely, meningitis, endocarditis, and septicemia.
4. **Management** of uncomplicated cervicitis caused by *N. gonorrhoeae* includes intramuscular ceftriaxone plus single-dose oral azithromycin for presumptive coinfection with *C. trachomatis* [see section VII.B.2.a.(4)]. Alternative therapy with single-dose oral cefixime and oral azithromycin should only be considered if ceftriaxone is unavailable. **Partners should also be treated.**

3. **PID.** This STI is an ascending infection in which pathogens from the cervix spread to the uterus and fallopian tubes.

a. **Epidemiology**

1. **PID is polymicrobial and may be caused by *N. gonorrhoeae, C. trachomatis,*** and nongonococcal, nonchlamydial aerobes and anaerobes.
2. **PID is more common in the first half of the menstrual cycle,** because menstruation enhances the spread of infection from the lower genital tract.

b. **Clinical findings and diagnosis.** The occurrence of particular signs and symptoms can lead to a presumptive diagnosis.

1. **Both** of the following must be present:
   a. **Pelvic or lower abdominal pain and tenderness**
   b. **Uterine or cervical motion tenderness, or unilateral or bilateral adnexal tenderness**
2. **One** of the following should also be present:
   a. **Temperature > 101°F (>38.3°C)**
   b. **Abnormal cervical mucopurulent discharge or cervical friability**
   c. **Presence of abundant numbers of white blood cells (WBCs) on saline microscopy of vaginal fluid**
   d. **Elevated erythrocyte sedimentation rate or C-reactive protein**
   e. **Laboratory documentation of *N. gonorrhoeae* or *C. trachomatis*** in the endocervix
3. **Specific criteria for a definitive diagnosis:**

a. **Endometrial biopsy**
b. **Transvaginal sonography or magnetic resonance imaging** demonstrating specific findings such as TOA and free pelvic fluid
c. **Laparoscopic findings** consistent with PID

c. **Management**
1. **Indications for hospitalization** include presence of an adnexal mass, uncertainty regarding diagnosis or compliance, pregnancy, or failed outpatient therapy.
2. **Inpatient treatment** includes intravenous cefoxitin or cefotetan plus intravenous or oral doxycycline, or intravenous clindamycin plus intravenous gentamicin.
3. **Outpatient treatment** includes single-dose intramuscular ceftriaxone and 14 days of doxycycline, with or without oral metronidazole.

4. **Urethritis.** This condition, which is defined as inflammation of the urethra, occurs more commonly in males. Females with urethritis typically have associated cervicitis.
a. **Epidemiology.** Urethritis is characterized as gonococcal (caused by *N. gonorrhoeae*) or nongonococcal (most commonly caused by *C. trachomatis*). Other causes of nongonococcal urethritis include *U. urealyticum, Mycoplasma genitalium,* HSV, and *T. vaginalis*.
b. **Clinical findings**
1. **Dysuria and increased urinary frequency**
2. **Mucopurulent urethral discharge**
3. **Asymptomatic infections are common.**
c. **Presumptive diagnosis**
1. **Mucopurulent urethral discharge**
2. **Greater than five WBCs per high-power field** on Gram stain of urethral secretions
3. **Greater than 10 WBCs per high-power field** on first-void urine specimen
4. **Positive leukocyte esterase** on first-void urine specimen
d. **Definitive diagnosis** (*C. trachomatis* or *N. gonorrhoeae*). The diagnosis is confirmed by analysis of material obtained by swabbing the urethra, or by examination of discharge, or by urine testing using methods described in sections VII.B.2.a.(2) or VII.B.2.b.(2).
e. **Management. Treatment** is the same as described in sections VII.B.2.a.(4) or VII.B.2.b.(4).

5. **Genital ulcers.** These lesions are most commonly caused by **HSV types 1 and 2, *Treponema pallidum* (syphilis), or *Haemophilus ducreyi* (chancroid)**. Clinical features, diagnosis, and management are described in **Table 3-5**.

6. **Genital warts**
a. **Epidemiology.** Genital warts are the **most common STI**.
1. **Genital warts** are caused by **HPV** and are transmitted by direct contact.
2. **HPV types 16 and 18** cause most cervical, vulvar, vaginal, and anal carcinomas, but often do not cause visible warts.
3. **External** genital warts (nononcogenic, low-risk HPV infection [**types 6 and 11**]) are also termed **condylomata acuminata**.
b. **Clinical findings**
1. **Itching, pain, and dyspareunia**
2. **Possibly visible on external genitalia**
3. **May be asymptomatic**
c. **Diagnosis**

1. **Warts** are diagnosed on direct visual inspection.
2. **Cervical cancer–causing HPV** is detected by **Pap smear,** by either conventional or liquid-based cytology tests.
3. **Special considerations. Prevalence of oncogenic HPV types is high among adolescents.** However, oncogenic HPV and squamous intraepithelial lesions caused by HPV are **more likely to regress in adolescents than in older women**.

d. **Management. Treatment is often difficult, and recurrence is common.** Therapies include topical imiquimod and trichloroacetic acid, cryotherapy, and surgical and laser removal. Twenty-five percent of genital warts spontaneously disappear within 3 months.

e. **Prevention.** Genital warts can be prevented with **HPV vaccines** [see section II.D.6] and consistent condom use.

Table 3-5
Genital Ulcers: Clinical Features, Diagnosis, and Management

	HSV-1 and -2	Primary Syphilis	Chancroid
Clinical features	Painful, multiple shallow ulcers Constitutional symptoms Inguinal adenopathy	Painless, single ulcer with well-demarcated border and clean base (chancre) Painless inguinal adenopathy	Painful, multiple ulcers with red, irregular borders and purulent bases Painful inguinal adenopathy; nodes may be fluctuant
Diagnosis	Typical lesions and one of the following: NAATs, including PCR assays. Positive HSV culture from lesion Positive DFA for HSV from lesion Elevated HSV-1 or -2 antibodies HSV on Pap smear	Typical lesion and one of the following: Reactive nontreponemal tests (VDRL or RPR) Reactive treponemal test (FTA-ABS) *Treponema pallidum* on darkfield microscopy, biopsy, or DFA of exudate or tissue	Typical lesions and positive culture for *Haemophilus ducreyi* Clinical features and negative tests for syphilis and HSV
Management	Oral acyclovir, valacyclovir, and famciclovir until resolution Severe infection with disseminated disease requires intravenous acyclovir	Intramuscular penicillin or oral doxycycline if allergic to penicillin	Oral azithromycin, erythromycin, or intramuscular ceftriaxone

HSV = herpes simplex virus; *NAAT* = nucleic acid amplification test; *PCR* = polymerase chain reaction; *DFA* = direct fluorescent antibody; *Pap* = Papanicolaou; *VDRL* = Venereal Disease Research Laboratory; *RPR* = rapid plasma reagin; *FTA-ABS* = fluorescent treponemal antibody absorption.

VIII. Menstrual Disorders

A. **Normal menstrual cycle**
   1. **Characteristics** of the **normal menstrual cycle**
      a. **Length** of menstrual cycle: 21–35 days
      b. **Duration** of menstrual flow: 2–8 days
      c. **Blood loss** during menstruation: 30–80 mL
   2. **Three phases of menstrual cycle** *(Figure 3-4)*
      a. **Follicular (proliferative) phase** begins with the onset of menstrual flow and ends with ovulation. This phase lasts 7–22 days.
         1. This phase **begins** with the pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which in turn causes the release of LH and FSH from the pituitary.
         2. **FSH** induces maturation of ovarian follicles, which produce increasing amounts of estradiol, which in turn causes endometrial thickening (proliferation).
      b. **Ovulation phase** occurs at midcycle after a **surge in LH release** secondary to peaking estradiol levels. The ruptured ovarian follicle develops into a functioning **corpus luteum**.
      c. **Luteal (secretory) phase** begins after ovulation and ends with menstrual flow. This phase lasts 12–16 days.
         1. **Progesterone,** produced by the functioning corpus luteum, creates a secretory endometrium.
         2. Without fertilization, the corpus luteum involutes. This leads to diminished progesterone and estradiol production, which in turn causes endometrial sloughing and GnRH release from the hypothalamus to start the cycle again.
   3. **Menstrual cycles** may be **irregular for 1–2 years after menarche** because of the lack of consistent ovulation.

B. **Dysmenorrhea**. This condition is the **most common menstrual disorder**.
   1. **Definitions.** Dysmenorrhea is defined as **pain associated with menstrual flow**.
      a. **Primary dysmenorrhea** refers to **pain that is not associated with any pelvic abnormality**. It is the **most common type of dysmenorrhea** during adolescence.
      b. **Secondary dysmenorrhea** refers to **pain associated with a pelvic abnormality,** such as endometriosis, PID, uterine polyps or fibroids, or a bicornuate uterus with obstruction of menstrual flow.
   2. **Etiology.** Primary dysmenorrhea is caused by **increased production of prostaglandins** by the endometrium, which results in excessive uterine contractions and systemic effects.
   3. **Clinical findings of primary dysmenorrhea**
      a. **Spasms of pain** in the lower abdomen
      b. Nausea, vomiting, diarrhea, headache, or fatigue
   4. **Management of primary dysmenorrhea.** Prostaglandin inhibitors, such as nonsteroidal anti-inflammatory agents, or oral contraceptives may be useful.

C. **Amenorrhea**
   1. **Definitions.** Amenorrhea is the **absence of menstrual flow**.
      a. **Primary amenorrhea** refers to the absence of any menstrual bleeding by **16 years of age** in an adolescent **with normal secondary sexual characteristics**, or the absence of menstrual bleeding by **14 years of age** in an adolescent **without secondary sexual characteristics**.
      b. **Secondary amenorrhea** refers to the absence of menses for either three menstrual

cycles or 6 months, **after regular menstrual cycles have been established**.

2. **Etiology.** Causes may be categorized on the basis of the presence or absence of normal genitalia and normal secondary sexual characteristics *(Table 3-6)*.
3. **Clinical evaluation**
    a. **Thorough history and physical examination,** including a pelvic examination
    b. **Pregnancy test** to confirm or rule out pregnancy
    c. **Thyroid-stimulating hormone** and **thyroxine levels** to confirm or rule out thyroid disorders
    d. **Fasting prolactin level** to identify a **prolactinoma**. If the prolactin level is high, neuroimaging is necessary to exclude a tumor of the sella turcica.
    e. **FSH and LH levels**
        1. **High FSH and LH levels** indicate ovarian failure. Chromosomal analysis should be performed to evaluate for Turner syndrome.
        2. **Low FSH and LH levels** indicate hypothalamic or pituitary suppression or failure. Visual fields and neuroimaging of the sella turcica should be performed to exclude tumor.

D. **Abnormal vaginal bleeding**

1. **Definitions**
    a. **Abnormal uterine bleeding (AUB)** causes **90%** of abnormal vaginal bleeding in adolescents. **AUB** describes a syndrome of **frequent, irregular menstrual periods,** often associated with **prolonged, painless bleeding**.
    b. **Polymenorrhea** is uterine bleeding that occurs at **regular intervals of <21 days**.
    c. **Menorrhagia** is **prolonged or excessive** uterine bleeding that occurs at **regular intervals**.
    d. **Metrorrhagia** is uterine bleeding that occurs at **irregular intervals**.
    e. **Menometrorrhagia** is **prolonged or excessive** uterine bleeding that occurs at **irregular intervals**.
    f. **Oligomenorrhea** is uterine bleeding that occurs at **regular intervals** but **no more often than every 35 days**.
2. **Etiology**
    a. **AUB** may result from **anovulatory cycles**.
        1. **The endometrium** becomes excessively thickened and unstable because of unopposed estrogen production.
        2. **Ovulation does not occur,** so progesterone is not available to stabilize the endometrium.
        3. **Bleeding** occurs spontaneously and frequently, and it is often prolonged because of unorganized, weaker-than-usual uterine and vascular contractions.
        4. **Many conditions** that cause amenorrhea, such as stress, drug abuse, chronic illness, thyroid disease, weight loss, excessive exercise, and polycystic ovary syndrome, may also cause AUB.
    b. **Complications of pregnancy,** including threatened or incomplete abortion, and ectopic pregnancy
    c. **Infections,** such as PID and cervicitis
    d. **Blood dyscrasias,** such as **von Willebrand disease** and immune thrombocytopenic purpura
    e. **Cervical or vaginal polyps** and hemangiomas
    f. **Uterine abnormalities,** including leiomyoma and endometriosis
    g. **Medications,** including salicylates, oral contraceptives, and anabolic steroids
    h. **Foreign bodies,** such as IUDs, retained condoms, or tampons
    i. **Trauma or sexual assault**

3. **Clinical evaluation**
    a. **History** should document the dates of the last three menstrual cycles, age at menarche, prior menstrual patterns, presence or absence of pain, and amount of bleeding.
    b. **Physical examination** should include a pelvic examination if bleeding is painful, prolonged, or associated with anemia or if the adolescent is sexually active. If the patient has never been sexually active, an external genital examination is important to document normal anatomy and vaginal bleeding.
    c. **Laboratory testing,** in most cases, should include a complete blood count, pregnancy test, evaluation for *N. gonorrhoeae* and *C. trachomatis*, and evaluation for a blood dyscrasia if very heavy bleeding is present within the first year of menarche resulting in severe anemia.
4. **Management. Treatment of AUB** involves cessation of bleeding, treatment for anemia, and prevention of endometrial hyperplasia.
    a. **Hormonal therapy should be used for all bleeding associated with anemia.** Combination oral contraceptives (COC) or progestin-only contraceptives are used to stabilize the endometrium and convert it to a secretory type. Intravenous hormonal therapy may be required for severe bleeding but is rarely indicated. An **oral antiemetic** may be administered before COC therapy, particularly in the first few days of treatment when two or three pills a day are required to stop the bleeding.
    b. **Iron** should be prescribed for patients with anemia.
    c. **Dilation and curettage** is also effective but rarely indicated in adolescents and should only be used if hormonal therapies fail.

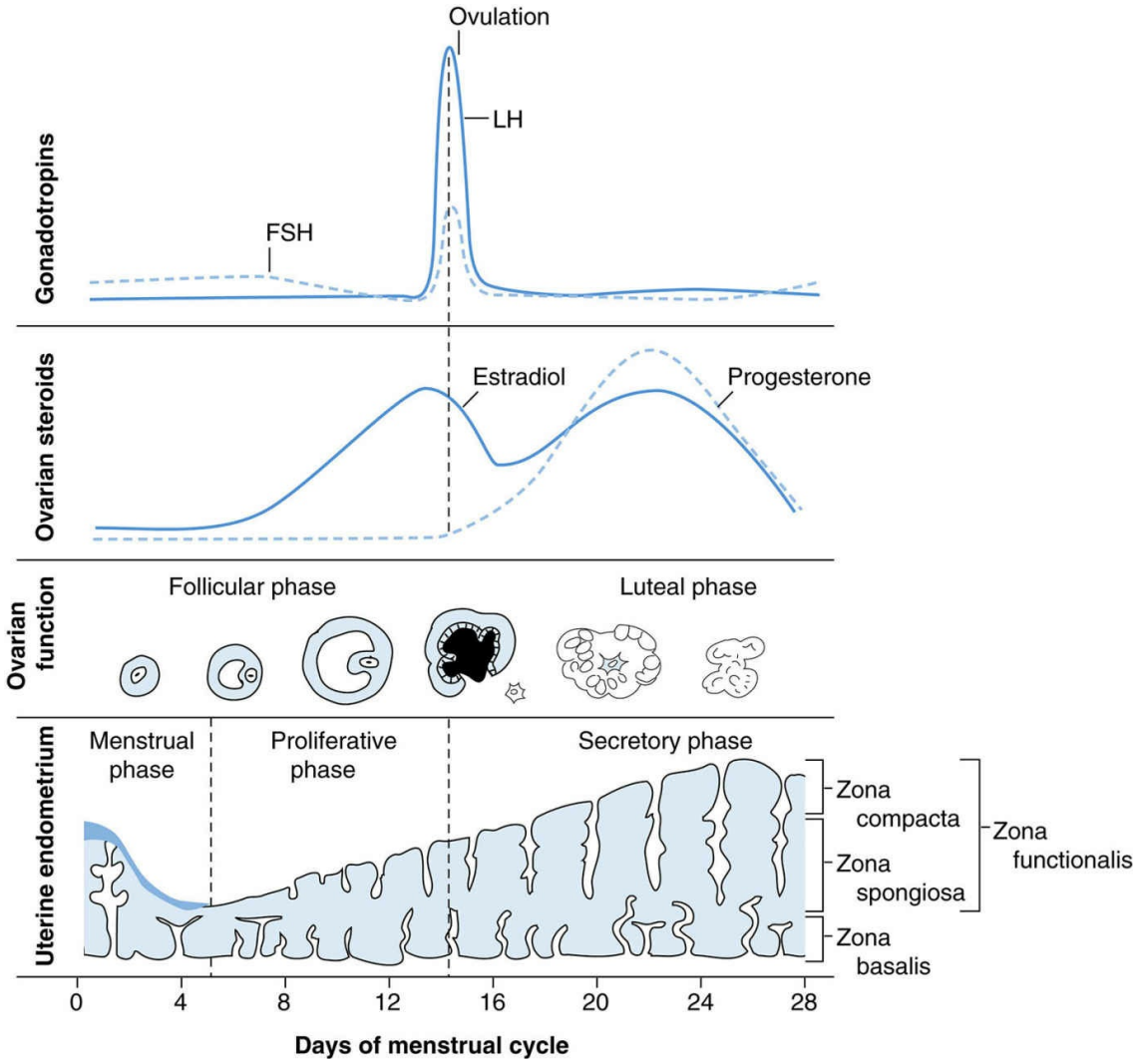


FIGURE 3.4 The menstrual cycle: pituitary, ovarian, and endometrial correlations. *FSH* = follicle-stimulating hormone; *LH* = luteinizing hormone.

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Table 3-6
Causes of Amenorrhea

Cause	Findings
Primary amenorrhea with normal genitalia and pubertal delay:	
Turner syndrome (46, XO)	Ovarian failure caused by gonadal dysgenesis
	High FSH and LH
Ovarian failure before puberty caused by radiation, chemotherapy, or infection	**High FSH and LH**
Hypothalamic or pituitary failure before puberty	**Low FSH and LH**
Primary amenorrhea with absent uterus and normal pubertal development:	
Testicular feminization syndrome (46, XY): X-linked defect in androgen receptor leading to inability to respond to testosterone	Female genital appearance; vagina ends in blind pouch; inguinal or intra-abdominal testes
	Low FSH and LH
Mayer–Rokitansky–Küster–Hauser syndrome (46, XX)	Vagina and uterus are congenitally absent
	Normal FSH and LH
Primary or secondary amenorrhea with normal genitalia and normal pubertal development:	
Hypothalamic suppression	**Low FSH and LH**

Medications and drug abuse Stress and chronic illness Exercise or weight loss	
Polycystic ovary syndrome	**High LH and high LH/FSH ratio**
	Obesity, hirsutism, and acne
Pituitary infarction (Sheehan syndrome) or pituitary failure	**Low FSH and LH**
Prolactinoma	**Low FSH and LH, high prolactin;** prolactin inhibits GnRH release
	Headache, visual field defect
Outflow tract obstruction Imperforate hymen Transverse vaginal septum Uterine adhesions	**Normal FSH and LH**
Premature ovarian failure	**High FSH and LH**
Pregnancy	
Endocrine disorders Thyroid disease Diabetes mellitus	

FSH = follicle-stimulating hormone; *LH* = luteinizing hormone; *GnRH* = gonadotropin-releasing hormone.

IX. Reproductive Health Issues in Males

A. **Gynecomastia** is a bilateral or unilateral increase in the glandular and stromal breast tissue normally found in up to **60% of male adolescents during puberty**.
   1. **Etiology is unknown.** However, gynecomastia is probably caused by increased sensitivity to estrogen, or increased peripheral conversion of adrenal androgens to estrogen.
   2. **Although gynecomastia is usually normal during puberty, the differential diagnosis** includes side effects of medications, testicular tumors, illicit drug use, anabolic–androgenic steroids, and thyroid and liver disease.
   3. **Laboratory studies are not necessary** if growth is normal, the adolescent is healthy, and puberty has begun.
   4. **Management** involves **reassurance**. Gynecomastia usually resolves within 12–15 months. Rarely does this condition require psychological and surgical intervention.

B. **Painful scrotal masses**
   1. **Torsion of the spermatic cord** is the **most common** and **most serious cause** of acute painful scrotal swelling.
      a. **Clinical findings**
         1. **Sudden onset** of scrotal, inguinal, or suprapubic pain, often accompanied by nausea and vomiting
         2. **Swollen, tender testicle** and scrotal edema with **absent cremasteric reflex on the affected side**
         3. **Pain relief** on elevation of twisted testicle, although this is often unreliable
      b. **Epidemiology.** Testicular torsion of the spermatic cord is the most common cause of testicular pain in *boys aged 12 years or older* and is uncommon in younger boys.
      c. **Diagnosis** is usually made by history and physical examination alone, although torsion may be confirmed by **decreased uptake** on **technetium 99m pertechnetate radionuclide scan** or **absent pulsations** on **Doppler ultrasound** of the scrotum.
      d. **Management** includes **surgical detorsion** of the involved testicle and **fixation of both testes** within the scrotum (the opposite testicle also has a high likelihood of torsion). Detorsion is a **urologic emergency that must be performed within 6 hours to reliably preserve testicular function**.
   2. **Torsion of the testicular appendage** may be confused with torsion of the spermatic cord.
      a. **Clinical findings**
         1. **Acute or gradual onset** of pain in testicular, inguinal, or suprapubic areas. Tenderness is most pronounced at the upper pole of the testicle.
         2. **"Blue dot sign"** on examination of the scrotum. This represents the cyanotic appendage visible through the skin of the scrotum.
      b. **Epidemiology.** Torsion of the "appendix testis" is the most common cause of testicular pain in *boys between 2 and 11 years of age* and is relatively rare in adolescents.
      c. **Diagnosis** is usually made by history and physical examination alone. **Doppler ultrasound and radionuclide scans** are **normal** or show **increased flow or uptake**.
      d. **Management** includes rest and analgesia. Pain usually resolves within 2–12 days.
   3. **Epididymitis** is infection and inflammation of the epididymis, occurring most commonly in sexually active males.
      a. **Etiology.** Epididymitis is most commonly secondary to infection with *N. gonorrhoeae* or *C. trachomatis.*
      b. **Clinical findings**

1. **Acute onset** of scrotal pain and swelling associated with urinary frequency, dysuria, or urethral discharge
2. **Swollen, tender** epididymis
3. **Elevation of the testis may relieve pain (positive Prehn sign).**

c. **Diagnosis** is made by urinalysis demonstrating increased WBCs, a positive Gram stain, and a positive NAAT of urine or urethral discharge. Doppler ultrasound shows **increased flow,** and a radionuclide scan demonstrates **increased uptake**.

d. **Management** is similar to that for cervicitis [see sections VII.B.2.a.(4) and VII.B.2.b.(4)]. In addition, analgesics and bed rest are appropriate. Patient should refrain from sexual intercourse for 7 days after treatment. Partners should be notified, evaluated, and treated.

C. **Painless scrotal masses**

1. **Testicular neoplasms** originate from germ cells within the testicle and are **one of the most common malignant solid tumors** in males 15–35 years of age. **Cryptorchidism** refers to testes that fail to descend into the scrotum, and this condition is associated with a higher risk of malignancy on both the affected side and the contralateral side.
   a. **Clinical findings**
      1. **Firm, irregular, painless** nodule on testicle
      2. **Solid mass** seen on scrotal transillumination
   b. **Diagnosis and evaluation**
      1. **Doppler ultrasound** of scrotum
      2. **Evaluation for serum tumor markers human chorionic gonadotropin** and **α-fetoprotein**
      3. **Evaluation** *for distant metastasis*
   c. **Management** includes surgery, radiation, and chemotherapy.
2. **Indirect inguinal hernia** occurs when the processus vaginalis fails to obliterate. This results in a defect within the abdominal wall that allows bowel to extend through the internal inguinal ring.
   a. **Clinical findings** include a **painless inguinal swelling**. Bowel sounds may be present on auscultation of the scrotum.
   b. **Diagnosis** is based on history and physical examination.
   c. **Management** includes referral for elective repair. Emergent referral is necessary if evidence of bowel incarceration is noted (erythema of overlying skin, pain, and tenderness).
3. **Hydroceles.** These are collections of fluid within the tunica vaginalis.
   a. **Clinical findings** include the presence of a **painless, soft, cystic** scrotal mass that may be smaller in the morning and larger in the evening.
   b. **Diagnosis** is based on history and physical examination. **Transillumination** of scrotum reveals a cystic mass.
   c. **Management** includes reassurance. If the hydrocele is very large or painful, referral for surgical repair is indicated.
4. **Varicoceles** result from dilation and tortuosity of veins in the pampiniform plexus. Varicoceles occur in **10–20%** of male adolescents.
   a. **Clinical findings**
      1. **Most commonly found in the left half** of the scrotum
      2. **Characterized as a "bag of worms"** appreciated on palpation, which diminishes in size when the patient is supine and enlarges with standing and with the Valsalva maneuver
   b. **Diagnosis** is based on history and physical examination.
   c. **Management** includes reassurance. If the varicocele is painful or very distended, or

is associated with a small testicle (indicative of diminished blood flow), urology referral is indicated.

Review Test

1. A 12-year-old boy has been brought to your office by his mother who is concerned that her son has not developed any signs of puberty. She recalls that her older daughter began pubertal development when she was younger than her son is now. Which of the following is correct regarding the normal sequence of pubertal development in males and females?
   A. Pubic hair growth is the first sign of puberty in females.
   B. Pubic hair growth is the first sign of puberty in males.
   C. Puberty begins in males approximately 12–18 months later than in females.
   D. Facial hair growth in males begins at the same time as pubic hair growth.
   E. Menarche occurs at the same time as thelarche.
2. A 15-year-old girl presents for a routine health care visit. During your HEADDSSS assessment (home, education and employment, activities, diet, drugs, sexual activity, suicide and depression, safety), she reveals that she has been sexually active with one partner (her current boyfriend). You emphasize the importance of effective contraception. Which of the following methods of contraception is associated with the highest failure rate with typical use?
   A. Oral contraceptive
   B. Intrauterine device
   C. Depomedroxyprogesterone acetate
   D. Female condom
   E. Male condom
3. A healthy-appearing short 15-year-old girl presents with primary amenorrhea, normal genitalia, and delayed pubertal development. Follicle-stimulating hormone and luteinizing hormone levels are high. Which of the following tests is most useful in diagnosing the most likely cause of her amenorrhea?
   A. Karyotype
   B. Prolactin level
   C. Thyroid function tests
   D. Pregnancy test
   E. Computed tomography scan of her sella turcica
4. A 10-year-old boy has had worsening left scrotal pain for the past 24 hours, a tender left testicle, and a bluish discoloration visible through his scrotal skin. Which of the following is correct regarding the evaluation and management of his scrotal pain?
   A. Urinalysis will demonstrate increased white blood cells.
   B. Cremasteric reflex will be absent on the affected side.
   C. Pain medication should be prescribed and bed rest recommended because this condition will resolve without surgical intervention.
   D. Immediate surgical intervention is indicated.
   E. Technetium 99m pertechnetate scan will show decreased uptake.
5. You are evaluating a 16-year-old girl who has had vaginal discharge for 5 days. Examination reveals purulent endocervical discharge. Her abdomen is nontender, she is afebrile, and she denies abdominal pain. Gram stain of the discharge reveals intracellular Gram-negative diplococci. Which of the following is the most appropriate treatment?
   A. Oral azithromycin
   B. Intramuscular ceftriaxone
   C. Hospitalization and treatment with intravenous clindamycin and intravenous gentamicin
   D. Intramuscular ceftriaxone plus oral azithromycin
   E. Oral penicillin plus oral doxycycline
6. A 15-year-old healthy boy presents for a routine health maintenance visit. On examination,

you note bilateral breast enlargement and sexual maturity rating 3 (Tanner stage) pubertal development. The remainder of the examination is unremarkable. Which of the following is the most appropriate next step in management?

A. Order chromosomal analysis.
B. Order studies of thyroid function.
C. Order studies of hepatic function.
D. Order a serum estrogen level.
E. Order no tests and provide reassurance that the condition will resolve spontaneously.

7. A 14-year-old girl presents with concerns that her current menstrual period, which is painless, has lasted 13 days and is associated with a moderate amount of bleeding. This menstrual period began 2 weeks after her previous period stopped, which lasted 15 days. She is not sexually active. A complete blood count reveals moderate anemia. Which of the following statements is correct regarding the management of this problem?
   A. Reassure her that her menstrual cycle is normal for her age and prescribe an iron supplement.
   B. Perform a complete pelvic examination, and if it is normal, reassure her that her condition is normal and no treatment is required.
   C. Perform an external genital examination, and if it is normal, prescribe a combined oral contraceptive.
   D. Prescribe progestin-only oral contraceptives. A genital examination is not necessary.
   E. Perform a dilation and curettage.
8. A 15-year-old girl is 9 weeks pregnant with her first child. She does not want to terminate the pregnancy and would like advice and pregnancy-related care. Which of the following statements regarding her pregnancy is correct?
   A. She is at no higher risk than other teens to eventually require public assistance.
   B. She would be expected to have a lower-than-usual risk of having a sexually transmitted infection.
   C. Her parents must be informed and provide consent for medical management of her pregnancy.
   D. Her infant would not be expected to have a higher-than-usual risk of neonatal problems.
   E. Despite her young age, she is at higher-than-usual risk of hypertension and preterm labor.
9. A 17-year-old girl is brought to your office at her parents' request. They are worried because she has had diminished interest in family activities, has been fighting more often with her parents, and is spending more time alone in her room. During the past 6 months, her school performance has worsened, and her school principal recently telephoned her parents about school absenteeism. In addition, parents have noticed that she is hanging out with a new group of friends and that her appetite seems diminished. Which of the following statements regarding the management of this adolescent is most likely to be correct?
   A. She has major depressive disorder and should be seen urgently by a psychiatrist.
   B. Reassurance should be provided, as her behavior is normal for age and psychosocial development.
   C. She should see a nutritionist with expertise in eating disorders.
   D. She should be evaluated for possible substance abuse.
   E. She and her parents should be interviewed together to uncover the cause of her problems.
10. A 16-year-old runaway adolescent presents to the free clinic with complaints of diffuse abdominal pain, fever, and nausea. She denies dysuria or vaginal discharge. On further questioning, she indicates that she has had five sexual partners during the past year and most of the time uses condoms for protection. Pelvic examination reveals moderate lower

abdominal tenderness and tenderness on palpation of her cervix and right ovary. No adnexal mass is appreciated. Which of the following statements regarding diagnosis and management is correct?

A. Hospitalization and treatment with intravenous cefoxitin and oral doxycycline are warranted.
B. Wet-mount saline microscopy will demonstrate motile protozoa, and oral metronidazole should be prescribed.
C. Outpatient treatment with oral doxycycline for 2 weeks, along with one dose of intramuscular ceftriaxone, is indicated.
D. Oral azithromycin alone should be prescribed for presumptive diagnosis of Fitz-Hugh–Curtis syndrome.
E. Outpatient treatment with single-dose oral ofloxacin and oral azithromycin is warranted after attempts are made to obtain parental consent.

11. A 14-year-old girl is brought to the office for a routine health maintenance visit. She appears very thin yet believes she is overweight and needs to lose 15–20 pounds. Her mother is concerned that her daughter frequently skips breakfast and eats only a small portion of her dinner, usually alone in her bedroom. She argues often with her parents, and she immediately goes to her room on coming home from the school or the gym. She has not started her menses. You believe that she may have an eating disorder. Which of the following is correct regarding the expected diagnosis?

A. Her menstrual cycles would be unaffected and normal.
B. Physical examination would demonstrate a lower-than-normal sexual maturity rating for age.
C. Withdrawal from friends would not occur because she will use them for support.
D. With further discussion at a subsequent medical visit, it is likely that she will gain insight into her illness and will seek treatment.
E. Her weight is likely to be 10% below her ideal body weight for age.

The response options for statements 12 and 13 are the same. You will be required to select one answer for each statement in the set.

A. *Haemophilus ducreyi*
B. *Treponema pallidum*
C. Herpes simplex virus type 2
D. Human papillomavirus
E. None of the above

For each patient, select the most likely causative organism.

1. An 18-year-old adolescent female with a single painless genital ulcer with a well- demarcated border and painless inguinal adenopathy.
2. A 16-year-old adolescent female with multiple painful ulcers with a purulent- appearing base and irregular borders as well as painful inguinal adenopathy.

Answers and Explanations

1. **The answer is C** [I.A.2]. Both puberty and somatic growth begin earlier in females. Puberty occurs 12–18 months later in males and begins with testicular enlargement. Puberty in females begins with breast development. Pubic hair begins to grow after the beginnings of breast development in females and testicular enlargement in males. Facial and axillary hair growth begins in males approximately 24 months after the growth of pubic hair begins. Menarche, the start of menstrual cycles, occurs an average of 2–3 years after thelarche, the beginnings of breast development.
2. **The answer is D** [VI.B.2.b and Table 3-4]. The female condom has the highest rate of failure with typical use among the methods listed. Failure is often related to lack of use during each episode of intercourse and lack of knowledge and awkwardness regarding proper placement. Depomedroxyprogesterone acetate and oral contraceptives are very effective contraceptive agents with low failure rates. Intrauterine devices and male condoms have a higher failure rate than hormonal contraception but are usually more effective in practice than the female condom.
3. **The answer is A** [VIII.C and Table 3-6]. This girl has primary amenorrhea, which is defined as the absence of menstrual bleeding either after 16 years of age in a girl with normal secondary sexual characteristics or, as in this case, after 14 years of age in a girl with delayed pubertal development. Disorders characterized by primary amenorrhea, normal genitalia, and delayed puberty include Turner syndrome, ovarian failure, and hypothalamic or pituitary failure. In this healthy-appearing, short girl, Turner syndrome (46, XO) is most likely, and thus a karyotype would be most useful for diagnosis. A prolactinoma and thyroid disease may result in either primary or secondary amenorrhea, but the follicle-stimulating hormone (FSH) level would be decreased or normal. A pituitary lesion would also usually result in normal or low FSH, and thus computed tomography or magnetic resonance imaging of the brain would be less useful. Pregnancy would be unlikely given the presence of pubertal delay.
4. **The answer is C** [IX.B.2]. This boy presents with classic findings of torsion of the testicular appendage, which is characterized by acute or gradual onset of scrotal pain, tenderness at the upper pole of the testicle, and a "blue dot sign" reflecting the cyanosis and torsion of the testicular appendage. This condition normally resolves without surgery, and rest and pain medication are indicated. Urinalysis is normal, and the cremasteric reflex is still present. Doppler ultrasound demonstrates normal or increased blood flow, and radionuclide imaging demonstrates normal or increased uptake on the affected side, unlike torsion of the spermatic cord.
5. **The answer is D** [VII.B.2.b]. The presence of Gram-negative intracellular diplococci confirms the diagnosis of *Neisseria gonorrhoeae* cervicitis. The correct treatment for uncomplicated cervicitis caused by *N. gonorrhoeae* includes intramuscular ceftriaxone or oral cefixime, if ceftriaxone is not available. However, any patient with *N. gonorrhoeae* also requires treatment for *Chlamydia trachomatis* because coinfection is very common. Thus, the most appropriate treatment includes therapy against *N. gonorrhoeae* and either oral single-dose azithromycin or 1 week of oral doxycycline for the treatment of presumptive *C. trachomatis.* Hospitalization is not indicated for uncomplicated cervicitis. The absence of abdominal pain or tenderness excludes pelvic inflammatory disease. Because of drug resistance, oral penicillin is inadequate for the treatment of *N. gonorrhoeae.*
6. **The answer is E** [IX.A]. Gynecomastia, the development of breast tissue, occurs in up to 60% of males during puberty. If a male adolescent is healthy and is progressing normally through puberty, as in this case, no laboratory tests are necessary, and reassurance alone is sufficient management. Neither an estrogen level nor a karyotype would be useful in light of a male

sexual maturity rating of 3. Although thyroid and liver disorders may result in breast enlargement, other signs or symptoms suggesting a systemic disease would likely be apparent on history or physical examination.

7. **The answer is C** [VIII.D.3 and VIII.D.4]. This girl likely has abnormal uterine bleeding (AUB), the cause of 90% of abnormal vaginal bleeding in adolescence. She is also moderately anemic, and as a result, needs hormonal therapy to stop the bleeding and regulate her menstrual cycles. Because of her moderate anemia, an external genital examination should be performed to rule out other causes of abnormal vaginal bleeding before prescribing hormonal therapy. A complete pelvic examination is not indicated because she is virginal. Either a daily progestin-only contraceptive or a combination oral contraceptive would be effective in stopping her bleeding. Dilation and curettage is rarely indicated and only performed when other therapies fail.
8. **The answer is E** [VI.A.2]. Adolescent pregnancy dramatically affects both the mother and infant. Teens who are pregnant are at a higher-than-usual risk of hypertension, anemia, and preterm labor. In addition, adolescent mothers have a high rate of not completing high school, have a higher-than-average rate of unemployment, and often need welfare assistance. Adolescents who are pregnant are also at a higher risk for sexually transmitted infections. In the majority of states, adolescents are entitled to seek pregnancy-related care without parental consent. Their infants are at higher-than-average risk for health problems, such as low birth weight.
9. **The answer is D** [IV.C]. The signs and symptoms of substance abuse include disturbance in mood or sleep, decline in school performance, truancy, alterations in family relationships and peer groups, and diminished appetite. These behaviors are not normal at any age. This adolescent does not meet the criteria for major depressive disorder, although depression can occur with, and result from, substance abuse. Decreased appetite alone is insufficient to diagnose anorexia nervosa or bulimia nervosa. Although both the adolescent and her parents may be interviewed jointly, she should also be interviewed independently to facilitate rapport and discussion of confidential issues.
10. **The answer is A** [VII.B.3]. The constellation of clinical findings, including lower abdominal pain and tenderness, adnexal tenderness, and cervical motion tenderness, are sufficient to make a clinical diagnosis of pelvic inflammatory disease (PID). Although many cases of PID can be effectively treated as an outpatient with oral medications, hospitalization is indicated for situations in which compliance with therapy may be problematic, as in a homeless or runaway adolescent. In addition, hospitalization is warranted for pregnant teens with PID, for those who have an adnexal mass suggesting a tubo-ovarian abscess, or for those who fail outpatient management. This patient's clinical findings are not consistent with *Trichomonas vaginalis,* which is diagnosed by a nucleic acid amplification test (NAAT) or wet-mount saline preparation, nor with Fitz-Hugh–Curtis syndrome (perihepatitis), which presents with right upper quadrant pain.
11. **The answer is B** [Table 3-3 and V.B]. This girl's history of low body weight, disturbed body image, and withdrawal from her family are consistent with anorexia nervosa. In addition to these characteristics, patients with anorexia nervosa also have amenorrhea, a weight 15% below an ideal body weight for age, an intense fear of gaining weight, delays in puberty and growth, and a preoccupation with food and excessive exercise to burn calories. In addition to withdrawal from family, teens with anorexia nervosa often withdraw from friends. Insight into the illness is lacking, and management of eating disorders is very challenging. Input from nutritionists and therapists and the involvement of a supportive family are essential.
12. **The answers are B and A, respectively** [Table 3-5]. Genital ulcers may be caused by chancroid (infection with *Haemophilus ducreyi*), syphilis (infection with *Treponema pallidum*), or herpes simplex virus types 1 and 2. Syphilis is characterized by a single painless ulcer that has a well-

demarcated border and a nonpurulent base (a chancre). In contrast, chancroid is characterized by painful ulcers that have irregular borders and a purulent base. Inguinal adenopathy is present in both diseases; however, it tends to be painful in chancroid and painless in syphilis. Herpes simplex virus also causes multiple painful shallow ulcers, but the base is nonpurulent. Human papillomavirus causes genital warts, not ulcers.

CHAPTER 4

Neonatology

David J. McCulley

I. Evaluation of the Newborn

Features of the newborn history and physical examination that differ from those of children and adolescents include the following:

A. **Pregnancy and maternal history. Information from the maternal record informs the assessment and care for all newborn infants.**
   1. **Maternal history:** age, gravidity, parity, prenatal laboratory studies, maternal obstetric history, and maternal medical history, including medications taken during the pregnancy
   2. **Pregnancy history:**
      a. Estimation of gestational age and evaluation of fetal growth
      b. Studies during pregnancy: genetic testing, fetal anomaly ultrasound or echocardiogram results
      c. Complications of gestation: twin gestation, fetal growth restriction (FGR), preeclampsia or premature onset of labor
   3. **Labor history:** spontaneous or induced labor, fetal monitoring during labor, need for and type of anesthesia, medications given during labor, risk of perinatally acquired infection, and need for instrumented or surgical delivery

B. **General appearance and initial assessment**
   1. Careful observation is necessary to assess respiratory, cardiovascular, and neurologic status immediately after birth. Evaluation should include work of breathing, perfusion, color, passive muscle tone, spontaneous activity, and response to stimulation. Abnormal signs should be noted, including central cyanosis (i.e., trunk, lips, tongue), increased work of breathing, poor perfusion, meconium staining, and depressed level of activity.
   2. **The need for advanced resuscitation** is indicated for the following:
      a. Abnormal response to routine stabilization and resuscitation
      b. Problems associated with preterm gestation
      c. Issues that require additional intervention, including congenital malformations
   3. When indicated, resuscitation should follow the **Neonatal Resuscitation Program** (**NRP**) **guidelines**.
   4. **Apgar scores** (**Table 4-1**) are a simple, systematic means of assessing objective data that indicate intrapartum stress and neurologic depression in newborns.
      a. Apgar scores are calculated at 1 and 5 minutes after birth, and additional scores are calculated every 5 minutes until a score ≥7 is obtained.
      b. The 1-minute Apgar score correlates with the infant's status at the beginning of the resuscitation, whereas the 5-minute Apgar score indicates the infant's progress in response to the resuscitation.
      c. The 1- and 5-minute Apgar scores do not predict long-term neurologic outcome.

C. **Neurologic examination** should include level of alertness, responsiveness to stimulation, spontaneous breathing, spontaneous movements, passive and active muscle tone, and primitive reflexes (see Chapter 2, Table 2-2).

D. **Craniofacial examination** should include head size, shape, and symmetry of facial features, while noting congenital malformations.
   1. **Head** examination should note size, shape, fontanels, and evidence of trauma.
      a. **Head size**
         1. **Microcephaly**, defined as **head circumference 2 standard deviations below the mean** or **below the third percentile** for gestational age, may be familial or caused by structural brain malformations, genetic syndromes, congenital infections (e.g., cytomegalovirus, toxoplasmosis), or fetal exposure to illicit

drugs, alcohol, or environmental toxins (see Chapter 1, section II.B.2.b).

2. **Macrocephaly,** defined as **head circumference 2 standard deviations above the mean** or **above the 97th percentile for gestational age**, may be caused by increases in any component of the cranium (brain, cerebrospinal fluid, or blood). Examples include increased intracranial pressure, increased brain tissue (megalencephaly, typically from metabolic or familiar causes), or an arteriovenous malformation.

b. **Cranial trauma can occur during both spontaneous deliveries and instrumented deliveries.**

1. **Caput succedaneum** (Figure 4-1) is a common finding and consists of a **midline** or **diffuse soft tissue swelling of the scalp** that "**crosses the cranial sutures**" (i.e., because the swelling is extrinsic to the bone, involvement can spread across a cranial suture line).
2. **Cephalohematoma** is a **subperiosteal hemorrhage** that is "**limited by the cranial sutures**" (i.e., because the hemorrhage is subperiosteal, and the periosteum is tacked down at the suture line, a cephalohematoma is well demarcated at the suture line and cannot spread beyond the cranial suture). Cephalohematomas usually involve the parietal or occipital bones (see Figure 4-1).
3. **Subgaleal hemorrhage** is rare, but can occur after **vacuum delivery,** and is caused by **shearing of the emissary veins.** Hemorrhage occurs into the space between the periosteum and scalp aponeuroses. It presents as a boggy swelling over the scalp with extension down the neck. **Subgaleal hemorrhage may be life-threatening, as massive blood loss may occur.**

c. **Fontanels and sutures** (see Chapter 1, section II.B.2, and Figure 1-3)

d. **Craniosynostosis** is premature fusion of the cranial sutures that may result in **abnormal head shape and size,** and can cause neurologic impairment if space for brain growth is inadequate (see Chapter 1, section II.B.2.d).

e. **Craniotabes** is **thinning or softening of the skull** with a "Ping-Pong ball" feel. It most commonly involves the parietal bone of premature infants, or term infants who have metabolic syndromes, although it can be observed in healthy term infants. Craniotabes typically self-resolves within weeks to months.

2. **Ears** should be examined for preauricular tags or sinuses, appropriate shape, rotation, and location, and to assess maturity. By term, the ears are firm and have assumed their characteristic shape.
3. **Eyes** should be examined for position, spacing, sloping, and evidence of trauma, with attention to the conjunctiva and sclera as well as the pupils, including response to light. An abnormal **red reflex** may be caused by cataracts, congenital glaucoma, retinoblastoma, or severe chorioretinitis.
4. **Nose** should be examined immediately for symmetry and evidence of **patency,** as **infants are predominantly obligate nasal breathers.** Evaluate for unilateral or bilateral **choanal atresia** by occluding the nares sequentially or by passing a nasogastric tube.
5. **Mouth** examination should include evaluation of symmetry, size, and shape.

a. **Clefting** of the lip and of the soft and hard palates is noted by inspection. A submucosal cleft, which is a cleft covered by a layer of mucous membrane, requires digital palpation to detect. Clefts may be isolated or associated with other dysmorphic features.

b. **Micrognathia**, a **small jaw**, may be isolated or associated with other findings. Consider **Pierre Robin sequence** when **micrognathia** is associated with **cleft palate, glossoptosis (downward displacement or retraction of the tongue), and**

obstruction of the upper airway (see Chapter 5, section IV.I.7).

c. **Macroglossia**, **enlargement of the tongue**, may be caused by vascular abnormalities, Beckwith–Wiedemann syndrome (hemihypertrophy, visceromegaly, macroglossia), hypothyroidism, and mucopolysaccharidosis.

d. **Neonatal teeth** are rare and typically are lower incisors. Neonatal teeth may be removed, especially if hypermobile, due to risk of impairing oral feeding, trauma, and possible aspiration of the tooth (see Chapter 1, section VI.D.1).

e. **Epstein pearls** are small, white epidermoid–mucoid cysts found on the hard palate that usually disappear within a few weeks.

E. **Neck and clavicle examination**

1. **Lateral neck** cysts or sinuses include **branchial cleft cysts** and **cystic hygromas**.
2. **Midline clefts or masses** may be caused by cysts of the **thyroglossal duct** or by **goiter** secondary to maternal antithyroid medication or transplacental passage of long-acting thyroid-stimulating antibodies.
3. **Neonatal torticollis,** an asymmetric shortening of the sternocleidomastoid muscle (SCM), may result from malposition in utero or trauma to the SCM during delivery with subsequent intramuscular hematoma formation (see Chapter 17, section II.A.1.a).
4. **Edema** and **webbing** of the neck suggest **Turner** or **Noonan syndrome**.
5. **Clavicles** should be examined for fracture. Clavicle fractures typically occur during delivery, especially in **large-for-gestational-age** (**LGA**) infants.

F. **Chest examination**

1. **Respiratory examination** should include evaluating the pattern of breathing and listening to breath sounds, noting symmetry, adequacy of air movement, and additional sounds (e.g., crackles, wheezes, stridor, and coarse breath sounds).
   a. **Respiratory distress** is diagnosed when **tachypnea** (respiratory rate > 60 breaths/minute), **increased work of breathing** (deep respirations, expiratory grunting, suprasternal/intercostal/subcostal retractions, nasal flaring), or **cyanosis** is present.
   b. Preterm infants breathe irregularly with short, apneic pauses lasting less than 5–10 seconds (**periodic breathing**) owing to immature control of breathing.
2. **Cardiac examination** should include observation of perfusion, heart rate (normal heart rate is 95–180 beats/minute and varies during feeding, sleep, or crying), rhythm, evaluation of heart sounds, including murmurs, and peripheral pulses.
   a. **Diminished femoral pulses.** Consider obstructive cardiac lesions, such as coarctation of the aorta, or depressed cardiac contractility.
   b. **Increased femoral pulses.** Consider patent ductus arteriosus (PDA).
3. **Accessory nipples**, if present, they are along the anterior axillary or midclavicular lines, and may grow because of the presence of glandular tissue in these areas.
4. **Congenital deformities,** including **pectus carinatum** (prominent and bulging sternum) and **pectus excavatum** (depressed sternum), are generally benign. **Chest asymmetry** as a result of absent or abnormal rib formation, or agenesis of the pectoralis muscle, is more serious.

G. **Abdominal examination.** Focus on size, shape, and color of the abdomen, while noting presence and quality of bowel sounds, and response to palpation.

1. **Umbilicus.** The umbilical cord should be inspected to confirm the presence of **two arteries and one vein** and the absence of a urachus [see section I.G.5]. The presence of a single umbilical artery may suggest additional congenital malformations, including heart and renal anomalies.
2. **Diastasis recti** is the separation of the left and right rectus abdominis muscles at the abdominal midline and is common, especially in premature and African American

infants. Treatment is not necessary because the condition resolves as the infant develops increased truncal tone and the rectus abdominis muscles grow.

3. An **umbilical hernia** occurs due to incomplete closure of the umbilical ring. The hernia is noticed as a soft swelling beneath the skin around the umbilicus, which often protrudes during crying or straining. Umbilical hernias occur more frequently in African American children and typically resolve spontaneously. Those that persist beyond 4–5 years of age or cause symptoms may require surgical treatment.
4. **Omphalocele and gastroschisis** [see sections XII.C.1 and XII.C.2]
5. **Persistent urachus** is due to failure of the urachal duct to close, resulting in a fistula between the bladder and the umbilicus. It typically presents with **urine draining from the umbilicus**.
6. **Abdominal masses** in the neonate may be caused by multiple abnormalities, including **hydronephrosis** (most common), multicystic kidneys, ovarian cysts, or other lesions. The **liver edge** is normally palpable 1–3 cm below the right costal margin in healthy term infants. If the liver is palpated on the left side, situs inversus or asplenia syndrome may be present.
7. The **anus** should be examined for position and patency. In some cases, an imperforate anus may not be visible. Anal patency can be confirmed with careful introduction of either a soft rubber catheter or a rectal thermometer.

H. **Genitalia examination.** The appearance of the genitalia changes with gestational age. Examination should include descriptions of the normal anatomic features while noting any anomalies.

1. **Female genitalia abnormal findings**
   a. A **hypertrophied clitoris** may result from virilization and androgen excess associated with **virilizing adrenal hyperplasia** (see Chapter 6, section III.E). Clitoral hypertrophy is also seen in **premature infants**.
   b. **Hydrometrocolpos** is caused by an **imperforate hymen with retention of vaginal secretions**. It presents as a small cyst between the labia at the time of birth, or as a lower midline abdominal mass during childhood.
2. **Male genitalia abnormal findings**
   a. **Hypospadias** is **ventral displacement** of the urethral meatus from its normal position at the tip of the penis to abnormal position at various locations along the ventral shaft. **Isolated** hypospadias is **not associated** with increased incidence of other urinary malformations; however, **hypospadias with cryptorchidism** (undescended testes) is associated with **disorders of sexual differentiation** (see Chapter 6, section III) and warrants further evaluation of the endocrine and genitourinary systems.
   b. **Epispadias** is a rare condition with displacement of the urethral meatus to the **dorsal surface** of the penis and is often associated with **bladder extrophy** (bladder protrusion from the abdominal wall with exposure of its mucosa).
   c. **Hydrocele** is a scrotal swelling caused by **fluid accumulation in the tunica vaginalis** adjacent to the testis. Although isolated hydroceles are typically asymptomatic and resolve spontaneously within a few weeks or months, some hydroceles are associated with inguinal hernias (see Chapter 3, section IX.C.3).
   d. **Cryptorchidism,** or **undescended testes**, may be associated with inguinal hernia, genitourinary malformations, hypospadias, and genetic syndromes. The testes typically descend spontaneously by 3–4 months and, in most cases, by 6 months. Testes that remain undescended are at risk of **testicular torsion, impaired fertility,** and **testicular cancer**.

I. **Spine examination.** The spine should be examined for evidence of **spina bifida,** including the

presence of hair tufts, hemangioma, lipoma, or dimples in the lumbosacral area. If a sacrococcygeal pilonidal dimple is present, a careful attempt to identify the base should be made to rule out a neurocutaneous sinus tract. A **myelomeningocele** (hernial protrusion of the cord and its meninges through a defect in the vertebral canal) may be present anywhere along the spine and is usually obvious at birth.

J. **Extremity examination.** The extremities should be examined to detect anatomic and functional abnormalities. The lack of spontaneous movements in the upper extremities may suggest fractures, infection, or brachial plexus injury.
   1. **Brachial plexus injuries:** Erb palsy and Klumpke palsy (see Chapter 17, sections I.A.1 and I.A.2)
   2. **Absence or hypoplasia of the radius** may be associated with **TAR syndrome** (*t*hrombocytopenia *a*bsent *r*adii), Fanconi anemia, and Holt–Oram syndrome.
   3. **Syndactyly** (fusion of the digits) or **polydactyly** (extra digits) may occur as isolated anomalies or as part of a genetic syndrome.
   4. **Edema** of the feet with hypoplastic nails is characteristic of **Turner** and **Noonan** syndromes.
   5. **Rocker bottom feet** is frequently seen in **trisomy 18**.
   6. The **hips** should be examined for **developmental dysplasia of the hips** (see Chapter 17, section III.A).

K. **Skin examination** findings vary with gestational age. As an example, skin texture is softer and thinner in premature infants.
   1. **Lanugo** is the thin hair that covers the skin of preterm infants and is minimally present in term infants.
   2. **Vernix caseosa** is a thick, white, creamy material that covers large areas of the skin in late preterm infants. It gradually decreases with increasing gestational age and is typically absent in postterm infants.
   3. The skin **color** is pink a few hours after birth, but **acrocyanosis** (cyanosis of the hands and feet) is frequently seen during the first 48–72 hours. In some infants, acrocyanosis can last throughout the first month of life, particularly when the infant is cold. Acrocyanosis and **cutis marmorata** (mottling of the skin with venous prominence) are common intermittent signs of the vasomotor instability characteristic of newborn infants.
   4. **Pallor** may be a sign of neonatal asphyxia, shock, sepsis, or anemia.
   5. **Jaundice** is **always abnormal if detected within the first 24 hours of birth.** Subsequently, it is frequently seen during the first few days after birth and, in most cases, is not associated with significant underlying disease, although it may require intervention [see section X].
   6. **Milia** are very small cysts formed around the pilosebaceous follicles that appear as tiny whitish papules seen over the nose, cheeks, forehead, and chin. They usually disappear within a few weeks and do not require treatment.
   7. **Slate gray patches** (hyperpigmented macules) are dark blue hyperpigmented macules over the lumbosacral area and buttocks of no pathologic significance. These areas of pigmentation are most frequently seen in Hispanic, Asian, and African American infants.
   8. **Pustular melanosis** is a benign transient rash characterized by small, dry superficial pustules or vesicles over a dark macular base. This rash is more frequently seen in African American infants. Lesions are filled with **neutrophils** and no treatment is required. Pustular melanosis must be differentiated from pathologic conditions that cause vesicular lesions, including viral infections (e.g., herpes simplex) and pustular bacterial infections.
   9. **Erythema toxicum neonatorum** is a benign rash seen most frequently in the first 72 hours after birth and characterized by erythematous macules, papules, and pustules

(resembling "flea bites") on the trunk and extremities but not on the palms and soles. The rash occurs in about 50% of full-term infants and is less common in preterm infants. Lesions are filled with **eosinophils** and no treatment is required.

10. **Nevus simplex** (or **"salmon patch"** or telangiectatic nevus) is the **most common vascular lesion of infancy.** It is composed of capillary proliferations and occurs in 30–40% of newborns as a pink macular lesion on the nape of the neck (**"stork bite"**), upper eyelids, glabella, or nasolabial region (**"angel kiss"**). It is often transient.
11. **Nevus flammeus,** or **"port wine stain,"** is a congenital vascular malformation composed of dilated capillary-like vessels (a form of capillary hemangioma), which may be located over the face or trunk and becomes darker with increasing age. Those located in the area of the ophthalmic branch of the trigeminal nerve (cranial nerve V-1) may be associated with intracranial or spinal vascular malformations, seizures, and intracranial calcifications (**Sturge–Weber syndrome**).
12. **Hemangiomas** are benign proliferative vascular tumors occurring in approximately 10% of infants. Often first noticed a few days after birth, they increase in size after birth for the next several months and subsequently resolve slowly within 18–24 months. Some hemangiomas can take years to fully resolve. **Hemangiomas that compromise the airway or functional structures (e.g., affecting vision, urination, swallowing) require intervention.**
13. **Neonatal acne** occurs in approximately 20% of newborns. It appears after 1–2 weeks of life and is virtually never present at birth. Typically, the lesions are comedones, but inflammatory pustules and papules may be present. Treatment is not necessary.

Table 4-1
Apgar Scoring System*

Score	0	1	2
Heart rate	Absent	<100 per minute	>100 per minute
Respirations	Absent	Slow, irregular	Good, crying
Muscle tone	Limp	Some flexion	Active motion
Reflex irritability (response to catheter in nose)	No response	Grimace	Cough, sneeze, cry
Color	Blue, pale	Body pink, blue extremities	Completely pink

*Five variables are evaluated at 1 and 5 minutes after birth, and each one is scored from 0 to 2. The final score is the sum of the five individual scores, with 10 representing the optimal score.

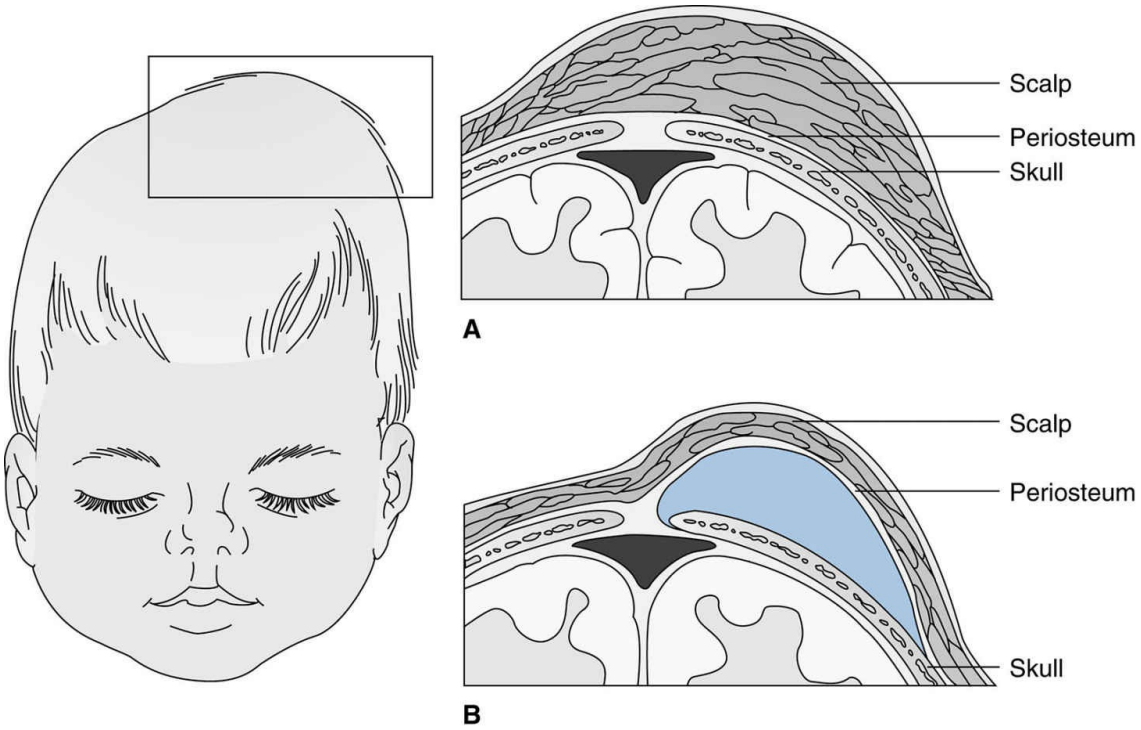

FIGURE 4.1 **A.** Caput succedaneum. From pressure of the birth canal, an edematous area is present beneath the scalp. Note how it crosses the midline of the skull. **B.** Cephalohematoma. A small capillary beneath the periosteum of the skull bone has ruptured, and blood has collected under the periosteum of the bone. Note how the swelling now stops at the midline.

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II. Abnormalities of Maturity

A. **Preterm delivery**

1. **Definition.** A **preterm delivery** is any delivery that occurs **less than 37 completed weeks from the first day of the last menstrual period.**
2. **Incidence.** Preterm delivery occurs in approximately 11% of all births; however, this figure varies widely across the United States and throughout the world. Multiple factors have been linked to increased risk of preterm birth, including young (<20 years) and advanced (>35 years) maternal age, lower socioeconomic status, lack of prenatal care, multiple gestation, and the use of assisted reproductive technology.
3. **Complications. Premature infants** may have multiple complications that affect every organ system and range from acute issues to chronic conditions that are lifelong in nature (**Table 4-2**).

B. **Postterm delivery**

1. **Definition.** A **postterm** delivery occurs **>42 weeks from the first day of the last menstrual period.** Up to 10% of deliveries occur beyond 42 weeks of gestation.
2. **Complications** include increased incidence of fetal and neonatal morbidity and death due to placental insufficiency and related severe intrauterine asphyxia, meconium aspiration syndrome (MAS), and polycythemia.

Table 4-2
Frequent Problems of Preterm Infants

Disrupted mother–father–infant interaction
Perinatal asphyxia
Hypothermia
Hypoglycemia
Hypocalcemia
Respiratory distress syndrome (hyaline membrane disease; surfactant deficiency syndrome)
Fluid and electrolyte abnormalities
Indirect hyperbilirubinemia
Patent ductus arteriosus
Intracranial hemorrhage
Necrotizing enterocolitis
Infections
Retinopathy of prematurity
Bronchopulmonary dysplasia
Anemia
Neurodevelopmental impairment

III. Growth Abnormalities

A. **Small-for-gestational-age (SGA) infants and FGR**

1. **Definition**
   a. **SGA:** Infants with a **birth weight below the 10th percentile** for their gestational age are **SGA. SGA** is a diagnosis based exclusively on the birth weight.
   b. **FGR:** Fetuses who **develop at less than their expected growth potential**, with an **estimated fetal weight below the 10th percentile** for gestational age, have **FGR. FGR** is a diagnosis made during gestation and is classified based on the pattern of intrauterine growth parameters. **Symmetric FGR** affects all growth parameters equally (head circumference, length, and weight), whereas **asymmetric FGR** affects birth weight but **preserves length and head circumference**.
2. **Etiology. Causes** of **FGR** are listed in **Table 4-3**.
3. **Clinical features. Clinical problems** of SGA infants are listed in **Table 4-4**.

B. **LGA infants**

1. **Definition.** Newborns are considered **LGA** if their birth weight is **above the 90th percentile** for gestational age. These infants should be distinguished from those with **high birth weight** (>4000 g). A newborn may be LGA with a birth weight above the 90th percentile for gestational age but not have an absolute birth weight above 4000 g.
2. **Etiology. Commonly due to** maternal diabetes. Additional causes include Beckwith–Wiedemann syndrome, Prader–Willi syndrome (see Chapter 5, section IV.E.2), and congenital hyperinsulinism (nesidioblastosis, with diffuse proliferation and dysfunction of pancreatic islet cells).
3. **Complications.** LGA infants have increased risk of **birth trauma** (such as shoulder dystocia, brachial plexus injury, and clavicular fracture), **hypoglycemia**, **polycythemia**, and **perinatal asphyxia.** LGA infants also have an increased association with **congenital malformations** and increased risk of **neonatal mortality** compared with age-matched appropriate-for-gestational age (AGA) infants.

Table 4-3
Causes of Fetal Growth Restriction

Type I: Early interference with fetal growth from conception to 24 weeks' gestation
Chromosomal anomalies (including trisomies 21, 13–15, and 18) Fetal infections (TORCH) Maternal drug use (chronic alcoholism, heroin, and cocaine) Maternal chronic illness (hypertension, severe diabetes mellitus)
Type II: Intrauterine malnutrition from 24 to 32 weeks' gestation
Inadequate intrauterine space (multiple pregnancies, uterine tumors, uterine anomalies) Placental insufficiency from maternal vascular disease (renal failure, chronic essential hypertension, collagen vascular diseases, pregnancy-induced hypertension) Small placenta with abnormal cellularity
Type III: Late intrauterine malnutrition after 32 weeks' gestation
Placental infarct or fibrosis Maternal malnutrition Pregnancy-induced hypertension Maternal hypoxemia (lung disease, smoking)

TORCH = *t*oxoplasmosis, *o*ther (syphilis), *r*ubella, *c*ytomegalovirus, *h*erpes simplex virus.

Table 4-4
Clinical Problems of Small-for-Gestational-Age Infants

Perinatal asphyxia
Hypothermia
Hypoglycemia
Polycythemia
Thrombocytopenia
Hypocalcemia
Meconium aspiration syndrome
Intrauterine fetal death
Hypermagnesemia (if the mother is treated with magnesium for hypertension or preterm labor)

IV. Cyanosis

A. **Definition.** Cyanosis is the **bluish discoloration of the skin and mucous membranes** that is directly related to the **absolute concentration of deoxygenated hemoglobin** (more than 3 g/dL of deoxygenated, reduced Hgb in the capillary blood).

B. **Clinical significance.** After birth, the **oxygen saturation in healthy term infants gradually increases over the first 10 minutes of life** and parallels the resolution of central cyanosis. **Persistent central cyanosis (trunk, lips, tongue) is an emergency** and requires immediate diagnosis and treatment. This is in contrast to **acrocyanosis (fingers, toes)** that is typical in healthy infants, is transient, and does not require further evaluation.

C. **Etiology.** The **causes** of central cyanosis are broad and include **impairments in ventilation** (e.g., central nervous system and airway abnormalities), **lung pathology** (e.g., imbalance of ventilation and perfusion, diffusion abnormalities), **right-to-left cardiac shunts** (e.g., the "5 T's" of cyanotic congenital heart disease: *t*etralogy of Fallot, *t*ransposition of the great vessels, *t*runcus arteriosus, *t*ricuspid atresia, and *t*otal anomalous pulmonary venous connection—see also Chapter 8, section IV), hematologic disorders (e.g., polycythemia), and **metabolic abnormalities** (e.g., hypoglycemia, hypocalcemia, hypothyroidism, and hypothermia). **Infection/sepsis** is also a common cause of cyanosis due to respiratory depression and lung pathology.

D. **Evaluation**

1. **Initial steps** include a detailed history and physical examination, serum electrolytes and glucose, arterial blood gas (ABG; ±100% oxygen test—see below), complete blood count (CBC), and chest radiograph (CXR). Additional tests may be warranted, including preductal (measured at the right wrist or hand) and postductal (measured in either lower extremity) oxygen saturation measurements, electrocardiogram, echocardiogram, and blood culture.
2. The **100% oxygen test (hyperoxia test):** ABG is performed before and after administration of 100% oxygen. The **hyperoxia test helps to distinguish between respiratory and cardiac causes of cyanosis**.
    a. **Hyperoxia test in infants with lung disease.** The PaO_2 **usually increases considerably** when 100% oxygen is given, often reaching levels greater than 150 mm Hg. **Cyanosis due to lung disease is typically due to ventilation–perfusion mismatch that is improved by giving 100% oxygen**.
    b. **Hyperoxia test in infants with heart disease. Cyanosis associated with congenital heart disease is due to right-to-left shunting of deoxygenated blood. Giving 100% oxygen does not significantly improve the Pa**O_2 because deoxygenated blood bypasses the pulmonary circulation. In infants with cyanotic congenital heart disease, the PaO_2 usually increases minimally (less than 10–15 mm Hg) and will almost never exceed 150 mm Hg.

E. **Management.** Immediate treatment of cyanosis may be necessary and often includes empiric administration of oxygen and correction of abnormalities of temperature, hematocrit, glucose, and calcium levels. In severely cyanotic infants, intubation and mechanical ventilation may be necessary until a diagnosis is made and definitive treatment is initiated. Infants with congenital heart disease may require treatment with prostaglandin (PGE_1) to maintain patency of the ductus arteriosus until surgical repair can be performed.

V. Respiratory Distress

A. **General concepts.** Respiratory problems are among the most common and significant causes of morbidity and mortality during the neonatal period. Some of the more common pulmonary causes of respiratory distress in the neonate include **respiratory distress syndrome (RDS;** also termed **hyaline membrane disease** and **surfactant deficiency syndrome**) in preterm infants, **transient tachypnea of the newborn** (**TTN**) from delayed clearance of fetal lung fluid in term infants during the first day of life, and **MAS** with **persistent pulmonary hypertension of the newborn** (**PPHN**) in full-term infants.

B. **Clinical features.** Manifestations include cyanosis, respiratory distress (which may be characterized by tachypnea, retractions, expiratory grunting, nasal flaring, and stridor), and decreased air entry or gas exchange. Many of these signs are nonspecific responses of the newborn to serious illness.

C. **Etiology.** Causes are extensive and involve multiple organ systems, because many conditions that produce neonatal respiratory distress are not primary diseases of the lungs (**Figure 4-2**).

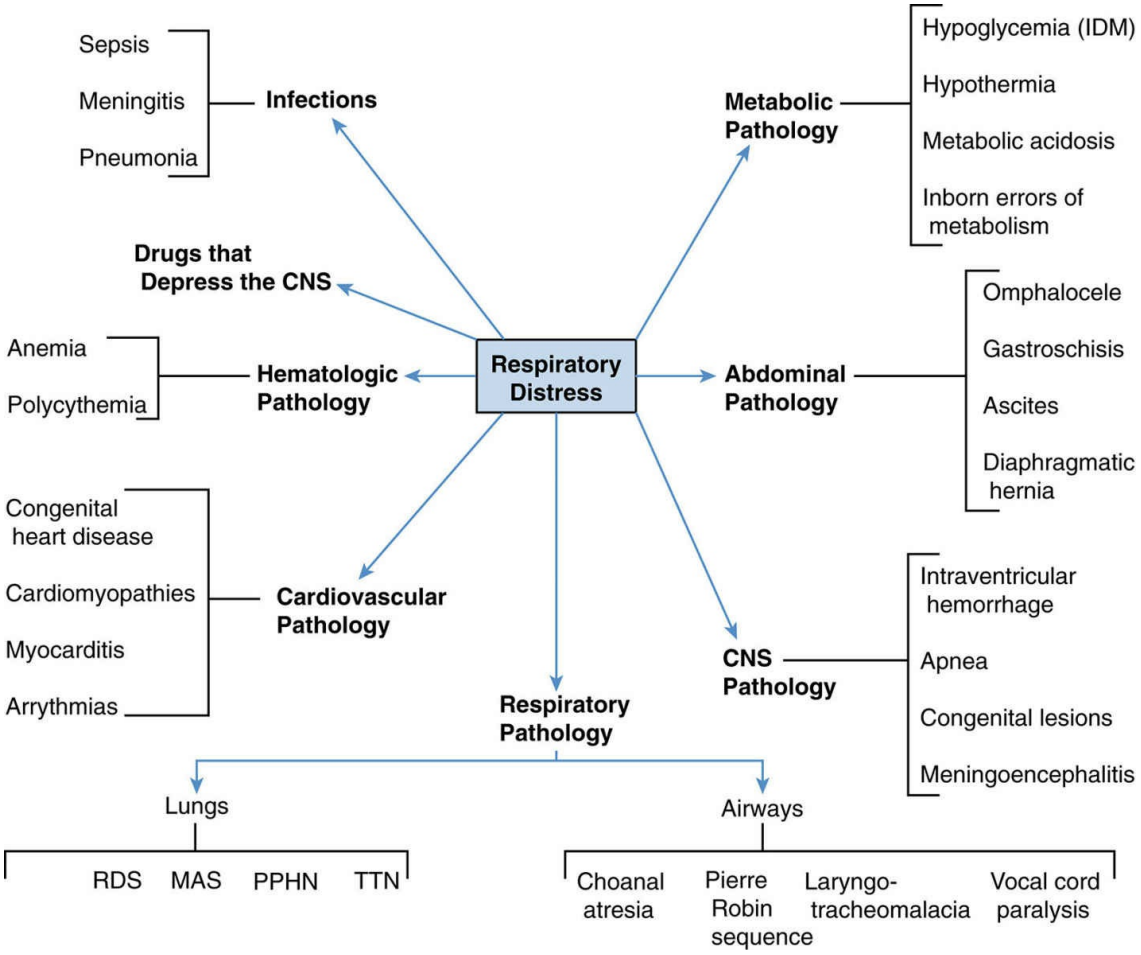

FIGURE 4.2 Differential diagnosis of respiratory distress in neonates. *CNS* = central nervous system; *RDS* = respiratory distress syndrome; *MAS* = meconium aspiration syndrome; *PPHN* = persistent pulmonary hypertension of the newborn; *TTN* = transient tachypnea of the newborn; *IDM* = infant of diabetic mother.

VI. Respiratory Distress Syndrome (RDS)

A. **Definition.** RDS is respiratory distress caused by a lack of surfactant, most frequently in preterm infants.

B. **Pathophysiology**

1. **Pulmonary surfactant** is the surface-active material that decreases alveolar surface tension and prevents atelectasis. Although surfactant is first noted in the lungs at approximately 23–24 weeks' gestation, a sufficient quantity of effective surfactant is produced only after 30–32 weeks' gestation.
2. **Assessment of fetal lung maturity** can be made by determining the presence of surfactant in amniotic fluid obtained by amniocentesis. A lecithin-to-sphingomyelin (**L:S**) **ratio** greater than 2:1 and the presence of **phosphatidylglycerol** (a minor phospholipid in surfactant) are indicators of fetal lung maturity.

C. **Epidemiology**

1. **Incidence.** RDS affects approximately 0.5% of all neonates and is the **most frequent cause of respiratory distress in preterm infants.** The incidence is **inversely related to gestational age** with greater than 90% of infants <28 weeks being affected, whereas only 10% of infants are diagnosed with RDS if born between 34 and 35 weeks. RDS is also more frequent and more severe in **white male infants.**
2. **Risk factors.** The risk of RDS increases with a low L:S ratio, prematurity, a mother with a previous preterm infant with RDS, maternal diabetes mellitus, neonatal hypothermia, and neonatal asphyxia.

D. **Clinical features.** Infants show **progressive respiratory distress** during the first 24–48 hours of life with tachypnea, retractions, expiratory grunting, and cyanosis. Symptoms are more severe and prolonged in preterm infants less than 31 weeks' gestation.

E. **Evaluation.** A **CXR** is diagnostic and shows diffuse atelectasis with a resulting pattern of **low lung volumes**, **diffuse homogeneous opacity** of both lungs with a fine, granular, **ground glass** appearance, and **air bronchograms** (darker open airways being highlighted by the surrounding brighter collapsed distal air sacs).

F. **Management**

1. **Supplemental oxygen** is often necessary.
2. **Continuous positive airway pressure (CPAP)** is used to maintain end-expiratory airway pressure, decrease atelectasis, and improve air exchange.
3. **Mechanical ventilation** via an endotracheal tube may be indicated if hypercarbia and respiratory acidosis develop.
4. **Exogenous surfactant** administered into the trachea is often curative.

G. **Complications**

1. **Acute complications** include air leaks (e.g., pneumothorax and pulmonary interstitial emphysema), intraventricular hemorrhage, and right-to-left shunting across a PDA.
2. **Chronic complications**
    a. **Bronchopulmonary dysplasia** (**BPD**). This term is often used to describe **chronic lung disease** (CLD) that can develop in preterm infants. BPD is defined as progressive pathologic changes in the immature lung that affect both the parenchyma and airways and alter normal lung growth, specifically with impairment of alveolar development. The criteria used to diagnose BPD continue to evolve and currently include the **need for supplemental oxygen or positive pressure ventilation beyond 28 days of age.** The severity of BPD is further subcategorized based on the amount of respiratory support required beyond 28 days; however, this subcategorization does not clearly predict pulmonary

outcome in later life.

b. **Retinopathy of prematurity** (see Chapter 18, section VII)

H. **Prognosis.** With aggressive treatment in an intensive care nursery, more than 90% of infants with RDS survive.

VII. Meconium Aspiration Syndrome (MAS)

A. **Definition**
   1. **Meconium** (first stools) is a material in the fetal gut consisting of water, mucopolysaccharides, desquamated skin and gastrointestinal mucosal epithelial cells, vernix, bile salts, and amniotic fluid.
   2. **MAS** describes an acute respiratory disorder caused by aspiration of meconium into the lungs of the fetus or neonate.

B. **Pathophysiology.** Meconium is often passed as a consequence of **fetal distress** (e.g., hypoxemia) in a near-term fetus and becomes more frequent after 42 weeks' gestation. The consistency of meconium-stained amniotic fluid (MSAF) varies from thin and slightly green to thick and dark green. MSAF can reach the distal airways and alveoli in utero if the fetus becomes hypoxic and develops gasping respirations, or this condition may occur at the time of birth with the first inspirations. In some infants with MSAF, aspirated meconium causes **respiratory distress** due to **mechanical obstruction** with both atelectasis and air trapping and **chemical pneumonitis** with diffuse inflammation. This combination results in **MAS**.

C. **Clinical features.** Patients with **MAS** typically present with mild or moderate respiratory distress within the first hours after birth. In severe cases, respiratory failure with profound hypoxemia and cyanosis occurs immediately after birth.

D. **Evaluation.** MAS is suggested by history of meconium noted at or before delivery and presence of respiratory distress. **CXR** reveals **increased lung volume** with **diffuse patchy areas of atelectasis** and **parenchymal infiltrates alternating with hyperinflation**. Pneumothorax or pneumomediastinum may occur.

E. **Management.** Prevention is key and requires obstetric and pediatric collaboration, including prevention of fetal hypoxemia and delivery after 41 weeks. Intrapartum suctioning of the airway has not proven to reduce the incidence of MAS; however, endotracheal suctioning of the infant to remove meconium from the airway is recommended if the infant is not vigorous at birth. **Oxygen** is usually required if MAS is present, and if MAS is severe, **mechanical ventilation** and treatment with **inhaled nitric oxide** (**iNO**) or **extracorporeal membrane oxygenation** (**ECMO**) may be necessary. Complications include persistent pulmonary hypertension of the newborn (PPHN), bacterial pneumonia, and long-term increased risk of reactive airway disease or asthma.

VIII. Persistent Pulmonary Hypertension of the Newborn (PPHN)

A. **Definition** and **pathophysiology.** PPHN is any condition other than congenital heart disease associated with abnormally **elevated pulmonary vascular resistance and decreased blood flow to the lungs** after birth. As a result, **deoxygenated blood shunts away from the pulmonary circulation** into the systemic circulation via the PDA and patent foramen ovale (PFO), a sequence that **mimics the fetal circulation** and causes **cyanosis with systemic hypoxemia**. It occurs most frequently in near-term, full-term, or postterm infants.

B. **Etiology.** Causes are extensive, but **perinatal asphyxia** and **MAS** are most common. The perinatal history is often remarkable for evidence of fetal distress.

C. **Clinical features.** Severity can **range from cyanosis to multisystem organ failure** due to inadequate oxygen delivery. PaO_2 is often significantly decreased and improves only minimally with increased supplemental oxygen. Pre- and postductal oxygen saturation and PaO_2 may be significantly different if there is large right-to-left shunt through the ductus arteriosus.

D. **Evaluation**
   1. **CXR** findings are variable because of the many causes of this syndrome. Pulmonary vascular markings are usually decreased in infants with idiopathic PPHN not caused by MAS or perinatal asphyxia.
   2. **Echocardiogram** is important to rule out congenital heart disease and to assess the degree of pulmonary hypertension, right-to-left shunting, and right ventricular function.

E. **Management**
   1. **Prevention of hypoxemia** is the cornerstone of therapy because hypoxemia is a potent pulmonary vasoconstrictor, whereas **oxygen is a potent pulmonary vasodilator.**
   2. **Mechanical ventilation** must be started early if oxygen alone is insufficient.
   3. **iNO** improves ventilation and perfusion matching while decreasing intrapulmonary shunting by **inducing pulmonary vasodilation** in well-ventilated regions of the lung.
   4. In severe cases, and for infants who do not respond to standard measures, high-frequency oscillatory ventilation (**HFOV**) and **ECMO** are necessary.

IX. Apnea of Prematurity

A. **Definition.** Apnea of prematurity is a **respiratory pause with no airflow lasting more than 20 seconds, or a respiratory pause of any duration if accompanied by bradycardia and cyanosis or oxygen desaturation** in a preterm infant. It occurs most commonly in infants less than 34 weeks' gestation.

B. **Categories of apnea.** Preterm infants can have apneic events for several reasons that are classified based on the respiratory activity observed during the event.
   1. **Central apnea** describes an episode with complete cessation of chest wall movement and no airflow. These episodes imply a lack of normal central respiratory drive.
   2. **Obstructive apnea** describes an episode with normal or increased chest wall movements and respiratory effort but without airflow. These episodes imply a normal respiratory drive that is impaired by obstruction of the airways.
   3. **Mixed apnea** is a combination of central and obstructive apnea and constitutes the **most frequent type** encountered in preterm infants.

C. **Etiology. Causes of apnea in preterm infants** include infection/sepsis, lung disease, hypothermia, hyperthermia, hypoglycemia, seizures, exposure to maternal medication or drugs of abuse, drug withdrawal, anemia, and gastroesophageal reflux, in addition to idiopathic apnea of prematurity.

D. **Idiopathic apnea of prematurity**
   1. **Incidence.** Frequency increases with decreasing gestational age, affecting 85% of infants <28 weeks' gestation and 25% of infants 33–34 weeks' gestation.
   2. **Clinical features.** Idiopathic apnea of prematurity occurs in the absence of any identifiable cause, usually appearing 24 hours after birth or during the first week of life, and resolving by 38–44 weeks' gestational age.
   3. **Management.** Idiopathic apnea of prematurity is a diagnosis of exclusion and therefore requires a search for other potential causes. Management principles include the following:
      a. Maintenance of a neutral thermal environment, treatment of hypoxia, and tactile stimulation (including rubbing the back or repositioning the infant, as needed).
      b. Acute respiratory support for severe episodes (including **bag and mask ventilation**) and chronic respiratory support to maintain adequate lung inflation (nasal **CPAP** or invasive **mechanical ventilation**) may be needed.
      c. **Respiratory stimulant medications** (**caffeine** or **theophylline**) may be used to limit the frequency and severity of apnea events.

X. Neonatal Jaundice

A. **Definition.** Jaundice is the yellow discoloration of mucous membranes and skin due to increased bilirubin levels. It usually occurs during the first week of life and is most frequently caused by indirect (unconjugated) hyperbilirubinemia that is **physiologic** in nature. **Visible jaundice** occurs in the neonate when the **serum bilirubin level exceeds 5 mg/dL**.

B. **Classification of jaundice**

1. **Physiologic jaundice.** This term describes the benign and self-limited **indirect hyperbilirubinemia** that typically resolves by the end of the first week of life and requires no treatment.
    a. **Causes of physiologic jaundice**
        1. Increased bilirubin load on hepatocytes due to breakdown of red blood cells after birth
        2. Delayed activity of the hepatic enzyme glucuronyl transferase
    b. **Clinical features** include jaundice in well-appearing infants with elevated indirect bilirubin levels. Peak serum concentrations in normal full-term infants reach 5–16 mg/dL by 3–4 days of life and begin decreasing before the end of the first week of life. In preterm infants, bilirubin levels continue to rise later than in term infants (reaching peak levels after 5–7 days) and have a more delayed and gradual decline (requiring 10–20 days before decreasing without treatment).
2. **Nonphysiologic jaundice.** This term describes jaundice that is secondary to pathophysiologic causes and may be further classified as follows:
    a. **Indirect hyperbilirubinemia** is an elevated bilirubin in which the **conjugated or direct component is <15% of the total bilirubin** level.
    b. **Direct hyperbilirubinemia** is a conjugated or **direct bilirubin level that is >15% of the total bilirubin** level. This is **always pathologic** in neonates.

C. **Differential diagnosis of indirect hyperbilirubinemia.** Possible causes include **physiologic jaundice, excessive bilirubin production, impaired bilirubin clearance, and defective conjugation** of bilirubin by the liver (**Figure 4-3**). Breastfeeding is associated with higher peak bilirubin levels compared with formula feeding, and the resulting indirect hyperbilirubinemia is of two types:

1. **"Breastfeeding jaundice"** typically occurs **during the first week of life** with increased bilirubin levels related to suboptimal milk intake. Poor intake leads to weight loss, dehydration, and decreased passage of stool. This sequence results in impaired bilirubin clearance and increased enterohepatic circulation of bilirubin.
2. **"Breast milk jaundice"** typically occurs **after the first week of life** and is likely related to breast milk's high levels of β-glucuronidase and high lipase content. In this case, the bilirubin is often highest in the second and third weeks of life; however, moderately elevated levels of bilirubin may persist until 10 weeks of life.

D. **Differential diagnosis of direct hyperbilirubinemia.** Possible diagnoses include obstruction of the hepatobiliary tree, neonatal infection, and metabolic disorders (**Figure 4-4**).

E. **Evaluation of hyperbilirubinemia** (see also Chapter 10, section XI.C)

1. **Bilirubin** is now routinely **checked in all infants at 24 hours of life** owing to the inability of visual inspection to accurately diagnose hyperbilirubinemia.
2. **Jaundice should always be evaluated under the following circumstances:**
    a. Jaundice appears at <24 hours of age.
    b. Bilirubin rises >5–8 mg/dL in a 24-hour period.
    c. The rate of rise between two sequential bilirubin measurements exceeds 0.5 mg/dL per hour (suggestive of hemolysis).

3. To evaluate **indirect hyperbilirubinemia,** infant and maternal blood types, Coombs test, CBC, reticulocyte count, and peripheral blood smear (for hemolysis) are necessary. Evaluation for sepsis may be considered.
4. To evaluate **direct hyperbilirubinemia,** hepatic and biliary ultrasound (to evaluate for biliary atresia and choledochal cyst), serologies for viral hepatitis, evaluation for metabolic disease, evaluation for α-1-antitrypsin disease, and liver biopsy may be warranted.

F. **Management**
1. **Serial bilirubin assessments, observation, and reassurance** are appropriate for **physiologic jaundice**.
2. **Phototherapy** creates water-soluble photoisomers of indirect bilirubin that are more readily excreted. Phototherapy may be indicated depending on the infant's gestational age at birth, postnatal age, bilirubin levels, and risk factors for significant jaundice and impairment of the blood–brain barrier (e.g., blood group incompatibility with hemolysis, suspected sepsis, or severe acidosis).
3. **Exchange transfusion** is performed for rapidly rising bilirubin levels and dangerously elevated bilirubin levels to prevent complications.

G. **Complications** include **acute bilirubin encephalopathy** and **kernicterus**.
1. Unconjugated bilirubin that is not bound by albumin can pass through the blood–brain barrier and produce **irreversible damage and neuronal cell death.** This typically does not happen unless the indirect bilirubin level is >25 mg/dL.
2. Bilirubin injury occurs most frequently within the **basal ganglia** and **brainstem nuclei** involved in vision, hearing, movement, language, and cognitive function.
3. **Clinical features** of **acute bilirubin encephalopathy** range from lethargy, hypotonia, and high-pitched cry to coma, apnea, seizures, and death. Rapid early treatment may prevent progression, irreversible brain injury, and **kernicterus.** Features of **kernicterus** include **choreoathetoid cerebral palsy, hearing loss,** and **oculomotor paralysis**.

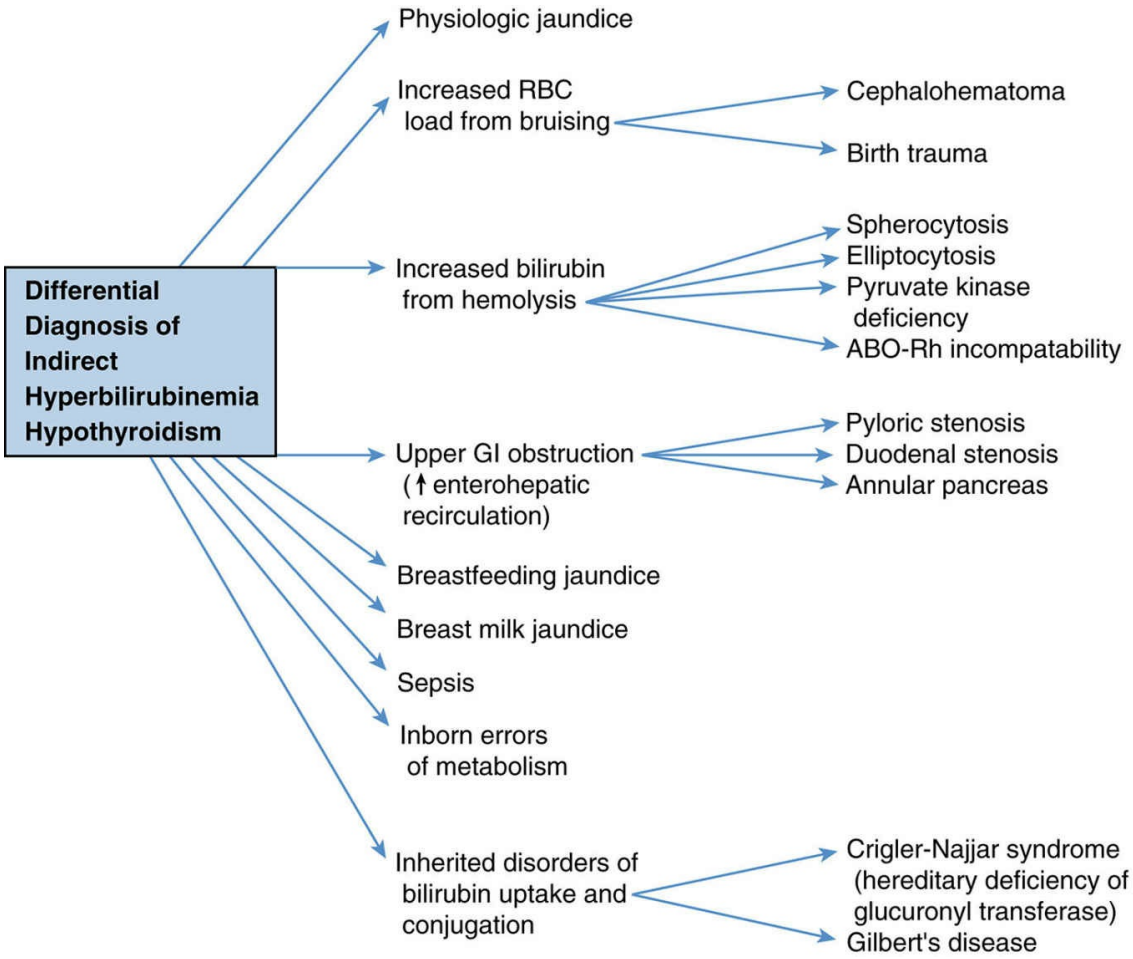

FIGURE 4.3 Differential diagnosis of indirect hyperbilirubinemia. *RBC* = red blood cell; *GI* = gastrointestinal.

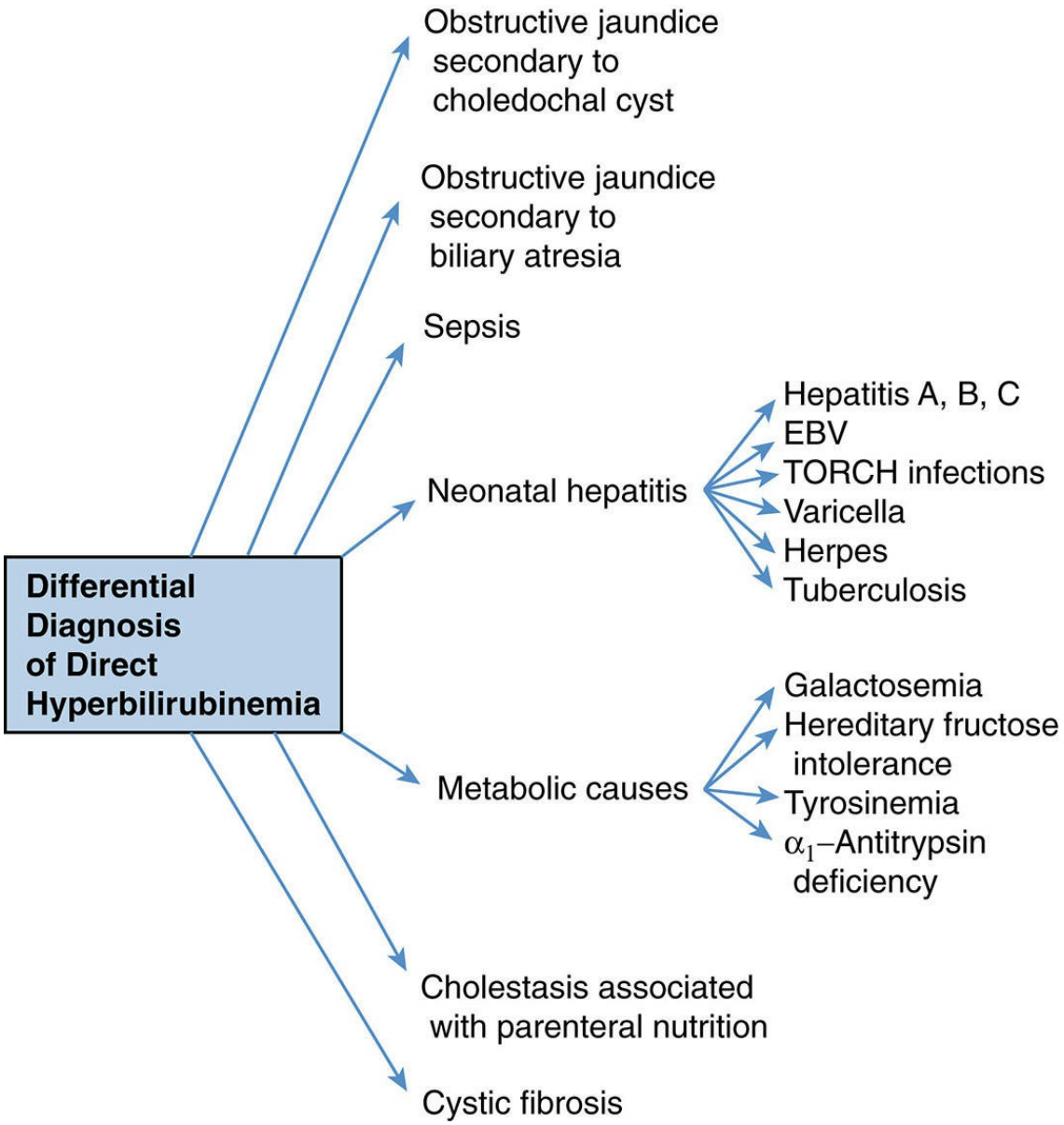

FIGURE 4.4 Differential diagnosis of direct hyperbilirubinemia. *EBV* = Epstein–Barr virus; *TORCH* = *t*oxoplasmosis, *o*ther (syphilis), *r*ubella, *c*ytomegalovirus, *h*erpes simplex virus.

XI. Fetal Exposure to Drugs of Abuse

A. **Epidemiology**
   1. **Incidence.** Fetal exposure to drugs of abuse is common: tobacco in nearly 20%, alcohol in 10%, and illicit drugs in 5% of all pregnancies.
   2. **Drugs used.** Most women who use illicit drugs take multiple drugs. Use of alcohol, cocaine, amphetamines, phencyclidine (PCP), and narcotics may compound the fetal risk in women already using tobacco, caffeine, or prescribed drugs.
   3. **Risk factors and clinical complications vary with the substance used.**
      a. **Mothers who use illicit drugs may also have** poor nutritional status, inadequate prenatal care, anemia, endocarditis, hepatitis, tuberculosis, HIV, sexually transmitted diseases, low self-esteem, and depression.
      b. **Obstetric complications** include placental abruption, precipitous delivery, and preterm labor and delivery.

B. **Clinical features** vary with the individual agent and include both **acute intoxication** and **chronic withdrawal** symptoms, as well as a combination of these problems. The most common signs are **jitteriness** and **hyperreflexia,** together with **irritability, tremulousness, feeding intolerance,** and **excessive wakefulness.** Presence of these symptoms in a neonate should alert the clinician to the possibility of drug exposure that may be identified by **toxicology screens of urine, meconium, or umbilical cord tissue**.

C. **Management** of infants born to women using drugs includes **early identification** in the neonatal period and **observation for signs of withdrawal.** Infants with fetal exposure to opiates (heroin, methadone, and related compounds) frequently require **narcotic replacement therapy** to minimize withdrawal symptoms, support feeding and weight gain, and **minimize risk of seizures.** Consultation with child protective services may be required.

D. **Infant mortality rates** range from 3 to 10%, and fetal demise can occur in utero from withdrawal. Causes of mortality include perinatal asphyxia, congenital anomalies, child abuse, and sudden infant death syndrome.

XII. Surgical Conditions of the Newborn

A. **Esophageal atresia with tracheoesophageal fistula (EA/TEF)**
   1. **Epidemiology.** This condition occurs in 1:3500 infants. The **most common type** of esophageal atresia (>90% of cases) involves proximal esophageal atresia with a distal tracheoesophageal fistula (see **Figure 4-5**).
   2. **Clinical features**
      a. **Polyhydramnios in utero in two-thirds of cases**, due to inability of the fetus to swallow amniotic fluid
      b. After birth, **copious oropharyngeal secretions with feeding difficulty,** with increased risk of choking and aspiration
      c. **Associated malformations** are found in 50% of patients with esophageal atresia, including vertebral, anorectal, cardiac, renal, and limb anomalies (VACTERL association) (see Chapter 5, section IV.I.2).
   3. **Evaluation and diagnosis.** An oral gastric tube is inserted until it meets resistance. Radiographs show the tube in the upper part of the thorax. In Esophageal atresia with distal tracheoesophageal fistula (Figure 4-5A), air that has crossed through the distal fistula from the trachea is seen in the stomach and intestine.
   4. **Management. Surgical repair** consists of ligation of the fistula and anastomosis of the two esophageal segments.

B. **Congenital diaphragmatic hernia (CDH)**
   1. **Overview.** The diaphragm develops between the fifth and eighth weeks of gestation. Abnormalities in the development of the diaphragm can allow herniation of the abdominal contents into the thorax, which in turn impairs appropriate growth and maturation of the lungs. Most cases involve the **left** diaphragm in the posterior and lateral area.
   2. **Epidemiology.** The **incidence** is 1:3500 live births.
   3. **Clinical features.** Newborns present with severe respiratory distress and **scaphoid abdomen due to displacement of the abdominal contents into the thorax.** Severe respiratory insufficiency from **pulmonary hypoplasia** and **pulmonary hypertension** is common in patients with CDH, due to mechanical compression of the lung and defective pulmonary vascular development. Breath sounds are decreased, and **bowel sounds may be heard in the chest.** The condition has a **wide spectrum of severity**.
   4. **Evaluation.** The diagnosis is often made by **prenatal fetal ultrasound,** noting the **abnormal position of the stomach** in the thorax and **rightward deviation of the heart** (in cases of left CDH). After birth, **chest radiographs reveal little or no gas in the abdomen, absence of the diaphragmatic dome, mediastinal shift to the contralateral side (usually to the right), and bowel loops in the thorax (usually on the left side).**
   5. **Management. Bag-and-mask ventilation should not be used** because this may distend the bowel and increase compression of the lung. **Intubation and mechanical ventilation with 100% oxygen should be initiated immediately.** Correction of acidosis, hypoxemia, and hypercarbia are paramount. Once the infant is stabilized, management includes **surgical reduction of the hernia and closure of the diaphragmatic defect.**
   6. **Complications and associations.** PPHN, pneumothorax, gastroesophageal reflux, intestinal obstruction, recurrent herniation, and progressive sensorineural hearing impairment may occur.
   7. **Prognosis** is worse with larger defects, presence of liver herniation into the thorax, more severe lung hypoplasia, and pulmonary hypertension. Fetal and neonatal mortality remains high (50% or greater) in infants in whom the condition is diagnosed before

25 weeks' gestation.

C. **Abdominal wall defects.** By the 10th week of gestation, the midgut enters the abdomen. If this process is disturbed, the result is an abdominal wall defect associated with a decrease in intra-abdominal volume. **Omphalocele** and **gastroschisis** are the most common defects, and both require surgical treatment.
   1. **Omphalocele** occurs in approximately 1:6000–8000 live births. The defect is a centrally localized herniation of abdominal organs through the umbilical ring with a true hernia sac (abdominal organs are **covered with a peritoneal sac**). **Omphalocele is frequently associated with other congenital anomalies,** including congenital heart defects (most commonly tetralogy of Fallot and atrial septal defects), Beckwith–Wiedemann syndrome, and chromosomal disorders (trisomy 13 or, less frequently, trisomy 18; see also Chapter 5, section IV.E.5).
   2. **Gastroschisis** is a congenital fissure of the anterior abdominal wall, usually located to the right of the umbilical cord stump (in the **right paraumbilical area**). There is no true hernia sac (**no peritoneal sac covering**), and the bowel is usually the only viscera that herniates. There is **no increased association with other extraintestinal anomalies;** however, there is an **increased incidence of other bowel abnormalities,** including malrotation and volvulus, and stenosis and atresia that are attributed to inadequate intestinal blood flow. The intestine of patients with gastroschisis may be affected by abnormalities in intestinal vascular supply or by inflammation due to exposure to the amniotic fluid. As a result, the intestine of gastroschisis patients may develop narrowed or atretic segments and cause bowel obstruction.

D. **Intestinal obstruction** may be functional or mechanical, and if mechanical, this condition may be acquired or congenital (see **Figure 4-6** for a complete differential diagnosis).
   1. Meconium is passed within 24 hours after birth in 90% of term infants and within 48 hours in 99% of term infants. **Meconium plug** is delayed passage of meconium (>24–48 hours after birth) due to **obstruction of the left colon and rectum** by dense dehydrated meconium. **Meconium plug** may occur not only in infants with **cystic fibrosis** or **Hirschsprung disease** but also in normal infants.
   2. **Intestinal atresia** is the **most common cause of obstruction in the neonatal period.** It can occur in the small or large bowel. Intestinal atresias are discussed in Chapter 10, section IV.C.
   3. **Meconium ileus** is **obstruction of the distal ileum** caused by inspissated (thickened and dried) meconium, secondary to deficiency of pancreatic enzymes. Meconium ileus is a common neonatal manifestation of **cystic fibrosis.**
      a. **Clinical features** include abdominal distension, lack of meconium passage, vomiting, and bowel perforation.
      b. **Diagnosis** is by abdominal radiographs that reveal intestinal distension with minimal air–fluid levels. Air remains trapped in the meconium; thus, there is no definite air–fluid interface. Fine gas bubbles may be seen mixed within meconium, producing a characteristic **soap-bubble** appearance.
      c. **Management** often includes an enema that may relieve the obstruction, and surgery for persistent obstruction and resection of injured bowel in cases with perforation. Early diagnosis and treatment are ixmportant to avoid intestinal perforation, meconium peritonitis, and volvulus.
   4. **Intestinal malrotation** may result in **volvulus** (loops of intestine twist if attached to a narrow band of mesentery) with restricted circulation to the rotated segment, leading to intestinal gangrene. Malrotation and volvulus are discussed in Chapter 10, section IV.B.
   5. **Hirschsprung disease,** or congenital aganglionic bowel disease, is caused by a **lack of caudal migration of the ganglion cells** from the neural crest. It results in **persistent**

contraction of a distal segment of colon, causing obstruction with proximal dilatation.

a. **Incidence** is approximately 1:5000 live births. Hirschsprung disease is five times more frequent in **male** infants, and in 80% of cases there is a family history.
b. **Clinical features** include constipation, vomiting, and abdominal distension.
c. **Diagnosis** is by **rectal biopsy revealing absence or paucity of ganglion cells.**
d. **Management** includes resection of the aganglionic segment.

E. **Necrotizing enterocolitis (NEC)**

1. **Epidemiology.** NEC is one of the most common surgical conditions in preterm neonates with an incidence as high as 8–10% in infants <30 weeks' gestation.
2. **Clinical features.** Manifestations include abdominal distension, abdominal tenderness, bilious emesis, bloody stools, and abdominal wall erythema. Cardiovascular compromise can result in metabolic acidosis and oliguria. In severe cases, NEC may progress rapidly and lead to thrombocytopenia, disseminated intravascular coagulation, and death.
3. **Diagnosis.** Classic radiographic findings include intestinal distension, thickened bowel wall, **pneumatosis intestinalis** (air in the bowel wall), and portal venous gas. Intestinal perforation results in pneumoperitoneum.
4. **Management**
   a. **Medical treatment** includes bowel rest with no oral feedings and gastric decompression, antibiotics, and parenteral fluids/nutrition. Supporting tissue perfusion with fluids and vasoactive medications may be required. Transfusion with platelets and fresh frozen plasma may also be required.
   b. **Surgical management** with exploratory laparotomy may be indicated, including for infants who develop pneumoperitoneum or necrotic bowel.
5. **Late complications** may include intestinal obstruction (e.g., adhesions, stenosis), and nutritional deficiencies (e.g., malabsorption, short gut syndrome), and cholestasis.
6. **Prevention.** The incidence of NEC is lower in preterm infants who receive enteral feedings with breast milk.

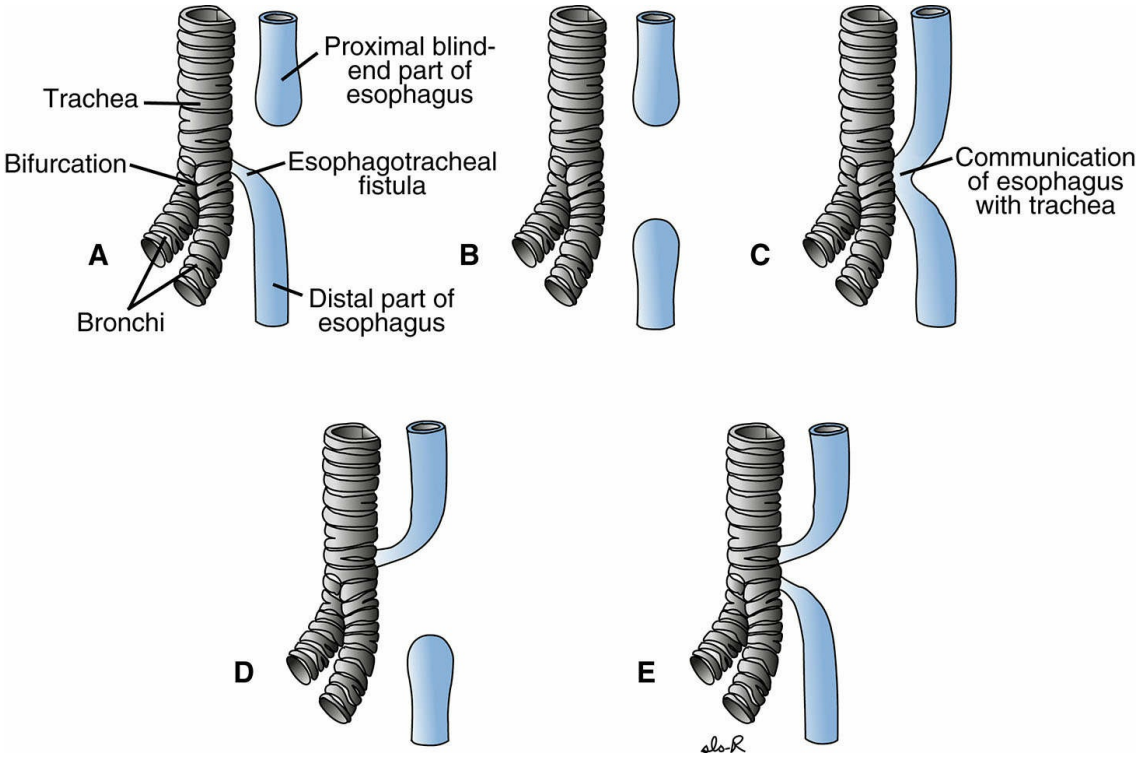

FIGURE 4.5 Types of tracheoesophageal anomalies.

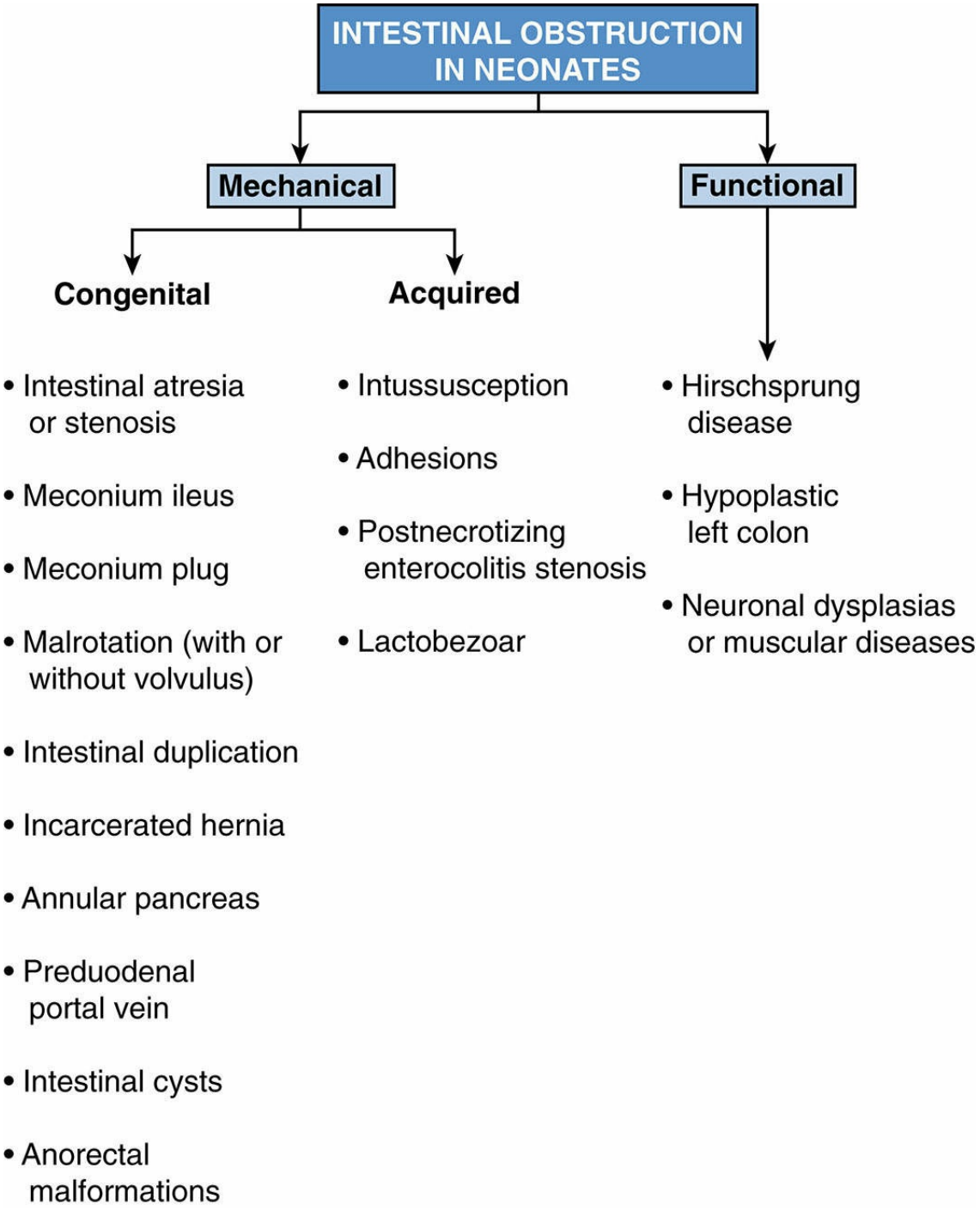

FIGURE 4.6 Differential diagnosis of intestinal obstruction in neonates.

XIII. Hypoglycemia

A. **Definition.** Hypoglycemia is defined as serum glucose concentration below 40 mg/dL.
B. **Etiology.** Causes are extensive and include the following:
    1. **Conditions that result in insulin excess. Infants of diabetic mothers (IDMs) commonly have transient hypoglycemia.** Persistent hypoglycemia may result from insulin-producing tumors or islet cell hyperplasia.
    2. **Conditions that result in diminished glucose production or substrate supply** include FGR and preterm infants, both having limited hepatic glycogen stores and immature gluconeogenesis; stressed infants who have been asphyxiated or have sepsis; infants with inborn errors of metabolism, such as galactosemia, hereditary fructose intolerance, and aminoacidopathies; and infants with endocrinopathies, such as growth hormone deficiency and panhypopituitarism.
C. **Clinical features.** The neonate may be asymptomatic or may present with diaphoresis, **jitteriness**, feeding problems, tachycardia, hypothermia, hypotonia, or **seizures**.
D. **Management.** Depending on the degree of hypoglycemia and associated symptoms or illness, interventions include either **oral feeding or intravenous glucose**.

XIV. Infants of Diabetic Mothers (IDMs)

A. **Pathophysiology.** Maternal hyperglycemia results in fetal hyperglycemia with subsequent fetal hyperinsulinemia. This causes increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis, augmented protein synthesis, and macrosomia.

B. **Clinical features**
   1. IDMs are large because of increased body fat and **visceromegaly,** primarily of the liver, adrenal glands, and heart.
   2. The skeletal length is increased in proportion to weight, but the head and face appear disproportionately small. The umbilical cord and placenta are also enlarged.
   3. IDMs appear plethoric with round facies.
   4. Although IDMs are usually LGA, they may be SGA secondary to placental insufficiency in women with severe diabetic-induced vascular complications.

C. **Complications**
   1. IDMs are at considerable risk for the perinatal difficulties summarized in **Table 4-5**.
   2. **Congenital anomalies,** such as **congenital heart disease**, are **two to four times more frequent** in IDMs than in normal infants.
   3. **Small left colon syndrome** is a condition occurring most frequently in IDMs, in which infants present with abdominal distension and failure to pass meconium secondary to the decreased caliber of their left colon.

Table 4-5
Clinical Problems of Infants of Diabetic Mothers

Increased risk before and at delivery
Sudden intrauterine death Large for gestational age Increased rate of birth trauma Increased rate of cesarean section Increased risk of asphyxia
Increased risk of common neonatal problems
Hypoglycemia Polycythemia Hypocalcemia Hypertrophic cardiomyopathy Persistent pulmonary hypertension of the newborn Respiratory distress syndrome Renal vein thrombosis
Increased risk of developing congenital malformations
Structural heart disease Central nervous system Musculoskeletal Small left colon syndrome Caudal regression syndrome (hypoplasia of the sacrum and lower extremities)

XV. Polycythemia

A. **Definition.** Polycythemia is defined as a **central venous hematocrit greater than 65%**.
B. **Epidemiology.** Polycythemia occurs in 2–4% of infants born at sea level.
C. **Etiology.** Causes include increased erythropoietin secretion secondary to placental insufficiency, increased red blood cell production by the fetus in response to hypoxemia, or increased placental transfusion from delayed cord clamping.
D. **Clinical features.** Manifestations include plethora, poor perfusion, cyanosis, poor feeding, respiratory distress, lethargy, jitteriness, seizures, renal vein thrombosis, and metabolic acidosis. There is an increased risk of NEC.
E. **Management.** Treatment includes **partial exchange transfusion,** in which blood is removed and replaced by the same volume of plasma substitute (normal saline).

Review Test

1. Soon after birth, a term newborn infant presents with increased oral secretions and mild respiratory distress. Which of the following is the most likely diagnosis?
   A. Persistent pulmonary hypertension of the newborn
   B. Pneumonia
   C. Esophageal atresia
   D. Respiratory distress syndrome (surfactant deficiency syndrome)
   E. Diaphragmatic hernia
2. An abdominal mass is detected on examination of a 2-day-old infant in the newborn nursery. Which of the following is the most likely cause of this abdominal mass?
   A. Ovarian cyst
   B. Hydronephrosis
   C. Wilms tumor
   D. Multicystic kidney
   E. Hydrometrocolpos
3. The parents of a 5-day-old term infant notice that he is jaundiced. Your physical examination is remarkable only for scleral icterus and jaundice. The infant's total bilirubin level is 15 mg/dL, with a direct component of 0.4 mg/dL. Which of the following is the most likely diagnosis?
   A. Breastfeeding jaundice
   B. Choledochal cyst
   C. Biliary atresia
   D. Neonatal hepatitis
   E. Breast milk jaundice
4. You are called to the delivery room to evaluate a newborn infant born at 37 weeks' gestation who has an abdominal wall defect noted on delivery. Based on your initial physical examination, you diagnose an omphalocele. Which of the following statements is consistent with this clinical diagnosis?
   A. To rule out gastroschisis definitively, an abdominal computed tomographic scan is necessary.
   B. Compared with gastroschisis, omphalocele is more frequently associated with other congenital malformations.
   C. This abdominal wall defect is just lateral to the umbilicus.
   D. The incidence of bowel obstruction is higher in this infant than in one with gastroschisis.
   E. Omphaloceles may be associated with trisomy 21.
5. You are evaluating a 3-day-old infant with significant respiratory distress. He was delivered by emergency cesarean section at 42 weeks' gestation because of fetal distress. You note that he has an oxygen saturation of 76% in room air that increases to 95% with administration of 100% oxygen. Which of the following statements most accurately supports your suspected diagnosis of persistent pulmonary hypertension of the newborn (PPHN)?
   A. This patient is likely to have an associated cyanotic congenital cardiac defect.
   B. PPHN occurs most frequently in premature infants but may occur in postterm infants.
   C. PPHN usually resolves spontaneously.
   D. This infant is likely to have significant left-to-right shunting.
   E. Adequate oxygenation is the best preventive measurement and treatment.
6. A male infant was born at 32 weeks' gestation via cesarean section because of bleeding from placenta previa. Soon after birth, he developed respiratory distress requiring supplemental oxygen and mechanical ventilation. Chest radiograph shows decreased lung volumes and a

diffuse ground glass pattern with air bronchograms. Which of the following is the most likely cause of this condition?

A. Persistent pulmonary hypertension of the newborn (PPHN)
B. Deficient surfactant
C. Fluid retention in the lungs
D. Bronchopulmonary dysplasia
E. Congenital heart disease

7. The parents of a term infant diagnosed with physiologic jaundice are very concerned that their child is at risk for brain damage. Which of the following statements regarding the infant's hyperbilirubinemia is most accurate?
   A. Breastfeeding, compared with formula feeding, is associated with higher peak serum bilirubin levels.
   B. Serum conjugated bilirubin concentration is the best predictor of bilirubin encephalopathy.
   C. Bilirubin encephalopathy does not occur in healthy term infants.
   D. Increased conjugated (direct) bilirubin levels cause neuronal damage, including choreoathetoid cerebral palsy, hearing loss, and opisthotonus.
   E. This infant's jaundice is expected to peak at 10–14 days of life.
8. A 2-day-old term male infant is being evaluated before discharge from the nursery. The parents are concerned about a skin rash on his face. As you perform the physical examination, you contemplate skin disorders that are benign compared with those that may indicate underlying pathology. Which of the following skin findings is most likely to be associated with underlying pathology?
   A. Pustular melanosis
   B. Nevus simplex
   C. Milia
   D. Nevus flammeus
   E. Erythema toxicum neonatorum (ETN)
9. At a routine health maintenance visit, a 2-week-old infant appears jaundiced. Laboratory evaluation reveals a total bilirubin level of 12.6 mg/dL with a direct bilirubin level of 6.9 mg/dL. Which of the following is the most likely diagnosis?
   A. Breastfeeding jaundice
   B. Breast milk jaundice
   C. Crigler–Najjar syndrome
   D. ABO incompatibility
   E. Choledochal cyst
10. A female infant born at 30 weeks' gestation develops abdominal distension, abdominal tenderness, and bloody stools on the third day of life. Which of the following statements regarding the most likely diagnosis is correct?
    A. The diagnosis is supported by a double-bubble sign on abdominal radiographs.
    B. The diagnosis is supported by pneumatosis intestinalis on abdominal radiographs.
    C. The diagnosis is supported by a soap-bubble appearance on abdominal radiographs.
    D. The infant will ultimately require pancreatic enzyme supplementation.
    E. The diagnosis has an increased association with Down syndrome.

Questions 11 and 12: The response options for statements 11 and 12 are the same. You will be required to select one answer for each statement in the set.

A. 2
B. 3
C. 4

D. 5
E. 6
F. 7
G. 8

In each case, select the infant's 1-minute Apgar score.

1. At 1 minute of life, a newborn's respiratory rate is slow and irregular with a heart rate of 120 beats/minute. There is some flexion of her upper and lower extremities; she grimaces when a catheter is placed into her nose; and she appears to be pink and well perfused, except for some cyanosis of the distal extremities.
2. At 1 minute of life, a newborn's respiratory rate is slow and irregular with a heart rate of 80 beats/minute. There is some flexion of his upper and lower extremities; he does not respond when a catheter is placed into his nose; and he is blue and pale.

You're called to the Nursery to evaluate a cyanotic infant with significant respiratory distress. After 100% oxygen is administered to the infant, there is almost no improvement in the PaO_2 (only 10 mm Hg). Which of the following is the patient's most likely diagnosis?

A. Tetralogy of Fallot
B. Pneumonia
C. Respiratory Distress Syndrome (RDS)
D. Meconium aspiration syndrome
E. Transient tachypnea of the newborn

Answers and Explanations

1. **The answer is C** [XII.A.3]. Esophageal atresia in a newborn is characterized by increased oral secretions as a result of the accumulation of saliva in the proximal esophageal pouch. Respiratory distress may occur if the infant aspirates this saliva. The presence of a distal tracheoesophageal fistula may also result in the passage of gastric contents to the trachea and lung, exacerbating the respiratory problem. Half of children with esophageal atresia have other congenital malformations, such as congenital heart disease. Both pneumonia and persistent pulmonary hypertension of the newborn also present with respiratory distress, but without increased oral secretions. Respiratory distress syndrome occurs less commonly in term infants, and increased oral secretions are not expected. Congenital diaphragmatic hernia usually presents with acute respiratory distress soon after birth in a newborn with a scaphoid abdomen. Bowel sounds can be heard on auscultation of the chest.
2. **The answer is B** [I.G.6 and I.H.1.b]. The most likely cause of an abdominal mass detected during the newborn period is of renal origin, with hydronephrosis being the most common cause. In female infants, an ovarian cyst, which is usually a benign tumor, is not as common as hydronephrosis. Wilms tumor and multicystic kidneys may present as abdominal masses but are also less common causes. Hydrometrocolpos, a retention of vaginal secretions, most commonly presents just after birth as a small cyst located between the labia, although during childhood, it may present as a lower midline abdominal mass.
3. **The answer is A** [X.C.1]. Breastfeeding jaundice is typically associated with indirect, or unconjugated, hyperbilirubinemia and is caused by suboptimal milk intake during the first week of life, which causes weight loss, poor hydration, and decreased stool output. The treatment of breastfeeding jaundice is hydration, which typically includes increasing the frequency of breastfeeding, along with observation and serial bilirubin assessments. Breast milk jaundice, which occurs later, after the first week of life, is thought to be associated with high levels of lipase and β-glucuronidase within breast milk. Choledochal cysts, biliary atresia, and neonatal hepatitis are more typical causes of direct, or conjugated, hyperbilirubinemia.
4. **The answer is B** [XII.C]. Omphalocele is more frequently associated with congenital malformations, such as congenital heart defects, and with genetic conditions, such as trisomy 13, and less commonly with trisomy 18, but not with trisomy 21. Omphalocele and gastroschisis are easily distinguished and diagnosed by inspection. An omphalocele occurs centrally through the umbilical ring, whereas gastroschisis is a lateral abdominal wall defect in which the abdominal contents herniate into the amniotic cavity and are directly exposed to amniotic fluid. Because of this difference in clinical presentation, both omphalocele and gastroschisis are diagnosed clinically without the need for radiographic confirmation. In gastroschisis, exposure to the amniotic fluid may cause inflammation of the bowel with subsequent bowel damage and risk of bowel obstruction.
5. **The answer is E** [VIII.A, VIII.C, and VIII.E]. One of the most common causes of persistent pulmonary hypertension of the newborn (PPHN) is perinatal asphyxia, resulting in increased pulmonary vascular resistance and significant right-to-left shunting through the foramen ovale or the ductus arteriosus. Oxygen is the most potent vasodilator of pulmonary vessels, and in most cases, increases of both alveolar and arterial partial pressures of O_2 produce a decrease in pulmonary vascular resistance and reversal of low blood flow to the lungs. By definition, PPHN excludes the presence of congenital heart disease. If left untreated, the hypoxemia caused by PPHN worsens the increased pulmonary vascular resistance, resulting in many cases in irreversible disease and death. In addition, PPHN occurs most commonly in near-term and full-term infants, as well as in postterm infants.
6. **The answer is B** [VI.A–H]. Respiratory distress syndrome (RDS), which is most common in

premature male infants, is caused by a lack or deficiency of surfactant, with alveolar atelectasis and hypoventilation. Chest radiographic findings usually include a diffuse ground glass pattern with air bronchograms. Pneumonia and sepsis should always be included in the differential diagnosis of RDS because their clinical presentations may be quite similar. Persistent pulmonary hypertension of the newborn (PPHN) is more common in term infants than in premature infants and results most frequently from perinatal asphyxia and meconium aspiration syndrome (MAS). Fluid retention in the lungs may cause respiratory distress, but it is usually mild. The chest radiograph usually shows normal or increased lung volume with increased vascular markings. Bronchopulmonary dysplasia (BPD) is a chronic complication of RDS. Some causes of cyanotic congenital heart disease may cause hypoxemia and respiratory distress after birth; however, the chest radiograph does not show a ground glass appearance, nor air bronchograms.

7. **The answer is A** [X.A–G]. Newborn infants who breastfeed have higher peak serum bilirubin values. However, hyperbilirubinemia alone is not a reason to discontinue breastfeeding. Bilirubin encephalopathy is caused only by unconjugated (indirect) bilirubin because of the ability of unconjugated bilirubin to cross the blood–brain barrier. Encephalopathy caused by indirect hyperbilirubinemia does occur in healthy term newborns, and for this reason, high bilirubin levels in this group of infants should not be ignored. Benign physiologic indirect hyperbilirubinemia is expected to peak in term infants at 3–4 days of life and in preterm infants at 5–7 days of life.
8. **The answer is D** [I.K.11]. Nevus flammeus or "port wine stain" located over the V-1 branch of the trigeminal nerve may herald Sturge–Weber syndrome, with its associated, and potentially very significant, underlying intracranial vascular malformations and calcifications. Pustular melanosis is a benign rash, characterized by small, dry vesicles over a dark macular base, more frequently seen in African American infants. Nevus simplex is the most common vascular lesion of infancy and is also completely benign and often transient, appearing as a "salmon patch" or "stork bite" on the nape of the neck. Milia are benign very small cysts formed around the pilosebaceous follicles that appear as tiny whitish papules over the nose, cheeks, forehead, and chin. Erythema toxicum neonatorum (ETN) is a benign rash usually present in the first 72 hours of life and seen in approximately 50% of all infants. ETN is characterized by erythematous macules, papules, or pustules on the trunk and extremities.
9. **The answer is E** [Figures 4-3 and 4-4]. This infant's presentation with hyperbilirubinemia and a markedly elevated direct bilirubin level is consistent with a choledochal cyst, a disorder that causes obstruction of the biliary tree. Both breastfeeding and breast milk jaundice are characterized by indirect, not direct, hyperbilirubinemia. Crigler–Najjar syndrome, or hereditary deficiency of glucuronyl transferase, would also be expected to result in an indirect, or unconjugated, hyperbilirubinemia. ABO incompatibility would lead to hemolysis, leading to an elevation of indirect bilirubin.
10. **The answer is B** [XII.E]. Necrotizing enterocolitis (NEC) is one of the most common surgical conditions in neonates, occurring most commonly in premature infants. Clinical features include abdominal distension, abdominal tenderness, residual gastric contents, bilious vomiting or bilious nasogastric aspirate, bloody stools, and, at times, abdominal wall erythema. Classic radiographic findings include abdominal distension, air–fluid levels, thickened bowel walls, and pneumatosis intestinalis (air within the bowel wall). In contrast, the double-bubble sign on abdominal radiographs is pathognomonic of duodenal atresia, which classically presents with nonbilious emesis and abdominal distension, but not with bloody stools. The presence of a soap-bubble appearance on abdominal radiographs is characteristic of meconium ileus, a presentation of cystic fibrosis during the neonatal period. Infants with meconium ileus would not be expected to pass bloody stools on the third day of life, but may require pancreatic enzyme supplementation if they are ultimately diagnosed

with fat malabsorption and cystic fibrosis. There is no known association between Down syndrome and NEC, although there is an association between Down syndrome and duodenal atresia.

11. **The answers are E and B, respectively** [Table 4.1]. The Apgar scoring system provides a simple, systematic, and objective assessment of intrapartum stress and neurologic depression. The female newborn earns 2 points for a heart rate >100 beats/minute, 1 point for slow and irregular respirations, 1 point for having some flexion of the extremities, 1 point for reflex irritability or grimace when a catheter is placed in her nose, and 1 point for her peripheral cyanosis or acrocyanosis, for a total Apgar score of 6 points. The male newborn earns 1 point for a heart rate <100 beats/minute, 1 point for slow and irregular respirations, 1 point for having some flexion of the extremities, 0 points for the absence of reflex irritability when a catheter is placed into his nose, and 0 points for his cyanosis, for a total Apgar score of 3 points.
12. **The answer is A** [IV.D.2 and V.A] The 100% oxygen test helps distinguish whether cyanosis is caused by cardiac or respiratory disease. When administered 100% oxygen, infants with primary lung pathology, such as neonatal pneumonia, meconium aspiration syndrome, transient tachypnea of the newborn or respiratory distress syndrome, have a very significant increase in PaO_2 levels. In contrast, patients with cyanotic congenital heart disease would not be expected to have such a significant rise in their PaO_2 level. For example, patients with Tetralogy of Fallot, a cyanotic congenital heart disease associated with reduced pulmonary blood flow, would not be expected to respond with any increase of significance in the PaO_2 level when given 100% oxygen. Note that other cyanotic congenital heart diseases with normal or increased pulmonary blood flow, like truncus arteriosus, may have some increase in the PaO_2 level, but nowhere near as much of an increase as that seen in infants with primary pulmonary disease.

CHAPTER 5

Genetic Disorders and Inborn Errors of Metabolism

Jessica Tenney, Derek Wong

I. Inheritance Patterns

A. **Mendelian inheritance** (**Figure 5-1**). The classic patterns of inheritance seen in single-gene disorders
   1. **Dominant inheritance**
      a. **Autosomal dominant** mode of inheritance is observed when an abnormal copy of a gene is located on one of the autosomes (chromosomes 1–22). Males and females have the same chance of being affected. If one parent is affected, the risk of having an affected child is 50% in each pregnancy.
      b. **X-linked dominant** mode of inheritance is observed when an abnormal gene is located on one X chromosome. An affected father will transmit disease to 100% of his female offspring and none of his male offspring, whereas an affected mother has a 50% chance of transmitting disease to any of her offspring.
   2. **Recessive inheritance**
      a. **Autosomal recessive** mode of inheritance is observed when there are no normal copies of a gene. If both parents are carriers, offspring will have a 25% chance of being affected. It is often seen in only one generation in a pedigree. Parental consanguinity increases the risk for autosomal recessive conditions.
      b. **X-linked–recessive** mode of inheritance is observed when there are no normal copies of the gene. Disease occurs when a son inherits the abnormal copy from his mother. There is no male-to-male transmission. Daughters who inherit one abnormal copy of the gene are usually asymptomatic, but some may be affected if there is skewed X-inactivation. For example, because one random X chromosome is inactivated in all cells of females, if the X chromosomes with the normal gene are disproportionately inactivated relative to the X chromosomes with the abnormal gene, the female may be affected. A female who inherits two abnormal copies will always be affected. A carrier mother has a 50% chance of having an affected son.

B. **Mitochondrial inheritance** is observed when a mutation occurs in one of the genes in the mitochondrial genome. The mitochondrial genome is housed separately from the nuclear genome and is **only inherited from the mother.** In a pedigree, offspring of an affected mother can show signs of disease, but an affected father will never have affected offspring.

C. **Multifactorial inheritance** occurs when a combination of genetic and environmental factors determines whether or not a disorder will manifest. The disorder will be seen in a particular family with increased frequency compared with that of the general population. Examples of multifactorial inheritance include cleft lip and palate, neural tube defects, developmental dysplasia of the hip, and pyloric stenosis.

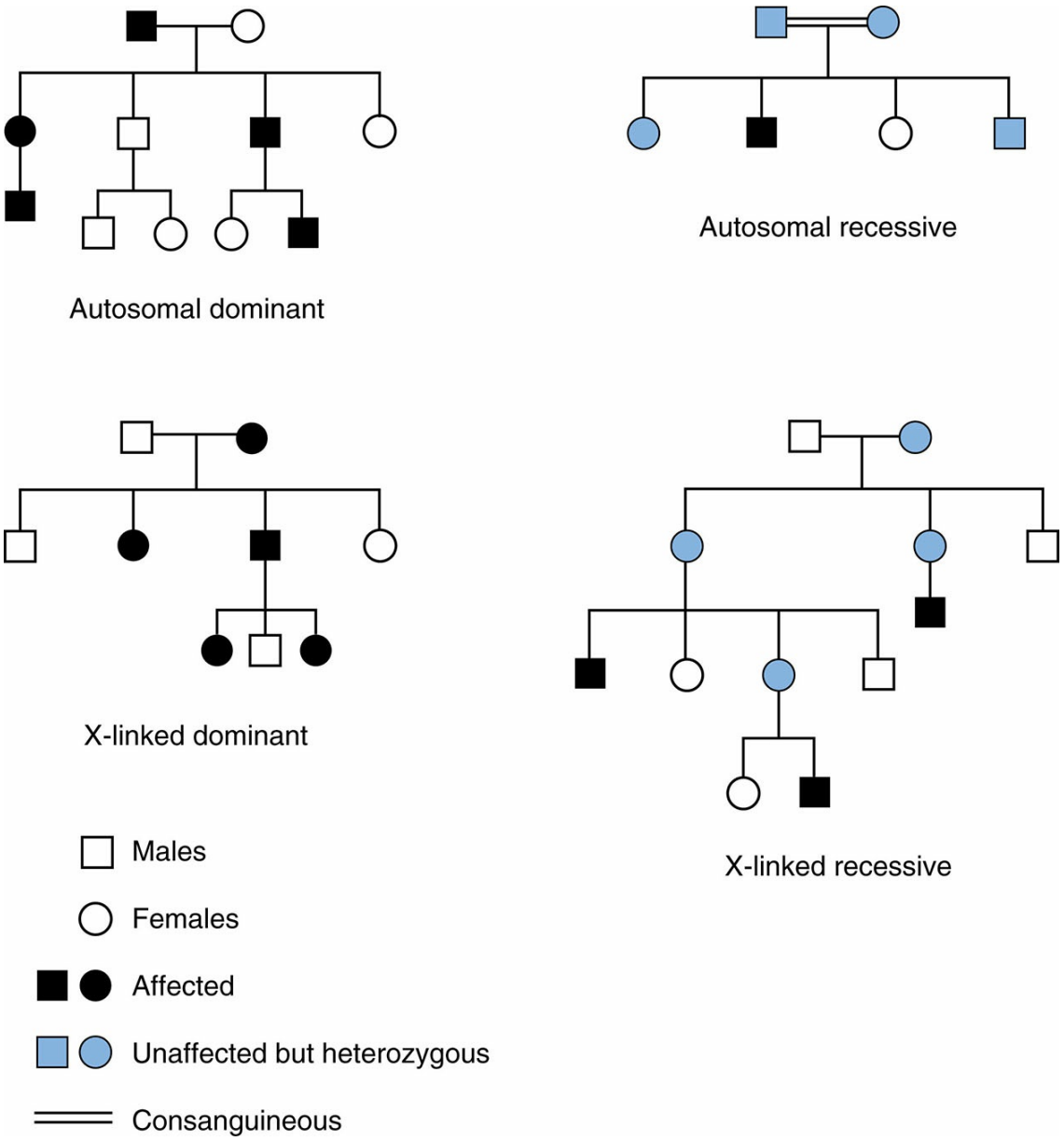

FIGURE 5.1 Pedigrees of different Mendelian inheritance patterns.

Adapted with permission from Sakala EP. BRS Obstetrics and Gynecology. 2nd Ed. Philadelphia: Lippincott Williams & Wilkins, 2000:52.

II. Types of Genetic Tests

A. **Karyotype analysis** is used to determine the number and structure of chromosomes. This may be used to diagnose a chromosomal trisomy, sex chromosome disorders, translocations, and larger deletions or duplications.
B. **Microarray** is currently the preferred first line test used to diagnose microdeletion/microduplication syndromes, such as 22q11.2 deletion syndrome [see section IV.D.1].
C. **Fluorescence in situ hybridization (FISH)** is a targeted test that may be also used to look for the presence of a specific sequence of DNA on a chromosome.
D. **Methylation studies** are performed to help diagnose specific imprinting disorders (e.g., Prader–Willi syndrome). When methyl groups are added to DNA, the activities of the DNA segment can change. This physiologic process plays a role in X chromosome inactivation and imprinting [see section IV.E.1.a], but also plays a role in pathologic processes such as aging, carcinogenesis, and the development of imprinting disorders such as Prader–Willi.
E. **Gene sequencing** is performed to look for mutations in a specific gene (e.g., fibrillin 1 sequencing to diagnose Marfan syndrome).
F. **Exome sequencing** looks for potential diseases causing mutations in the protein coding regions (exons) of nearly the entire genome. It is useful when there is a broad differential diagnosis of genetic conditions.

III. Fetal Evaluation and Prenatal Diagnosis

A. **Maternal serum markers**
   1. **α-Fetoprotein (AFP)** is elevated with fetal neural tube defects, multiple gestation pregnancies, underestimated gestation age, ventral abdominal wall defects, fetal demise, or fetal edema or skin defects. Low AFP levels are associated with overestimated gestation age, trisomies 18 and 21, and intrauterine growth retardation.
   2. **Triple/quadruple markers** are used in conjunction with ultrasound findings as a noninvasive method to assess the fetus for the possibility of trisomy syndromes. The three classic second-trimester screening markers are **AFP, unconjugated estriol (uE3), and the β-subunit of human chorionic gonadotropin (β-HCG).** More recently, the use of **inhibin-A** has been introduced to increase the detection rate of Down syndrome.
      a. Trisomy 21 is suggested by findings of **low AFP and uE3 and high β-HCG and inhibin-A.**
      b. Trisomy 18 is suggested by **low levels of AFP, uE3, and β-HCG**

B. **Ultrasound** is used to assess gestation age and fetal growth and to evaluate for major fetal anomalies. The finding of **increased nuchal translucency** may indicate the presence of **trisomies 13, 18, and 21 and Turner syndrome, as well as structural anomalies such as congenital heart disease.**

C. **Genetic evaluation of the fetus**
   1. **Chorionic villus sampling (CVS)** is the use of villus tissue from the chorion of the trophoblast that is collected at 10–13 weeks' gestation. Karyotype, gene sequencing, and enzyme analyses from CVS can be used to assess for genetic and metabolic disorders.
   2. **Amniocentesis** is the use of amniotic fluid containing sloughed fetal cells collected at 16–18 weeks' gestation. This technique can be used to assess for the same genetic diseases as CVS.
   3. **Percutaneous umbilical blood sampling** involves obtaining a sample of fetal blood to assess for hematologic abnormalities, genetic disorders, infections, and fetal acidosis. It can also be used to administer medications or blood transfusions to the fetus.
   4. **Noninvasive prenatal testing (NIPT)** involves the isolation of fetal cells extracted from a cell-free DNA sample of maternal blood. It is used for assessment of fetal trisomies 13, 18, and 21, and has the potential to replace more invasive forms of sampling for all genetic tests in the future.

IV. Common Genetic Disorders

A. **Terminology**
   1. **Malformations** are defects that result from the intrinsically abnormal development of a structure or set of structures (e.g., anencephaly, congenital heart disease).
   2. **Deformations** occur when extrinsic (mechanical) forces impinge on the development of otherwise normal tissue (e.g., clubfoot).
   3. **Disruptions** occur when normal tissue is irreparably destroyed, altering the subsequent formation of the structure (e.g., amniotic bands).
   4. **Syndromes** are recognizable patterns of symptoms or abnormalities that suggest a specific underlying disorder.

B. **Trisomy syndromes**
   1. **Trisomy 21 (Down syndrome) is the most common chromosomal disorder.** The incidence is about 1:700 live births. The risk increases in advanced maternal age, with a sharper rise in prevalence rates seen every year after the age of 35 years.
      a. **Clinical features.** See *Table 5-1* and *Figure 5-2.*
      b. **Diagnosis** is on the basis of clinical features and genetic testing that demonstrates three copies of chromosome 21. Note that about 3–4% of individuals have Down syndrome due to a translocation. A karyotype is needed to distinguish full trisomy 21 from a translocation. **If a parent carries a translocation, the recurrence risk for subsequent children with Down syndrome is higher.**
   2. **Trisomy 18 (Edwards syndrome)**
      a. **Clinical features** include severe intellectual disability, prominent occiput, low-set ears, micrognathia, congenital heart disease, rocker-bottom feet, and clenched hands with overlapping digits.
      b. **Prognosis** is poor, as 90% of children die by 1 year of age.
   3. **Trisomy 13 (Patau syndrome)**
      a. **Clinical features** include severe intellectual disability, cutis aplasia, microphthalmia, coloboma, congenital heart disease, polydactyly, and midline defects such as agenesis of the corpus callosum and cleft lip and palate.
      b. **Prognosis** is poor, as 50% die by 1 month of age and 90% die by 1 year of age.

C. **Sex chromosome syndromes**
   1. **Turner syndrome (XO)** occurs in females with complete or partial absence of a second X chromosome.
      a. **Epidemiology**
         1. Monosomy X is found in 45% of affected individuals, whereas the remainder of cases are due to either a structural abnormality of the second X chromosome or mosaicism.
         2. The incidence is 1:2500–3000 female live births.
      b. **Clinical features**
         1. **Short stature** is present in 95% of individuals with Turner syndrome. Growth hormone can be used to increase final height.
         2. **Webbed neck** with low posterior hairline
         3. Broad chest with widely spaced nipples **(shield chest)**
         4. Congenital lymphedema. May have swelling of the hands and/or feet at birth
         5. Cardiac defects: **coarctation of the aorta**, bicuspid aortic valve, hypoplastic left heart
         6. Ovarian dysgenesis leads to **primary amenorrhea** and lack of secondary sex characteristics in most patients. Estrogen therapy can be used to promote

secondary sex characteristics.
7. Most individuals have normal intelligence.
8. Renal malformations, hypothyroidism, diabetes, and hearing loss are also associated with Turner syndrome.

2. **Klinefelter syndrome (XXY)** is the most common genetic cause of male infertility.
   a. **Epidemiology**
      1. The incidence is 1:500–1000 male live births.
      2. Risk increases with advancing maternal age.
   b. **Clinical features**
      1. **Tall stature**, thin, with relatively long legs, and gynecomastia
      2. *Hypogonadism* results in small testicles, underdeveloped secondary sex characteristics, oligo- or azoospermia, and decreased bone density.
      3. Learning disabilities are common, especially in the areas of verbal comprehension and reading. There is an increased risk of psychosocial and behavioral problems.
      4. There is also an increased risk for developing mediastinal germ cell tumors (starting in adolescence) and breast cancer.
3. **XYY** males may be taller than average but have normal sexual development. Intelligence is usually normal, but there is increased risk for learning disabilities and behavioral problems.

D. **Chromosomal (micro) deletion syndromes**
1. **22q11.2 deletion syndrome (DiGeorge, velocardiofacial syndrome)** occurs when a portion of the q arm of chromosome 22 is missing. The deletion can be de novo or inherited. The mnemonic **CATCH-22** can be used to remember the findings of this disorder (**C**ardiac defects, **A**bnormal facies, **T**hymic hypoplasia, **C**left palate, **H**ypocalcemia**,** and deletion on chromosome **22**)
   a. **Epidemiology.**
      1. The incidence of 22q11.2 deletion syndrome is about 1 in 4000 live births.
   b. **Clinical features**
      1. **Cardiac:** congenital heart disease, especially conotruncal malformations (**tetralogy of Fallot,** ventricular septal defect)
      2. **Palatal abnormalities:** velopharyngeal incompetence, cleft palate, submucous cleft, and bifid uvula
      3. **Abnormal facies:** hooded eyelids, hypertelorism, overfolded or squared off helices, prominent nasal root, bulbous nasal tip, and micrognathia
      4. **Thymic hypoplasia** can result in **immunodeficiency.** Parathyroid hypoplasia can result in **severe hypocalcemia,** and therefore, calcium should be monitored in any newborn with suspected 22q11.2 deletion.
      5. Intellectual and learning disability
      6. Other associations include renal anomalies, hearing loss, and gastrointestinal anomalies.
2. **Williams syndrome** results from a deletion on chromosome 7 (7q11.23) that includes the elastin gene.
   a. **Epidemiology.**
      1. The incidence of Williams syndrome is about 1 in 20,000 births.
   b. **Clinical features**
      1. Distinctive facial features ("Elfin facies") include prominent forehead, widely spaced eyes, upturned and full nasal tip, long philtrum, distinctive wide mouth, and stellate/lacy iris pattern.
      2. Cardiovascular disease (elastin arteriopathy): **Supravalvar aortic stenosis** is

the most common location.
3. Abnormalities of connective tissue may result in a hoarse voice or hernias.
4. Intellectual disability, with a very friendly personality
5. Endocrine problems include hypocalcemia, hypercalcuria, and hypothyroidism.

3. **Cri du chat syndrome** results from a deletion of the short arm of chromosome 5 (5p). It is characterized by *catlike cry in infancy,* microcephaly, downslanting palpebral fissures, developmental delay, and intellectual disability.

E. **Imprinting disorders**

1. **Key concepts**
   a. **Genomic imprinting** results in differences in gene expression depending on whether the gene is inherited from the mother or father. Disease occurs when the copy from the appropriate parent cannot be expressed. An example occurs in an imprinted region of chromosome 11q. Angelman syndrome occurs when there is a deletion or other mechanism that causes a missing maternal copy of the region, and Prader–Willi syndrome occurs if there is a missing paternal copy of the region. The mnemonic "P is for Prader–Willi and paternal deletion" may be used to remember the molecular basis of these conditions.
   b. **Uniparental disomy (UPD)** occurs when both copies of one chromosome come from the same parent.
2. **Prader–Willi syndrome**
   a. **Clinical features**
      1. In infancy, patients demonstrate *hypotonia and feeding difficulties,* usually resulting in failure to thrive. In childhood, *patients develop hyperphagia leading to obesity*.
      2. Almond-shaped eyes, strabismus, down-turned mouth, hypopigmentation, small hands and feet, short stature, and hypogonadism
      3. Behavioral problems, intellectual disability, and learning disabilities
   b. The most common cause is a deletion in a region within the **paternally inherited chromosome 15**. The second most common cause is maternal UPD of chromosome 15.
   c. **Diagnosis** is by methylation analysis.
3. **Angelman syndrome**
   a. **Clinical features**
      1. Severe developmental delay, speech impairment, and *happy demeanor with inappropriate laughter and smiling.*
      2. Jerky movements and ataxic gait is sometimes described as "**puppetlike.**"
      3. Microcephaly, seizures, large mouth, widely spaced teeth, and prognathia (prominent mandible)
   b. The most common cause is a deletion in a region within the **maternally inherited chromosome 15.**
4. **Diagnosis** is by methylation analysis.
5. **Beckwith–Wiedemann syndrome**
   a. **Clinical features**
      1. *Overgrowth disorder* characterized by macrosomia, **macroglossia,** and visceromegaly
      2. Can have hemihyperplasia, ear creases/pits, and **omphalocele**
      3. Increased risk for embryonal tumors (**Wilms tumor**, neuroblastoma, etc.)
   b. This syndrome has several different etiologies, all of which affect imprinting on chromosome 11p15.5.

c. **Diagnosis** can be established by clinical criteria, methylation studies, microarray, or specific gene sequencing.

6. **Russell–Silver syndrome**
   a. **Clinical features**
      1. Intrauterine growth retardation/**small for gestational age (SGA)**, **short stature**, **normal head circumference**, and **asymmetry** (limb, body, or face)
      2. **Triangular facies**, frontal bossing, or prominent forehead. The patient can also have café-au-lait macules.
   b. It has been associated with hypomethylation of a region that regulates expression of insulin-like growth factor 2.
   c. Diagnosis is largely based on clinical characteristics.

F. **Triplet repeat expansion disorders.** Certain genes are sensitive to increasing (expanding) the number of nucleotide repeats in a specific gene segment. The number of repeats can increase with each generation, but the disorder only occurs once the number of nucleotide repeats in a gene expands beyond a specific threshold. Once the threshold is reached, this expansion can become even larger, causing earlier onset and more severe symptoms, which is a phenomenon known as **anticipation.**

1. **Fragile X syndrome**
   a. This is caused by expansion of the number of *CGG repeats* in the *FMR1* gene on the X chromosome. It has an X-linked recessive mode of inheritance. Full mutation = >200 repeats
   b. **Clinical features**
      1. *Developmental delay* and mild to severe **intellectual disability.** Behavioral abnormalities including **autism** and attention deficit/hyperactivity disorder
      2. **Macrocephaly**, long face, prominent jaw, **protruding ears. Macroorchidism** develops in adolescence.
      3. Females with full mutation may have behavioral problems and developmental delays, but most have normal intelligence quotient (IQ).
2. **Myotonic dystrophy**
   a. **Genetic mechanism**
      1. The severe form is caused by expansion of the number of CTG repeats in the *DMPK* gene.
      2. Expansion of the repeats occurs much more frequently in mothers.
   b. **Clinical features**
      1. *Progressive muscular weakness* starting at any time during childhood
      2. Other features include cataracts and cardiac conduction abnormalities.

G. **Connective tissue disorders**

1. **Marfan syndrome**
   a. An autosomal dominant disorder caused by mutations in the gene that codes for **fibrillin.** Mutations can either be inherited or sporadic.
   b. **Clinical features.** Characteristic findings involve the ocular, skeletal, and cardiovascular systems.
      1. Myopia, **lens dislocation,** and retinal detachment
      2. **Tall stature with long extremities**, long fingers (arachnodactyly), pectus deformity, scoliosis, pes planus, **decreased upper-to-lower segment ratio**, increased arm span-to-height ratio
      3. **Aortic root dilatation**, mitral valve prolapse, and valvular regurgitation. **Note: Patients with aortic root dilatation are at increased risk for aortic dissection.** β-blockers +/− angiotensin receptor blockers are prescribed to help prevent or slow progressive aortic enlargement.

4. Patients are at risk for spontaneous pneumothorax.

2. **Ehlers–Danlos syndrome, classic type**
    a. An autosomal dominant disorders caused by mutations in genes that code for *type V collagen.* Mutations can be inherited or sporadic.
    b. **Clinical features.** Characterized by **skin hyperextensibility, abnormal wound healing, and joint hypermobility.** Skin may be described as soft and/or velvety in texture, with bruising caused by fragile blood vessels. Tissue fragility and poor wound healing results in widened atrophic scars.

H. **Skeletal disorders**
1. **Achondroplasia**
    a. An autosomal dominant disorder caused by mutations in *FGFR3.* The majority of cases result from a sporadic mutation. Advanced paternal age (>45 years old) increases the risk of having an affected child.
    b. **Achondroplasia is the most common cause of disproportionate short stature.**
    c. **Clinical features**
        1. Craniofacial findings include macrocephaly, **prominent forehead**, low nasal bridge, and midface hypoplasia.
        2. Characteristic skeletal findings:
            a. **Rhizomelic (proximal limb) shortening of the limbs,** bowed legs, and **trident appearance** of the hands.
            b. Lumbar gibbus deformity (structural, sharp-angled kyphosis resulting in a prominent "hump" on the back) in infancy that resolves once the patient starts walking. Lumbar lordosis then develops.
        3. Normal intelligence with delayed acquisition of motor milestones
        4. Recurrent middle ear dysfunction and obstructive sleep apnea
        5. Increased risk for foramen magnum stenosis and compression of the craniocervical junction. Patients should therefore be monitored for signs of hydrocephalus and spinal cord compression.
2. **Osteogenesis imperfecta (OI)**
    a. Most cases are due to autosomal dominant mutations in genes that encode for chains of **type I collagen.** Type I is the most common and the mildest form of OI. Patients with Type II OI are the most severely affected, and rarely survive beyond the first weeks of life. Type III is the most severe type among those who survive the neonatal period.
    b. **Clinical features of Type I OI**
        1. Characterized by **blue sclera and frequent fractures after minimal or no trauma.** Easy bruising. Fractures usually heal without resulting deformity.
        2. Normal stature or slightly shorter than the rest of the family
        3. May have yellow or grayish brittle teeth (dentinogenesis imperfecta) which are at increased risk for breakage.
        4. Progressive hearing loss in adulthood

I. **Additional disorders**
1. **Noonan syndrome**
    a. Autosomal dominant disorder caused by mutations in certain genes involved in the RAS/MAPK pathway.
    b. **Clinical features**
        1. Characterized by **short stature, congenital heart defect, pectus deformity, and characteristic facies**
        2. Craniofacial findings are most prominent in infancy and include low-set, posteriorly rotated ears, wide-spaced eyes (hypertelorism), eyelid ptosis, and

downslanting palpebral fissures.
3. **Pulmonary valve stenosis** is the most common cardiac defect. All patients are at risk for developing hypertrophic cardiomyopathy during their lifetime.
4. Patients can have short, webbed neck with low posterior hairline, and broad chest with widely spaced nipples. Affected females are sometimes initially misdiagnosed with Turner syndrome (which is associated with left-sided heart defects vs. Noonan syndrome with right-sided heart defects).
5. Patients may have developmental delay and/or intellectual disability.

2. **VACTERL (VATER) association**
   a. A group of malformations generally observed as a sporadic occurrence in an otherwise healthy family. The etiology is unknown. **Clinical findings overlap with those seen in Fanconi anemia**, which should be ruled out in anyone presenting with VACTERL.
   b. **Clinical features**
      1. **V—v**ertebral defects
      2. **A—a**nal atresia
      3. **C—c**ardiac defects
      4. **TE**—tracheoesophageal (**TE**) fistula
      5. **R—r**enal dysplasia
      6. **L—***l*imb/radial defects
3. **CHARGE Syndrome**
   a. An autosomal dominant disorder most often caused by a spontaneous mutation
   b. **Clinical features**
      1. **C—***c*olobomas of the iris or retina. Usually results in impaired vision
      2. **H—h**eart defects such as conotruncal defects and aortic arch abnormalities
      3. **A—**choanal **a**tresia or stenosis
      4. **R—r**etarded growth and development
      5. **G—g**enital abnormalities, including genital hypoplasia
      6. **E—e**ar anomalies, including abnormal outer ear shape, hearing loss, and ossicular and temporal bone abnormalities
      7. Cranial nerve dysfunction is another important feature.
4. **Cornelia de Lange syndrome**
   a. Generally observed as a sporadic occurrence in an otherwise healthy family. Autosomal dominant and X-linked mutations have been found.
   b. **Clinical features**
      1. Characteristic facies include **synophrys** (single eyebrow resulting from both eyebrows growing into one another), **long eyelashes**, small upturned nose, and microcephaly.
      2. SGA, failure to thrive, and small stature
      3. **Hirsutism**
      4. Upper limb malformations
      5. Developmental delay, intellectual disability, and behavioral problems
5. **Neurofibromatosis type 1 (see also Chapter 19, Table 19-3)**
   a. Autosomal dominant disorder caused by mutations in *NF1.* Half of the cases are inherited, and the remainder are spontaneous mutations.
   b. **Clinical features**
      1. Characteristic findings include **multiple café-au-lait macules**, axillary and inguinal freckling, cutaneous and/or plexiform neurofibromas, iris hamartomas (**Lisch nodules**), and osseous dysplasia.
      2. Increased risk for malignant peripheral nerve sheath tumors (PNETs), optic

nerve gliomas, and central nervous system (CNS) gliomas
3. Learning disabilities are seen in half of patients.

6. **Potter syndrome**
   a. A **deformation** sequence that results from compressive forces exerted on a developing fetus subjected to prolonged oligohydramnios. The oligohydramnios may have resulted from bilateral renal agenesis, other urinary tract defects, or a chronic leak of amniotic fluid.
   b. **Clinical features** include lung hypoplasia, abnormal limb positioning, and characteristic **"Potter facies"** (compressed facial appearance, with large ears flattened against the head).
7. **Pierre Robin sequence**
   a. A sequence that can be seen as an isolated finding or as part of a specific multiple malformation syndrome. Clinical findings result from mandibular hypoplasia, which leads to a cascade of other features.
   b. **Clinical features** include micrognathia, glossoptosis (posterior displacement of the tongue), and cleft palate (often a U-shaped cleft).
8. **Amniotic band syndrome** occurs when rupture of the amniotic sac during pregnancy results in small strands of amnion wrapping around areas of the fetus's body, causing deformation and/or amputation.

J. **Syndromes caused by teratogens**(**Table 5-2**)
1. **Diabetic embryopathy**
   a. Increased risk for congenital malformations occurs in infants born to mothers with type 1 or type 2 diabetes, especially when the Hgb A_1C level is >12 just before conception and/or in the early first trimester.
   b. The infant may have isolated or multiple malformations, including **caudal regression syndrome** (sacral agenesis), neural tube defects, renal malformations, cardiac defects, or craniofacial abnormalities.
2. **Fetal alcohol syndrome (FAS)**
   a. FAS is caused by maternal alcohol consumption during pregnancy. Prenatal exposure to alcohol can cause a wide range of findings, with FAS being the most severe. No amount of alcohol is considered safe, but the risk for FAS is higher with binge drinking or chronic alcohol consumption during pregnancy.
   b. **Clinical features**
      1. Microcephaly, short palpebral fissures, smooth philtrum, and thin upper lip
      2. Developmental delay, intellectual disability, and attention deficit hyperactivity disorder
      3. Infants may be SGA.
      4. Cardiac defects may occur (ventricular septal defects are most common).
3. **Fetal hydantoin syndrome**
   a. Infants born to mothers taking phenytoin during pregnancy are at increased risk for specific malformations.
   b. **Clinical features**
      1. Microcephaly, wide anterior fontanelle, hypertelorism, short nose, wide mouth
      2. Low hairline, short neck, hypoplastic nails
      3. Developmental delays

Table 5-1
Clinical Features and Complications Associated with Down Syndrome, with Recommendations for Screening

Clinical Features	Complications

Craniofacial features	**Atlantoaxial instability** (1–2%)
Brachycephaly	**Anemia**
Epicanthal folds	Check hemoglobin annually
Upslanting palpebral fissures	**Leukemia** (1% of patients but more common than the general population)
Brushfield spots (speckled irides)	
Protruding tongue	**Celiac disease** (5%)
Hypotonia	**Early onset Alzheimer disease**
Intellectual disability	**Obstructive sleep apnea** (50–75%)
	Sleep study by 4 years of age
Musculoskeletal features	**Hearing problems** (75%)
Clinodactyly	Hearing screens needed every 1–2 years
Single palmar creases	**Thyroid disease**
Wide space between first and second toes (sandal gap)	Annual TSH screening
Gastrointestinal features	**Cataracts, glaucoma, and refractive errors**
Duodenal atresia	Annual ophthalmologic examinations
Hirschsprung disease and omphalocele	
Pyloric stenosis	
Cardiac defects (40%)	
Endocardial cushion defects (most common)—echocardiogram at birth	

TSH = thyroid-stimulating hormone.

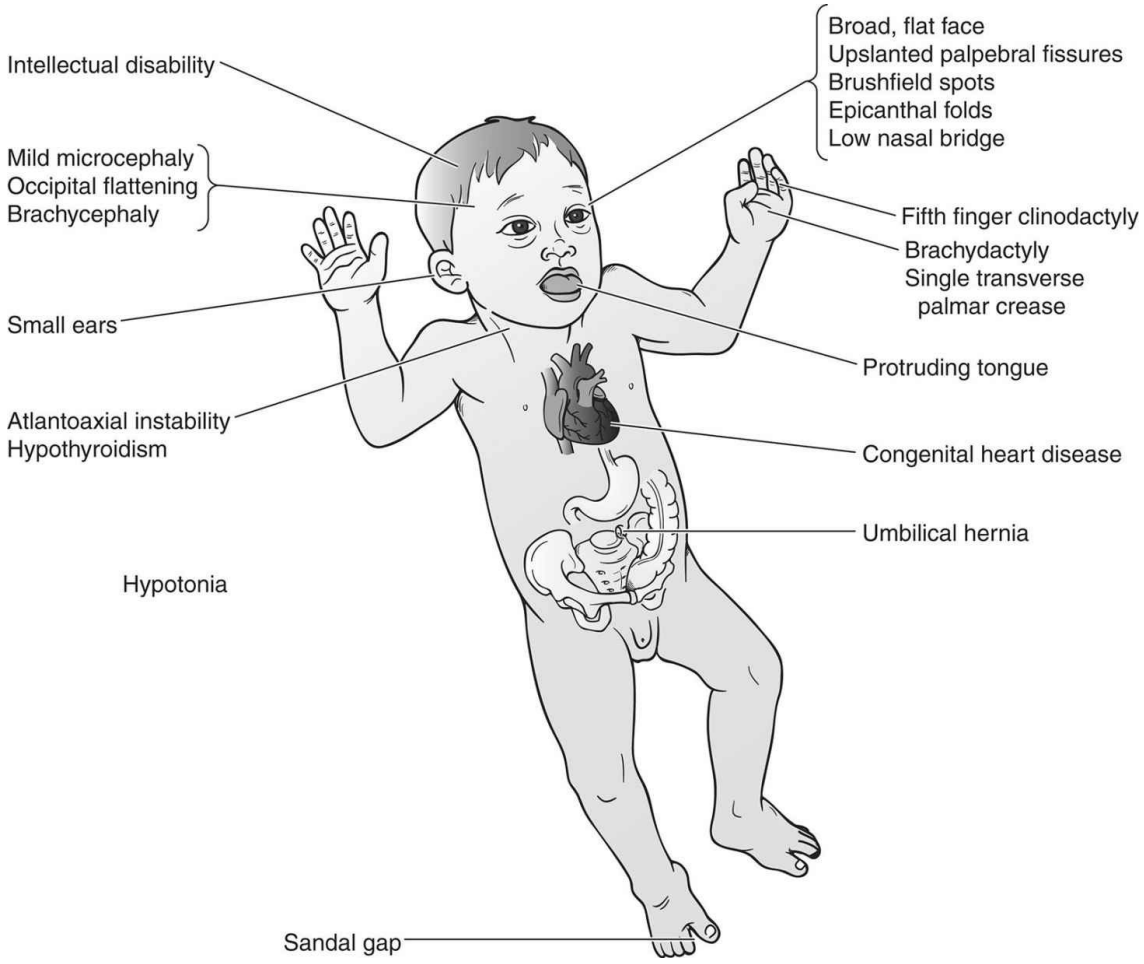

FIGURE 5.2 Clinical features of Down syndrome.

Table 5-2
Teratogens and Associated Anomalies

Drugs	Associated Anomalies
Alcohol	Microcephaly; short palpebral fissures; long, smooth philtrum; variable intellectual disability; and congenital heart disease
Cigarette smoking	Small for gestational age
Cocaine	Premature birth
Diethylstilbestrol (DES)	Increased risk of vaginal adenocarcinoma and genitourinary anomalies
Isotretinoin	Small low-set ears, micrognathia, depressed nasal bridge, cardiac defects, thymic hypoplasia, and central nervous system malformations
Lithium	Ebstein anomaly
Phenytoin	Wide anterior fontanelle, short nose, wide mouth, microcephaly, low hairline, hypoplastic nails, and developmental delay
Thalidomide	Phocomelia (malformed extremities resulting in flipperlike appendages)
Valproic acid	Neural tube defects
Warfarin	Hypoplastic nose with depressed nasal bridge, stippled epiphyses, and hypoplastic nails

V. General Concepts of Inborn Errors of Metabolism (IEM)

A. IEM are a heterogeneous group of diseases that can present in a variety of ways. Individually, each disease is rare but causes significant morbidity and mortality.
B. Disorders occur when a specific step in a metabolic pathway is disrupted in some way (defective enzyme, receptor problem, etc.), resulting in the accumulation of toxic metabolites.
C. Each individual disorder may have several subtypes that can vary in level of severity. Unless otherwise stated, the severe/classic form of each disorder is discussed below.
D. An overview of different categories of IEM, including examples of conditions within each category, is summarized in **Figure 5-3.**
E. **Clinical features** (**Table 5-3**)
    1. IEM should be considered in patients with the following clinical presentations.
        a. An otherwise healthy newborn who develops an **acute severe illness** within the first few hours to weeks of life
        b. **Acute and recurrent episodes** of altered mental status, vomiting, acidosis, organ failure, or ataxia
        c. **Chronic and progressive symptoms** such as developmental delay or regression of developmental milestones, intellectual disability, or seizures
    2. **Age of onset.** Age of onset is variable depending on the type of IEM. Some disorders that present in infancy have less severe forms that can present later in infancy, childhood, adolescence, or even adulthood.
    3. **Family history**
        a. Most IEM are inherited in an **autosomal recessive fashion**, but several are X-linked recessive. A history of parental consanguinity may be seen in patients with autosomal recessive disorders.
        b. There might be a family history of neonatal death.
        c. For recessive conditions, there may be an affected sibling, and for X-linked disorders, there may be an affected brother or maternal uncle.
    4. **Key point: Sepsis is much more common than metabolic disease.** However, it is important to keep in mind that the **presenting symptoms of IEM may be similar to those of sepsis**, and patients with IEM are vulnerable to sepsis.
F. **Laboratory evaluation and management**(**Table 5-4**) depends on presenting features and clinical status of patient (acute episode or stable between episodes). Newborn screening programs can diagnose several IEM before symptoms develop; however, the specific disorders that are screened differ from state to state.

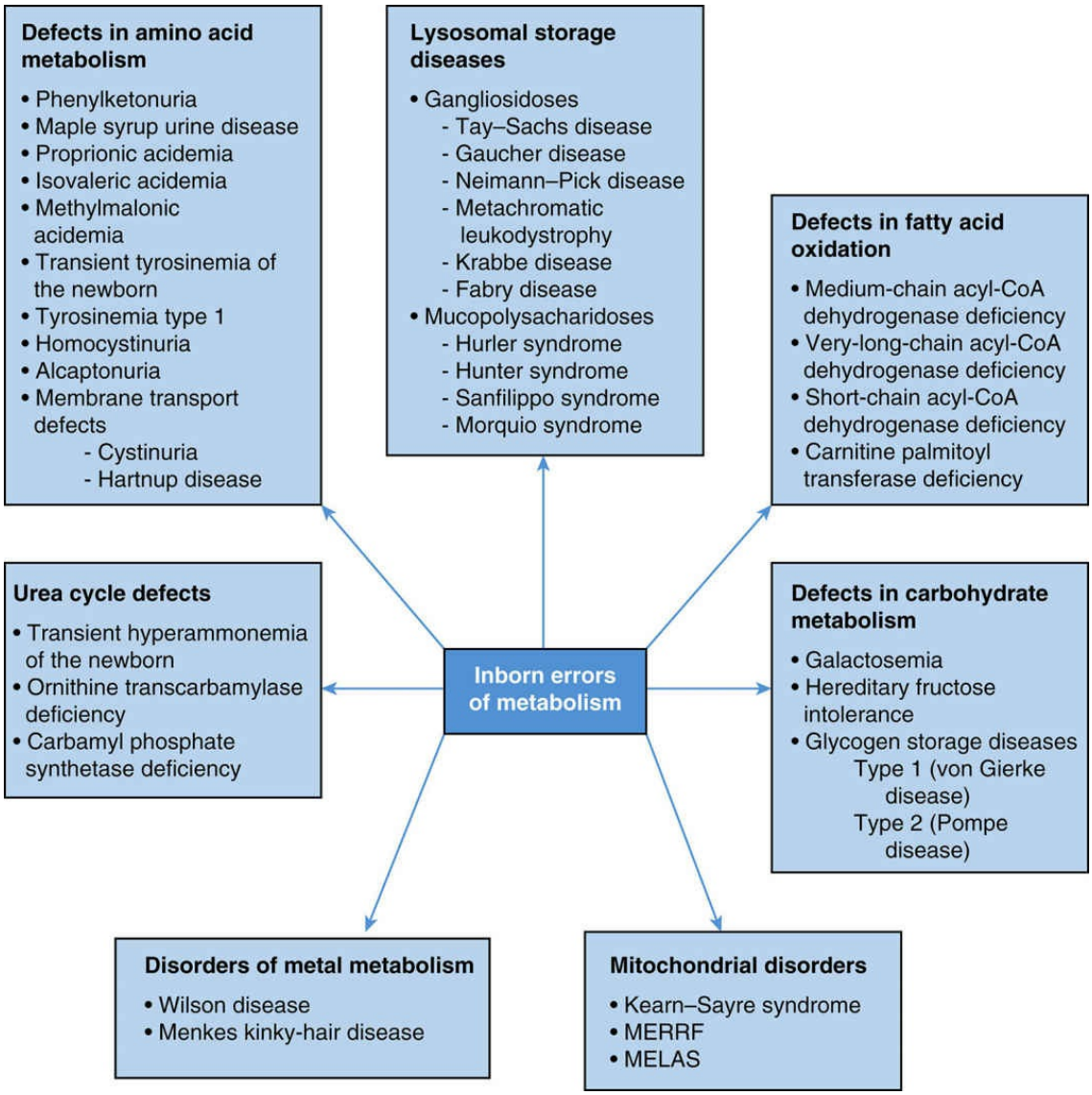

FIGURE 5.3 Summary chart of inborn errors of metabolism. *MELAS* = *m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*trokelike episodes; *MERRF* = *m*yoclonic *e*pilepsy and *r*agged-*r*ed *f*ibers.

Table 5-3
Typical Clinical Features of Inborn Errors of Metabolism (IEM)

General symptoms:	
Lethargy or coma	
Poor feeding	
Intractable hiccups	
Unusual odor (especially when acutely ill):	
Odor:	**IEM:**
Mousy/musty	Phenylketonuria
Sweet maple syrup	Maple syrup urine disease
Sweaty feet	Isovaleric or glutaric acidemia
Boiled cabbage	Tyrosinemia type I
Neurologic:	

Hypotonia
Unexplained developmental delay
Unexplained and difficult to control seizures
Ophthalmologic:
Cherry-red macula, cataracts, or corneal clouding
Gastrointestinal:
Unexplained vomiting
Hepatomegaly
Splenomegaly
Metabolic:
Hypoglycemia may be associated with fatty acid oxidation disorders or carbohydrate disease
Elevated NH_3 without acidosis is suggestive of urea cycle defects
Elevated NH_3, metabolic acidosis, and elevated anion gap are suggestive of organic acidemias
Urinary ketones in a newborn are unusual and may indicate an IEM such as maple syrup urine disease

NH_3 = ammonia.

Table 5-4

Initial Evaluation for Inborn Errors of Metabolism

Test	Reason for Test
Initial studies	
Serum glucose	Rule out hypoglycemia
CBC with differential	Some organic acidemias may cause pancytopenia
Urinalysis	Assess for ketones: Presence of ketones is especially suspicious in newborns, because they do not normally produce ketones well
Arterial blood gas and serum electrolytes	In older children, absence of ketones with hypoglycemia is suspicious for fatty acid oxidation defect Assess for urine-reducing substances: Positive reducing substances with a negative dipstick for glucose is suggestive of galactosemia Assess for anion gap metabolic acidosis
Plasma NH_3	Rule out urea cycle defects or organic acidemias Mild elevations can be nonspecific
If metabolic acidosis is present:	
Serum lactate and pyruvate	Rule out lactic acidemias or organic acidemias
Urine organic acids	Rule out organic acidemias

If increased ammonia is present:	
Plasma amino acids	If elevated, then suspect aminoacidopathies
Urine organic acids	If elevated, suspect organic acidemias. If elevated orotic acid, suspect ornithine transcarbamylase deficiency

CBC = complete blood count; NH_3 = ammonia.

VI. Defects in Amino Acid Metabolism

The characteristics of phenylketonuria (PKU), tyrosinemia type 1, and maple syrup urine disease are summarized in **Table 5-5**. Other examples of defects of amino acid metabolism are described in this section.

A. **Homocystinuria.** An autosomal recessive disorder caused by cystathionine β-synthase deficiency, resulting in increased levels of homocysteine and methionine
   1. **Clinical features**
      a. **Marfanoid body habitus** (tall, slender), scoliosis, and pes planus
      b. Myopia. **High risk for lens dislocation.** Note that in *Marfan syndrome, the lens more often dislocates superiorly, whereas in homocystinuria, the lens more often dislocates inferiorly.*
      c. **Developmental delay**, with variable intellectual disability
      d. **Thromboembolism** can occur in any vessel, increasing the risk of stroke and systemic thrombosis, as well as developmental delay.
      e. **Key point:** If a patient is developmentally delayed and has a marfanoid habitus, perform screening tests for homocystinuria. Homocystinuria screening should also be performed in patients who test negative for Marfan syndrome.
   2. **Diagnosis**
      a. Plasma amino acids
         1. Increased homocysteine in plasma
         2. Increased methionine in plasma
      b. Genetic testing confirming homozygous mutations
   3. **Management**
      a. Special diet (methionine restricted, cystine enhanced)
      b. Betaine therapy (lowers homocysteine levels and reduces risk for thromboembolism)
      c. Some patients are responsive to treatment with vitamin B6.

B. **Urea cycle disorders (UCDs).** They result from deficiencies in one of the enzymes involved in the urea cycle. The urea cycle is responsible for the metabolism of excess nitrogen into urea. Defects in the urea cycle result in accumulation of ammonia, which is toxic, especially to the nervous system. The age of onset and severity of the different UCDs varies. **All of the UCDs are autosomal recessive, except ornithine transcarbamylase (OTC) deficiency, which has X-linked recessive inheritance.**
   1. **OTC deficiency**
      a. **Epidemiology: the most common of the UCDs**
      b. **Clinical features:** Male infants become symptomatic in first 48 hours of life with poor feeding, hypotonia, and hyperventilation, which can rapidly progress to lethargy, coma, and seizures.
      c. **Diagnosis of OTC deficiency**
         1. Initial labs usually include a blood gas showing **respiratory alkalosis** due to hyperventilation.
         2. Plasma ammonia concentration **>200 μmol/L**
         3. **Low or absent plasma citrulline** and high urine ototic acid level
      d. **Management of OTC deficiency** includes a low-protein diet and modalities to decrease ammonia levels. Medications can "scavenge" ammonia (e.g., sodium benzoate binds with ammonia and provides an alternative pathway to excrete nitrogen). For severe episodes of hyperammonemia, hemodialysis and/or liver transplant may be indicated.

e. **Prognosis of OTC deficiency** is variable, depending on the severity of hyperammonemic episodes. In most cases, at least some degree of developmental delay and intellectual disability will be present.

2. **Transient hyperammonemia of the newborn** is a self-limited disease that may present in premature infants within the initial 24–48 hours of life. Symptoms are nonspecific and can be similar to those of a UCD. Aggressive treatment of hyperammonemia is required to prevent neurologic sequelae.

C. **Organic acidemias.** The most common organic acidemias are caused by abnormal amino acid catabolism of branched-chain amino acids, and are characterized by urinary excretion of nonamino organic acids.

1. **Propionic aciduria** (**PA**) and **methylmalonic aciduria** (**MMA**) typically present after the first few days of life with vomiting, poor feeding, hypotonia, and other neurologic symptoms, which will progress if left untreated. Laboratory studies show metabolic acidosis, hyperammonemia, and ketotic hypoglycemia. Hyperammonemia results from inhibition of one of the urea cycle enzymes, and measurement of urine organic acids will diagnose the disorders.
2. **Isovaleric acidemia.** Presentation is similar to PA and MMA. Patient may also have an **odor of sweaty feet.**
3. **Glutaric acidemia type I.** This diagnosis should be considered in any infant with **macrocephaly**, basal ganglia changes on magnetic resonance imaging (MRI), and a **movement disorder** exacerbated by intercurrent illness.

Table 5-5
Characteristics of Selected Defects in Amino Acid Metabolism

	Phenylketonuria (PKU)	Maple Syrup Urine Disease	Tyrosinemia Type I
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive
Clinical features	Developmental delay Infantile hypotonia Mousy or musty odor Progressive mental retardation Eczema Decreased pigment (light eyes and hair) Mild PKU may present in early childhood with developmental delay, hyperactivity	Progressive vomiting and poor feeding Lethargy, hypotonia, and coma Developmental delay Maple syrup odor in urine Hypoglycemia and severe acidosis during episodes	Episodes of peripheral neuropathy Chronic liver disease Odor of rotten fish or cabbage Renal tubular dysfunction
Diagnosis	↑ Phenylalanine: Tyrosine ratio in serum	↑ Serum and urine branched-chain amino acids	Succinylacetone in urine
Management	Phenylalanine-restricted diet	Dietary protein restriction	Dietary restriction of phenylalanine, tyrosine, NTBC Liver transplant
Prognosis	Near-normal intelligence if diet restriction begun < 1 month of age	Protein restriction within 2 weeks of life may avert neurologic damage	Death by 1 year of age if disease begins in infancy Increased risk of hepatocellular carcinoma and cirrhosis

NTBC = 2-2 nitro-4-trifluoromethylbenzoyl 1,3-cyclohexanedione.

VII. Defects of Carbohydrate Metabolism

A. **Galactosemia** is an autosomal recessive disorder caused by galactose-1-phosphate uridyltransferase (GALT) deficiency.
   1. **Clinical features.** Patients are *unable to metabolize galactose and are therefore unable to tolerate lactose.* Symptoms start in newborns after ingesting lactose in breast milk or milk-based formulas.
      a. Feeding problems, failure to thrive, vomiting, and diarrhea
      b. Jaundice, hypoglycemia, hepatomegaly, liver failure, renal failure, and bleeding
      c. Patients are at *increased risk of developing Escherichia coli sepsis.*
      d. Developmental delay
      e. Cataracts
      f. Even treated patients may have long-term effects:
         1. Intellectual disability and neurologic defects, including ataxia
         2. Ovarian failure in females
   2. **Diagnosis**
      a. Increased red blood cell (RBC) galactose-1-phosphate in blood
      b. Absent or markedly decreased GALT activity in RBCs
      c. Urinary reducing substances (a nonspecific finding)
   3. **Management** includes restricting galactose intake and a lactose-free diet.
   4. **Prognosis** varies depending on the severity of initial symptoms before diagnosis and compliance with treatment. Even with treatment, patients may demonstrate speech defects and learning disabilities.

B. **Glycogen storage diseases (GSDs)**. A group of autosomal recessive disorders of glycogen metabolism that result in glycogen accumulation in various organs.
   1. **GSD type I (von Gierke disease)** is most commonly caused by **glucose-6-phosphatase deficiency.**
      a. **Clinical features**
         1. Often presents by 3–4 months of age with **hypoglycemia**, lactic acidosis, **hepatomegaly**, hyperuricemia, hyperlipidemia, **short stature**, and **cherubic facies.**
         2. Patients may develop hepatic adenomas that are at increased risk for malignant transformation to hepatocellular carcinoma.
      b. **Management** includes frequent feedings with complex carbohydrates and cornstarch to avoid hypoglycemia.
   2. **GSD type II (Pompe disease)** is caused by a deficiency of the lysosomal enzyme ***α*-glucosidase.**
      a. **Clinical features**
         1. Often presents in the first two months of life.
         2. Should be considered in the differential diagnosis of a profoundly hypotonic infant with failure to thrive, cardiomegaly, and macroglossia (large tongue).
         3. Additional findings include hepatomegaly, wide QRS complex, and elevated blood creatine kinase levels.
      b. **Management** includes supportive care for symptoms and enzyme replacement therapy.

C. **Hereditary fructose intolerance** is an autosomal recessive disorder caused by **aldolase B deficiency** that affects the ability to digest fructose.
   1. **Clinical features**
      a. Symptoms typically develop after fructose- and sucrose-containing foods are

introduced into the diet.

b. Symptoms include diarrhea, bloating, and abdominal pain.
c. Continued fructose ingestion can result in failure to thrive, as well as liver and kidney disease.

2. **Management** involves avoidance of fructose-containing foods and beverages.

VIII. Fatty Acid Oxidation Disorders

Fatty acid oxidation is a major source of energy and ketone generation. Fatty acid oxidation defects can have variable effects on different tissues and organ systems, but typically affected children present with **hypoketotic hypoglycemia** at different ages. **Medium-chain acyl-CoA dehydrogenase deficiency (MCAD) is the most common disorder.**

A. **Clinical features of MCAD.**
    1. Usually presents between 4 months to 4 years of age after a period of fasting or during an illness that caused vomiting.
B. **Presenting signs and symptoms of MCAD** include hypoglycemia, encephalopathy and liver dysfunction. **MCAD may resemble Reye syndrome and accounts for 5% of cases of sudden infant death.**
C. **Diagnosis of MCAD** is made by the presence of **abnormal urine organic acids and an abnormal acylcarnitine profile.** Plasma amino acids are normal.

IX. Lysosomal Storage Diseases

A. **Mucopolysaccharidoses** (**MPSs**) are caused by defects in enzymes required to break down glycosaminoglycans, resulting in accumulation of molecules in various organs. Patients are usually normal at birth but will show features of this disorder in the first few years of life. Common features include **short stature, intellectual disability, hepatosplenomegaly, and skeletal abnormalities.** X-rays may show **dysostosis multiplex** (a constellation of bony abnormalities that include a J-shaped sella turcica; malformed, ovoid, or beaklike vertebrae; short and thickened clavicles; and oar-shaped ribs). **Most MPSs are inherited in an autosomal recessive manner, with the exception of Hunter syndrome that is X-linked.**

1. **Hurler syndrome (MPS type I)** is an autosomal recessive disorder caused by α-l-iduronidase deficiency.
    a. **Clinical features**
        1. Hepatosplenomegaly, short stature, and **corneal clouding**
        2. Progressive **coarsening** of facial features, large tongue, umbilical hernia, hearing loss, and cardiomyopathy
        3. Kyphosis, stiff joints, and joint contractures
        4. Severe classic forms have developmental regression and death in childhood.
    b. **Diagnosis** may be made by increased urinary glycosaminoglycans, by enzyme assays, and by genetic testing.
    c. **Management** includes enzyme replacement therapy, bone marrow transplant, and supportive care.
2. **Hunter syndrome (MPS type II)** is an **X-linked recessive** disorder caused by a deficiency of idurontate-2-sulfatase.
    a. **Clinical features** overlap with those seen with Hurler syndrome, except that there is **no corneal clouding** ("a hunter needs to see clearly!). In severe classic forms of the disease, death usually occurs by later adolescence.
    b. **Diagnosis** is by a urine mucopolysaccharide spot test, by an enzyme assay, and by genetic testing.
    c. **Management** includes enzyme replacement therapy and supportive care.

B. **Sphingolipidoses.** A group of *autosomal recessive disorders* caused by defects in lipid metabolism. The following three disorders have high carrier frequency in the Ashkenazi Jewish population. Diagnosis is based on demonstration of deficient enzyme activity and/or by genetic testing.

1. **Gaucher disease type I** is caused by **β-glucocerebrosidase** deficiency and is the **most common lysosomal storage disease.** Clinical features include hepatosplenomegaly, cytopenias (anemia, thrombocytopenia, and leukopenia), and bone disease (osteopenia, lytic lesions, and fractures). Bleeding and complaints of "growing pains" may be presenting complaints. Bony disease results in an **Erlenmeyer flask appearance** of the distal femur on radiographs. **Gaucher cells** (foamy macrophages) are found on bone marrow biopsy. Management includes enzyme replacement therapy. More severe patients are classified as type II or III and have CNS manifestations.
2. **Tay–Sachs disease** is a **neurodegenerative disorder** caused by **hexosaminidase A** deficiency. Symptoms are usually apparent by 6 months of age. Clinical features include an increased startle reflex, hypotonia, loss of developmental milestones, hearing loss, **cherry-red spot** on the macula, and macrocephaly. As the disorder progresses, patients develop blindness, seizures, and autonomic dysfunction. Death usually occurs by 5 years of age.
3. **Niemann–Pick disease types A and B** are neurodegenerative disorders caused by **acid**

sphingomyelinase deficiency. Symptoms are usually noted by 3 months of age. There is a wide range of clinical features, but **hepatosplenomegaly** and progressive neurologic deterioration are constant features. A cherry-red spot may also be seen. Death usually occurs by 3 years of age.

X. Mitochondrial Disorders

These disorders affect multiple organ systems and may arise from mutations in the mitochondrial DNA (present in multiple copies per cell) or the nuclear DNA. Examples of mitochondrial DNA disorders include **Kearns–Sayre syndrome** (ophthalmoplegia, pigmentary degeneration of the retina, hearing loss, heart block, and neurologic degeneration) and **MELAS** (*m*itochondrial *e*ncephalopathy, *l*actic *a*cidosis, and *s*trokelike episodes). Diagnosis is based on clinical features, laboratory studies and genetic testing. Management is predominantly supportive but depends on the specific disorder.

XI. Disorders of Metal Metabolism

A. **Wilson disease** is an autosomal recessive **disorder of copper metabolism** that results in copper accumulation in various tissues, including the liver, brain, and cornea.
   1. **Clinical features**
      a. **Hepatic dysfunction.** Symptoms may include jaundice, hepatomegaly, hepatic failure, and cirrhosis.
      b. **Neurologic findings** include changes in intellect and behavior, dystonia, dysarthria, basal ganglia symptoms (Parkinson-like), seizures and dementia. *Wilson disease should be considered in a child who presents with new-onset behavior problems and difficulty learning.*
      c. **Kayser–Fleischer rings** are dark rings that encircle the iris due to copper deposition in Descemet's membrane.
   2. **Diagnosis**
      a. **Decreased serum ceruloplasmin** and increased serum copper
      b. Increased urine copper excretion
      c. Increased copper deposition on liver biopsy
   3. **Management** includes copper chelating agents such as **penicillamine** and avoidance of copper-containing foods.

B. **Menkes disease** is a progressive neurodegenerative **X-linked recessive** disorder caused by a **defect of copper transport.** Symptoms generally present at around 2–3 months of age with hypotonia, loss of developmental milestones, seizures, and failure to thrive. Physical features include hair that is sparse, lightly pigmented, and/or **kinky.** Diagnostic studies include **low serum copper and ceruloplasmin**, as well as low copper in tissues.

Review Test

1. A 1-week-old male infant is brought to the emergency department because of vomiting and decreased feeding for 3 days. On examination, you find that he is jaundiced and has hepatomegaly. The infant is admitted to the neonatal intensive care unit, but later he dies of *Escherichia coli* sepsis. Urine-reducing substances are positive. Which of the following is the most likely diagnosis?
   A. Gaucher disease
   B. Galactosemia
   C. Glycogen storage disease type 1
   D. Hurler disease
   E. Niemann–Pick disease
2. The parents of a 15-year-old boy consult you because they are concerned that their son has been acting strangely for the past 6 months. The boy has developed ataxia, tremors, and seizures. His father reports that his son seems to have developed a different personality. On examination, you note that the boy has brown rings at the edge of his corneas bilaterally. Which of the following is the best serum laboratory screen for the most likely diagnosis?
   A. Aluminum
   B. Lead
   C. Porphobilinogen
   D. Zinc
   E. Ceruloplasmin
3. A 6-year-old girl is brought to the clinic for a routine health maintenance visit. Her growth was normal until 2 years of age, when her height started to fall off the growth curve, steadily decreasing to below the fifth percentile. On examination, she has a webbed neck with a normal range of motion, a shield chest with widely spaced nipples, and scoliosis. Past medical history is significant for repaired coarctation of the aorta at 3 years of age. Which of the following is the most likely diagnosis?
   A. Noonan syndrome
   B. Achondroplasia
   C. Turner syndrome
   D. Russell–Silver syndrome
   E. Marfan syndrome
4. The mother of a 6-year-old boy brings her son to the office for a second opinion regarding her child's developmental delay. Your nurse takes the initial history and reports that he was adopted from another country. He was born at term by normal spontaneous vaginal delivery and seemed normal at birth, but has not been meeting his developmental milestones. After assessing his vital signs, your nurse pulls you aside and states, "That mother has no control over her child! He is hyperactive, still in diapers, and he stinks!" You walk into the examination room and immediately notice a mousy, musty smell. Which of the following is the most likely diagnosis?
   A. Phenylketonuria
   B. Tyrosinemia type I
   C. Maple syrup urine disease
   D. Homocystinuria
   E. Cystinuria
5. During a health maintenance visit, the parents of a 9-month-old infant note that their infant is unable to sit alone or roll over and startles very easily to sound. On examination, you note a cherry-red macula and poor eye contact. Which of the following is correct regarding the likely

diagnosis?

A. Hearing loss is a common complication of this condition.
B. Radiography of the lower extremity reveals an Erlenmeyer flask–shaped distal femur.
C. Radiography of the extremities reveals dysostosis multiplex.
D. Mild developmental delay is expected.
E. Microcephaly should be apparent.

6. A 5-day-old male infant is brought to the emergency department in coma. The infant's diaper has a sickly sweet smell. Laboratory results reveal no acidosis, hypoglycemia, or hyperammonemia, but there are significant amounts of ketones in the urine. Maple syrup urine disease is in the differential diagnosis. Which of the following statements regarding the acute management of this patient is correct?
   A. Antibiotics are not indicated because the infant likely has an inborn error of metabolism.
   B. Intravenous glucose should be administered.
   C. Total parenteral nutrition with protein and lipids should be started.
   D. Sodium benzoate should be administered.
   E. Enteral feeds with a soy-based formula should be given.
7. A 14-year-old boy with mental retardation has been referred to you. The underlying cause of his mental retardation has never been identified. On physical examination, you note that he has large ears and large testes. Which of the following syndromes is associated with mental retardation and these physical findings?
   A. Klinefelter syndrome
   B. Down syndrome
   C. Prader–Willi syndrome
   D. Williams syndrome
   E. Fragile X syndrome
8. A 4-month-old male infant has been brought to your office for a routine health maintenance evaluation. You note that his height is below the third percentile, yet his head circumference is at the 75th percentile. Facial findings include a prominent forehead and hypoplasia of the midface region. He also has trident-shaped hands and bilateral short femurs and upper arms. Which of the following is a potential complication of this patient's likely disorder?
   A. Lumbar kyphosis in late childhood
   B. Atlantoaxial instability
   C. Spinal cord compression
   D. Aortic dissection
   E. Delayed puberty
9. The mother of a 5-year-old boy is very concerned and shows you a note from his kindergarten teacher. The boy is very active, easily distracted, and unable to perform skills at the same level as others in his class, and the teacher expresses concern and wonders whether the boy could have a severe learning problem. On examination, you note that the boy's height and weight are at the 50th percentile, but his head appears very small. In addition, he has short palpebral fissures and a long, smooth philtrum with a thin upper lip. The remainder of the examination is normal. Which of the following is the most likely diagnosis?
   A. Angelman syndrome
   B. Down syndrome
   C. Fetal phenytoin syndrome
   D. Fetal alcohol syndrome
   E. Prader–Willi syndrome
10. A 12-year-old boy is brought to the office for a routine health maintenance visit by his parents. They report that he has struggled in school, requiring some special educational assistance since kindergarten, but has been otherwise healthy. Examination reveals that the boy is very

tall (>95th percentile) with long, thin arms with fingers of normal size. Mild scoliosis is evident. On auscultation, a murmur consistent with mitral regurgitation is audible. Based on the likely diagnosis, which of the following would you also expect to find on further evaluation?

A. Increased upper-to-lower segment ratio
B. Downward lens subluxation
C. Aortic root dilatation
D. Joint laxity
E. Hypogonadism

11. You are called to the newborn nursery to evaluate a 1-day-old female infant with unusual physical findings. On examination, you note that the neonate's hands are clenched with overlapping digits and her lower extremities are extended and crossed. You also note the presence of rocker bottom feet and delicate, small facial features. Which of the following chromosomal abnormalities is the most likely cause of the patient's features?

A. Trisomy 13
B. Trisomy 18
C. Trisomy 21
D. Deletion on chromosome 7
E. Absence of a region on paternally derived chromosome 15

The response options for statements 12–14 are the same. You will be required to select one answer for each statement in the following set.

A. Ehlers–Danlos syndrome
B. Cri du chat syndrome
C. Osteogenesis imperfecta
D. Williams syndrome
E. Angelman syndrome
F. Hurler syndrome
G. Hunter syndrome
H. Tay–Sachs disease
I. Gaucher disease
J. Homocystinuria

For each patient, select the most likely genetic condition.

1. Six-year-old boy with coarsened facial features, stiff joints, and a cloudy cornea
2. Four-year-old boy with microcephaly, hypertelorism, mental retardation, and a deletion on the short arm of chromosome 5
3. Fourteen-year-old girl with joint laxity, easily bruisable skin, and a defect in type V collagen

Answers and Explanations

1. **The answer is B** [VI.A]. Galactosemia should always be considered in the differential diagnosis of any newborn who develops hypoglycemia and has hepatomegaly. Infants with galactosemia develop vomiting and diarrhea after feeding with either breast milk or cow's milk–based formulas, because both types of feeding contain galactose. Soy milk does not contain galactose, which means that an infant who is fed a soy formula will not be symptomatic, which delays the diagnosis. Infants with galactosemia are vulnerable to *Escherichia coli* sepsis, and if the condition is not diagnosed, they may die in early infancy. Children with Gaucher disease present with neurodegeneration, splenomegaly, and bony changes (the most characteristic of which is an Erlenmeyer flask–shaped distal femur). After the first year of life, individuals with Hurler disease present with developmental delay, coarse facies, corneal clouding, and dysostosis multiplex. Individuals with with Niemann–Pick disease may present with hepatomegaly and seizures, but hypoglycemia and *E. coli* sepsis are not typical features of these diseases. Patients with glycogen storage disease type 1 may have hepatomegaly and hypoglycemia, but they will not have urine-reducing substances, and they do not have a special propensity to get *E. coli* sepsis.
2. **The answer is E** [XI.A.2]. Wilson disease should always be considered in a patient with personality changes, ataxia, and seizures. The patient's signs and symptoms are suggestive of Wilson disease, which is caused by a defect in copper excretion leading to copper deposition in the brain, eyes, and liver. Kayser–Fleischer rings, which represent copper deposition in Descemet's membrane, are pathognomonic for Wilson disease. The most commonly used screening test for Wilson disease is a low serum ceruloplasmin, which is very suggestive of the disorder. None of the other answer choices are associated with the signs and symptoms present in this patient. Aluminum, zinc, or lead does not cause the signs and symptoms seen in this patient. Serum porphobilinogen, while not addressed given the scope of this text, is elevated in acute intermittent porphyria, which may present with weakness, abdominal pain and autonomic instabilty.
3. **The answer is C** [III.C.1]. Girls with Turner syndrome are usually diagnosed in childhood after an evaluation for short stature, or during adolescence after an evaluation for delayed puberty. Patients with Turner syndrome classically have a webbed neck with a low posterior hairline, a shield chest with widely spaced nipples, and transient swelling of the hands and feet during the newborn period. Noonan syndrome can occur in females and has similar physical findings, but affected patients usually have right-sided heart lesions (e.g., pulmonary stenosis). Patients with Turner syndrome have left-sided heart lesions (e.g., coarctation of the aorta). Patients with achondroplasia are short from birth with shortening of the proximal long bones (rhizomelic short stature), those with Russell–Silver syndrome have short stature with skeletal asymmetry, and those with Marfan syndrome are tall, not short.
4. **The answer is A** [Table 5-5]. Patients with mild phenylketonuria (PKU) may present in childhood with developmental delay, hyperactivity, and a classic mousy or musty odor. Although newborn screening identifies the vast majority of cases, patients who are born in countries without newborn screening can present with untreated PKU. Patients with tyrosinemia type I present with peripheral neuropathy and renal and liver disease, and may produce an odor of rotten fish or cabbage. Children with mild maple syrup urine disease may also present with developmental delay, but their urine has a sweet maple syrup odor. Neither homocystinuria nor cystinuria has a peculiar odor as a feature; however, patients with homocystinuria may have developmental delay as a result of strokes from their hypercoagulable state.
5. **The answer is A** [IX.A.1]. The infant has infantile Tay–Sachs disease, a devastating

progressively neurodegenerative disease caused by hexosaminidase A deficiency. The onset of disease is in early infancy when the infant presents with a hyperactive startle and loses eye contact. Classic features include a cherry-red macula, enlarging head circumference, neurodegeneration with severe developmental delay, progressive blindness, and seizures. Death usually occurs by 5 years of age. An Erlenmeyer flask–shaped distal femur is a feature of Gaucher disease and not Tay–Sachs disease. Dysostosis multiplex (bony abnormalities that include a thickened skull, malformed vertebrae, and abnormal ribs and clavicle) is found in patients with mucopolysaccharidoses (e.g., Hunter and Hurler syndromes).

6. **The answer is B** [IV.C]. In general, the acute management of an inborn error of metabolism involves supplying a source of energy that can be used, removing toxic metabolites, and preventing continued exposure to the offending substance. Glucose is a basic energy source that can be used in any patient, regardless of the inborn error of metabolism, and should be administered intravenously in a patient who is markedly hypoglycemic and in coma or shock. Sodium benzoate is a scavenger agent that would be useful to facilitate ammonia excretion, but this patient does not have hyperammonemia. Although the patient's condition is likely to be an inborn error of metabolism (maple syrup urine disease, given the diaper odor consistent with the odor of maple syrup), sepsis is more common and can present in a similar fashion. Therefore, initial management should include intravenous antibiotics. Patients with maple syrup urine disease cannot adequately metabolize branched-chain amino acids; therefore, offering parenteral nutrition with protein would continue the toxic exposure. Soy formulas, while appropriate for galactosemia, still contain a full amount of branch-chain amino acids, and similar to regular formulas would overwhelm the patient's ability to metabolize the branched chain amino acids, resulting in toxic exposure as well.
7. **The answer is E** [III.C.2]. The characteristic physical features of fragile X syndrome include large ears, macrocephaly, and large testes. Klinefelter syndrome is characterized by tall stature, gynecomastia, and a small penis and testes; Down syndrome, by characteristic facial features, endocardial cushion defects, duodenal atresia, mental retardation, single palmar creases, and a wide space between the first and second toes; Prader–Willi syndrome, by infantile hypotonia, hypogonadism, short stature, and obesity and hyperphagia later in childhood; and Williams syndrome, by a loquacious very friendly personality, supravalvular aortic stenosis, and hypercalcemia. Testes are unaffected in Down syndrome and in Williams syndrome.
8. **The answer is C** [III.D.2.c]. This patient's physical features are consistent with achondroplasia, the most common skeletal dysplasia. Potential complications of this disorder include cord compression caused by foramen magnum stenosis, obstructive sleep apnea, and orthopedic problems such as genu varum and back pain caused by lumbar lordosis during late childhood. Atlantoaxial instability (a complication of Down syndrome), aortic dissection (a complication of Marfan syndrome), or delayed puberty is not associated with achondroplasia.
9. **The answer is D** [IV.E.3]. This patient's physical characteristics, along with learning problems and attention deficit/hyperactivity disorder, are consistent with fetal alcohol syndrome. Angelman syndrome is associated with severe mental retardation and a small head, although a puppetlike gait and inappropriate bouts of laughter are also characteristic. Down syndrome is also associated with mental retardation; however, the facial characteristics include upslanting palpebral fissures, epicanthal skin folds, and a protruding tongue. Fetal phenytoin syndrome is associated with mental retardation, nail and digit abnormalities, and cardiac defects. Prader–Willi syndrome is associated with hypogonadism, almond-shaped eyes, short stature, and hyperphagia with obesity during childhood.
10. **The answer is B** [V.A]. The clinical features of homocystinuria and Marfan syndrome overlap considerably; however, this patient most likely has homocystinuria based on the presence of cognitive delay and a marfanoid body habitus with fingers of normal length (i.e., no

arachnodactyly). All of these features are seen in homocystinuria but are not expected to be seen in Marfan syndrome. In addition, patients with homocystinuria usually have downward lens subluxation (upward lens subluxation is found in Marfan syndrome) and large, stiff joints (joint laxity is found in Marfan syndrome). Patients with both disorders have a decreased upper-to-lower segment ratio. Hypogonadism is absent in both disorders.

11. **The answer is B** [III.B.2]. The findings of scissoring of the lower extremities, clenched hands with overlapping digits, rocker bottom feet, and delicate small facial features are consistent with the diagnosis of trisomy 18, the second most common trisomy syndrome after trisomy 21. Trisomy 21 is the cause of Down syndrome and is associated with hypotonia, prominent epicanthal folds, upslanting palpebral fissures, and single palmar creases. Trisomy 13 is associated with midline defects of the brain and forebrain. Features include microphthalmia, holoprosencephaly, and cleft lip and palate. Absence of a region on the paternally derived chromosome 15 is the cause of Prader–Willi syndrome, a disorder associated with neonatal hypotonia, hypogonadism, almond-shaped eyes, and short stature. A deletion on chromosome 7 causes Williams syndrome, characterized by elfin facies and a loquacious personality.
12. **The answers are F** [IX.B.1]**, B** [III.A.14]**, and A** [III.A.6]**, respectively.** Hurler syndrome, a mucopolysaccharidosis in which glycosaminoglycans deposit in various tissues causing a progressive clinical picture, is characterized by corneal clouding, changes to the bone termed dysostosis multiplex, organomegaly, and progressively coarsened facies, including frontal bossing, widened nasal bridge, and thickening of the nasopharyngeal tissues. Hunter syndrome is similar but does not have corneal clouding.

    Cri du chat syndrome, caused by a partial deletion on the short arm of chromosome 5, is characterized by slow growth, microcephaly, mental retardation, hypertelorism, and a classic catlike cry.
    Ehlers–Danlos syndrome is caused by a defect in type V collagen that results in hyperextensible joints, fragile blood vessels that cause easily bruised skin, tissue paper–thin scars, and cardiovascular complications (e.g., mitral valve prolapse and aortic root dilatation that can lead to dissection).

CHAPTER 6

Endocrinology

Srinath Sanda

I. Short Stature

A. **General concepts**

1. **Definition.** Short stature is defined as **height that is 2 standard deviations (SDs) below the mean height of the population (i.e., below the third percentile), or 2 SDs below the midparental height (MPH).**
    a. **Normal variant short stature** describes a child with short stature and a normal growth velocity.
    b. **Pathologic short stature** describes a child with short stature **and a suboptimal growth velocity.**
2. **Key point: It is critical to evaluate growth velocity and not just absolute height** when evaluating short stature. Growth velocity is ideally calculated over at least a 6-month period. Using measurements collected over a shorter period of time may result in inaccurate growth velocity calculations.
3. **Key point:** Children who grow **2 inches per year (5 cm per year) between 3 years of age and puberty usually do not have an endocrinopathy or underlying pathologic disorder.**
4. In the first 2 years of life, a downward shift in the height percentile is not uncommon and may reflect *familial (or genetic) short stature, or constitutional delay of growth and puberty (CDGP).*
5. All patients with short stature who are more than 2 SDs below the mean or who have a growth velocity less than 5 cm per year are considered to have a pathologic growth disorder until proven otherwise.
6. **Determining the targeted MPH** is important in evaluating all patients with short stature (**Figure 6-1**).
    a. Most children, when they have completed their growth, are within ±2 SDs, or 4 inches, of their MPH.
    b. A major discrepancy between a child's present growth percentile and the targeted MPH percentile suggests a pathologic state.

B. **History**

1. **Perinatal history.** Assess for prematurity or intrauterine growth retardation (IUGR) or small for gestational age (SGA). A history of neonatal hypoglycemia, prolonged jaundice, and/or microphallus suggests **hypopituitarism resulting in growth hormone (GH) deficiency.**
2. **Chronic diseases** such as hypothyroidism, renal failure, central nervous system (CNS) disease, severe asthma with frequent and prolonged steroid use, sickle cell anemia, celiac disease, and inflammatory bowel disease may manifest as short stature.
3. **Chronic use of drugs,** such as steroids or stimulants for attention deficit/hyperactivity disorder, that result in significant appetite suppression and poor weight gain may lead to short stature.
4. **Family history, especially parental growth and pubertal histories, is important.** To evaluate for constitutional delay of growth and puberty, or CDGP [see section I.D.1], ask whether the family history is positive for males with "late growth spurts" in high school or college and the age of maternal menarche.
5. **Social history** is critical because children who live in neglected or hostile environments may exhibit short stature because of **psychosocial deprivation.**
6. **Review of systems** should include questions about cold intolerance and constipation (hypothyroidism), abdominal pain, diarrhea or bloody stools (inflammatory bowel disease), and headaches and vomiting (brain tumor).

7. **Dental history.** Delayed dental eruption may suggest CDGP or GH deficiency.

C. **Physical examination**
   1. **Accurate height and weight** should be plotted on a US National Center for Health Statistics (NCHS) growth chart, along with previous growth points, to assess the child's growth pattern. The MPH should be noted on the growth chart.
   2. **Measure the patient's upper-to-lower (U/L) body segment ratio.**
      a. **Lower segment** = pubic symphysis to the heel
      b. **Upper segment** = total height minus lower segment
      c. **Normal ratios**
         1. Birth = 1.7
         2. 3 years of age = 1.3
         3. >7 years of age = 1.0
      d. **Abnormal U/L ratio** suggests **disproportionate short stature** [see section I.D.2.b].
   3. Thorough physical examination should include a funduscopic examination, assessment for midline defects (central incisors, cleft palates, etc.), assessment of thyroid size, evaluation for stigmata of genetic syndromes (e.g., web neck, shield chest, and abnormal carrying angles are suggestive of Turner syndrome; see Chapter 5, section IV.C.1), scoliosis screening, and Tanner staging (see Chapter 3, section I.A.2).

D. **Categorization of short stature** (**Figure 6-2**)
   1. **Normal variant short stature** refers to children with **short stature and normal growth velocity**. The two most common categories of normal variant short stature are **familial** (or genetic) short stature and **CDGP**.
      a. **Familial (or genetic) short stature** is defined as a height at least 2 SDs below the mean but within 2 SD of MPH with a **normal bone age, a normal onset of puberty, and a minimum growth velocity of 2 inches (or 5 cm) per year.**
      b. **Constitutional delay of growth and puberty (CDGP)** is defined as short stature with a *delayed bone age, late onset of puberty and a minimum growth velocity of 2 inches (or 5 cm) per year.*
   2. **Pathologic short stature.** Pathologic short stature, in which height fall more than 3 SDs below the mean with **abnormal growth velocity** (i.e., growth velocity less than 2 inches [or 5 cm] per year), may be categorized as **proportionate** or **disproportionate.**
      a. **Proportionate short stature** is defined as short stature with a normal U/L ratio [see section I.C.2.c]. It is important to distinguish between prenatal onset and postnatal onset.
         1. Causes of **prenatal-onset proportionate** short stature include
            a. **Environmental exposures** (e.g., in utero exposure to tobacco and alcohol)
            b. **Chromosomal disorders** (e.g., Down syndrome, Turner syndrome)
            c. **Genetic syndromes** (e.g., Russell–Silver syndrome, Prader–Willi syndrome; see Chapter 5, sections IV.E.5 and IV.E.2, respectively)
            d. **Viral infection** early in pregnancy (e.g., cytomegalovirus, rubella)
         2. Causes of **postnatal-onset proportionate** short stature
            a. **Malnutrition**
            b. **Psychosocial causes** (e.g., neglect, child abuse)
            c. **Organ system diseases**, including gastrointestinal diseases (inflammatory bowel disease, celiac disease), cardiac diseases (cyanotic congenital heart disease), renal diseases (renal failure, renal tubular acidosis), chronic lung diseases (cystic fibrosis, asthma), and endocrinopathies (hypothyroidism, GH deficiency, and cortisol excess; see also section I.F)
      b. **Disproportionate short stature** is defined as short stature in patients who are short

legged with an increased U/L ratio, suggesting rickets or a skeletal dysplasia.
    1. Consider **rickets** in patients with frontal bossing, bowed legs, low serum phosphorus level, and high serum alkaline phosphatase [see section X.C].
    2. Consider some form of **skeletal dysplasia** (e.g., achondroplasia) in patients who are short with short limbs (see Chapter 5, section III.H).

E. **Evaluation of pathologic short stature**
    1. **Laboratory studies**
        a. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), thyroxine (T_4), thyroid-stimulating hormone (TSH), tissue transglutaminase IgA (TTG IgA), total serum IgA, serum electrolytes including calcium and phosphorus, and serum creatinine and bicarbonate levels should be obtained.
        b. **Insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGF-BP3)** are indirect measures for GH deficiency. **Random GH level should not be measured outside of the neonatal period**, as most GH is released in a pulsatile fashion.
        c. Chromosome analysis in girls to evaluate for Turner syndrome
        d. GH stimulation testing (with agents such as clonidine or arginine) may be needed.
    2. **Radiographic studies**
        a. **Bone age** determination (anterior–posterior [AP] film of the left hand and wrist to assess the characteristics of the epiphyses or growth plates) is helpful to compare with chronologic age (**Table 6-1**).
        b. Neuroimaging (magnetic resonance imaging [MRI] is preferable with thin cuts through the pituitary) is appropriate if GH deficiency or concerns for other CNS pathology exist. It is not otherwise part of the routine evaluation of children with short stature.
    3. **Key point:** Patients with poor growth velocity with normal screening laboratory results, but low IGF-1 and delayed bone age, should have an additional workup for GH deficiency (i.e., GH stimulation testing).

F. **Endocrinopathies that cause short stature**
    1. **GH deficiency is uncommon.**
        a. **Clinical features.** A neonatal history of prolonged neonatal jaundice, hypoglycemia, microphallus, cryptorchidism, and midline defects (e.g., cleft palate) may be present. Neonates with GH deficiency are typically not SGA. Older children with GH deficiency may have obesity and cherubic facies. The growth curve demonstrates poor growth velocity (less than 2 inches or 5 cm per year).
        b. **Causes** include brain tumors, prior CNS irradiation, CNS vascular malformations, autoimmune diseases, head trauma, and congenital midline defects. (Consider GH deficiency in patients with a single central maxillary incisor or with cleft palate.)
        c. **Evaluation**
            1. **Imaging studies.** See I.E.2.a and I.E.2.b. *Key point:* All patients with GH deficiency must have neuroimaging, preferably with an MRI with thin cuts through the pituitary.
            2. **Laboratory studies.** Low IGF-1 and IGF-BP3 levels, as well as a poor response on GH stimulation testing (with l-DOPA [L-3,4-dihydroxyphenylalanine], arginine, glucagon, or clonidine)
        d. **Management.** Treatment includes daily subcutaneous injections of recombinant GH until a bone age determination demonstrates that the patient has reached nearly maximal growth potential (by about 13–14 years of age in girls and 15–16 years of age in boys). In cases of CNS tumors, GH should not be used until the tumor has been treated.

2. **Hypothyroidism.** The most common cause of hypothyroidism is Hashimoto thyroiditis [see section IX.B.2.b]. Patients will present with increased TSH, low T_4, and positive antithyroid peroxidase antibodies.
3. **Hypercortisolism.** The most common cause of hypercortisolism is iatrogenic, as a result of prolonged use of steroids [see section IV.E]. Patients present with a history of poor growth and increasing weight gain, purpuric stretch marks and a dorsal neck fat pad on examination, with delayed bone age.
4. **Turner syndrome** (see also Chapter 5, section IV.C.1). Female patients who are missing a part or all of one of the X chromosomes may present with short stature or lack of puberty. GH treatment has been shown to improve the ultimate height of these patients. **Key point:** All girls with short stature should have a karyotype, as the physical features of Turner syndrome can be subtle.

$$\text{MALE MPH} = \frac{\text{Father's height} + \text{Mother's height} + 5 \text{ inches}}{2}$$

$$\text{FEMALE MPH} = \frac{\text{Father's height} + \text{Mother's height} - 5 \text{ inches}}{2}$$

FIGURE 6.1 Determination of midparental height (MPH). Most patients, when they have completed their growth, will be within ±2 standard deviations, or 4 inches, of the MPH. For example, if a boy has a father who is 5 feet 9 inches in height and a mother who is 5 feet in height, then the MPH is 5 feet 7 inches ± 4 inches.

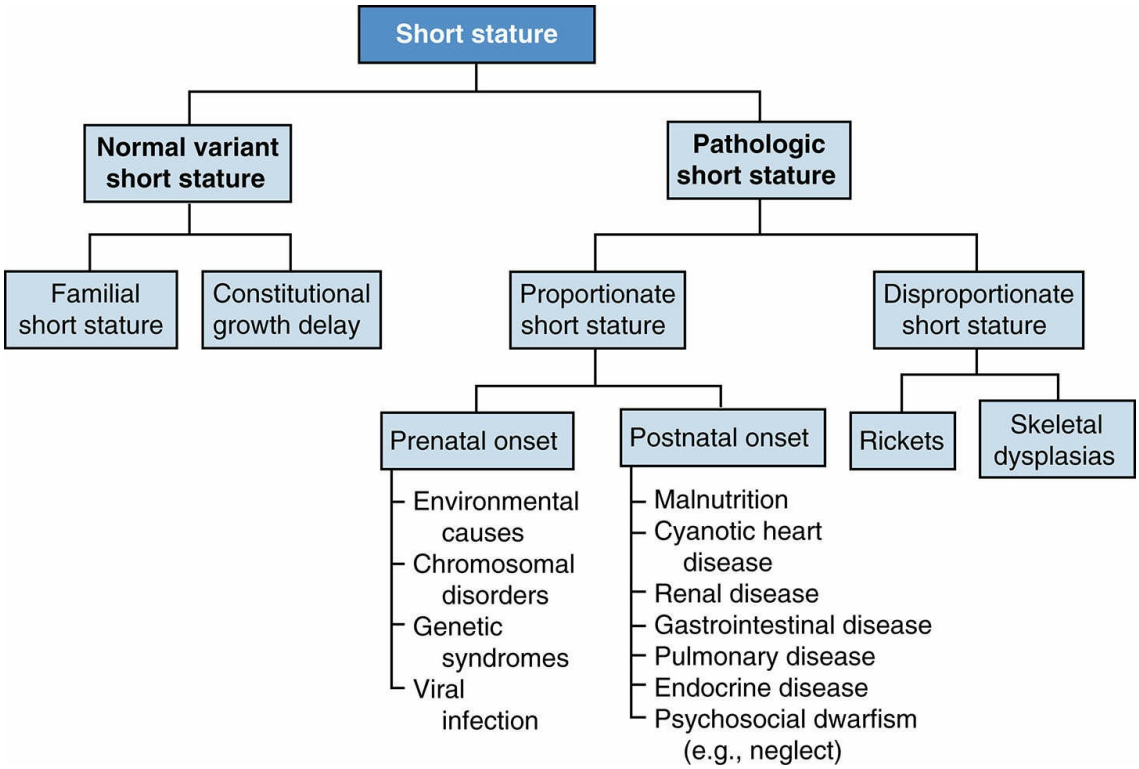

FIGURE 6.2 Differential diagnosis of short stature.

Table 6-1
Using Bone Age in the Differential Diagnosis of Short Stature

Bone Age = Chronologic Age	Bone Age < Chronologic Age
Familial short stature	Constitutional short stature
Intrauterine growth retardation	Hypothyroidism
Turner syndrome	Hypercortisolism
Skeletal dysplasia	Growth hormone deficiency
	Chronic diseases

II. Disorders of Puberty

A. **Normal puberty (see also Chapter 3, section I.A.2)**
   1. In the prepubescent state, sex steroids (testosterone and estradiol) are suppressed owing to an inactive hypothalamic–pituitary–gonadal axis (HPGA).
   2. Puberty begins when there is a reduction in this hypothalamic inhibition, resulting in activation of the HPGA.
   3. The HPGA releases gonadotropin-releasing hormone (GnRH) from the hypothalamus, which binds to receptors in the pituitary gland and causes the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
   4. **Female puberty.** The different stages of pubertal development are defined as follows. **It is important, however, to be aware that the age of onset and subsequent course of hormonal and physical changes during puberty are variable.**
      a. **Onset is between 8 and 13 years of age.**
      b. **Thelarche** is the onset of breast development as a result of the release of estrogen, and **adrenarche** is the onset of pubic or axillary hair development as a result of the release of adrenal androgens. *Breast buds are usually the first sign of puberty,* although in 15% of girls, pubic hair develops first.
      c. **Menarche** is the onset of the menstrual cycle. **Menstruation** begins at 9–15 years of age, with a mean onset of 12.5 years of age.
      d. **FSH** stimulates the ovaries to produce ovarian follicles, which in turn produce estrogen.
      e. **LH** is responsible for the positive feedback in the middle of the menstrual cycle, resulting in the release of an egg.
      f. **Tanner staging.** See Chapter 3, section I.A.2.c.
   5. **Male puberty**
      a. **Onset is between 9 and 14 years of age.**
      b. *Testicular enlargement is usually the first sign of puberty* (≥4 mL as measured with an orchidometer or >2.5 cm in length).
      c. Seventy-five percent of the testicular volume is the seminiferous tubules.
      d. **FSH** in boys stimulates the Sertoli cells in the seminiferous tubules of the testes to produce sperm.
      e. **LH** in boys stimulates the testicular Leydig cells to produce androgens, which in turn are responsible for penile enlargement and the growth of axillary, facial, and pubic hair.
      f. **Tanner staging.** See Chapter 3, section I.A.2.c.
   6. African American children may develop secondary sexual characteristics earlier than other children.
   7. Moderate to severe obesity may be associated with sexual precocity.

B. **Precocious puberty**
   1. **Definitions**
      a. **Girls:** presence of *breast development or pubic hair before 8 years of age*
      b. **Boys:** presence of *testicular changes, penile enlargement, or pubic or axillary hair before 9 years of age*
   2. **Categories**
      a. **Premature thelarche**
         1. **Definition.** There is visible or palpable breast tissue only, with no other secondary sexual characteristics. The growth pattern should be normal, and no pubic hair should be apparent.

2. **Epidemiology.** This is a **common and benign** condition usually presenting in the first 2 years of life.
3. **Etiology.** This condition is caused by a transient activation of the HPGA, resulting in transient ovarian follicular stimulation and a release of low levels of estrogen.
4. Generally no workup is necessary as long as no other secondary sexual characteristics (clitoromegaly, pubic hair, enlarged labia minora, pink vaginal mucosa) or growth spurts are noted. Patients should be followed, and if progressive enlargement of the tissue is noted, they should be referred to a pediatric endocrinologist.

b. **Premature adrenarche**
1. **Definition.** Early onset of pubic or axillary hair growth without the development of breast tissue or enlarged testes.
2. **Epidemiology.** This condition is *more common in girls* than in boys.
3. **Classic presentation** occurs after 5 years of age, with the onset of pubic hair growth, axillary hair growth, and apocrine odor. No breast tissue or testicular enlargement is noted, and there is no clitoromegaly. Growth is normal without advancement of bone age.
4. Most patients should have a bone age radiograph, as well as laboratory testing for morning levels of 17-hydroxyprogesterone (17-OHP), as some patients with nonclassic congenital adrenal hyperplasia (CAH) may present with premature adrenarche.
5. In most cases, no treatment is indicated.

c. **Central (or isosexual) precocious puberty (CPP)**
1. **Definition.** The early onset of gonadotropin-mediated (i.e., mediated by FSH and LH) puberty.
2. **Epidemiology. Girls** have a higher incidence of CPP than boys.
3. **Clinical features**
    a. **In girls,** physical examination shows breast development, pubic hair, and rapid growth.
    b. **In boys,** physical examination shows testicular enlargement, pubic hair, and rapid growth.
4. **Etiology**
    a. **In girls,** most cases are **idiopathic.**
    b. **In boys,** sexual precocity tends to be pathologic, and all patients need evaluation with an MRI of the head.
    c. **CNS abnormalities that may cause CPP** include hydrocephalus, CNS infections, cerebral palsy, benign hypothalamic hamartomas, malignant tumors such as astrocytomas and gliomas, and severe head trauma.
    d. **Hypothyroidism** may rarely present with CPP, but in this case, there is **poor growth and a delayed bone age** (unlike all other causes of sexual precocity in which growth is accelerated).
5. **Evaluation**
    a. **FSH, LH,** and **sex steroid levels are elevated.** In particular, unstimulated gonadotropin testing should be done with **ultrasensitive or pediatric-specific assays,** and not routine LH and FSH assays that are designed for use in adults.
    b. The **GnRH stimulation test** can demonstrate premature activation of the hypothalamus. Access to GnRH agonists (GnRHa) is limited in the United States; therefore, short-acting GnRHa such as leuprolide acetate

are used in stimulation tests.

1. By injecting synthetic GnRHa into a patient, the LH response, and to a lesser degree the FSH response, can be used as an assessment of the activation of the HPGA. Patients with CPP have a **dramatic increase in LH** secretion when compared with baseline levels.
2. On the other hand, prepubertal patients whose HPGA has not yet been activated, and patients with peripheral precocious puberty (PPP) in which peripherally produced sex steroids suppress pituitary gonadotropin secretion, would be expected to have a **flat response** (i.e., no increase in LH secretion) on injection of synthetic GnRHa.

c. **An MRI of the head** should be performed in **all boys,** and in girls with any neurologic symptoms (e.g., headaches or seizures) or with rapid pubertal changes.

d. Thyroid tests (TSH and T_4) should be performed to rule out hypothyroidism.

d. **PPP or heterosexual gonadotropin-independent puberty**

1. **Definition.** Precocious puberty that is independent of the HPGA (i.e., caused by the **peripheral production** of male or female sex steroids and not FSH- or LH-mediated). **The hallmark of PPP is suppressed unstimulated gonadotropin levels and/or a flat response on GnRHa stimulation testing, because the HPGA has not been activated.**
2. **Clinical features**
   a. **Boys** present with either feminization (gynecomastia) or with premature onset of pubic hair. Note that there is **usually no testicular enlargement** because these patients do not have an increase in FSH, which would stimulate seminiferous tubule enlargement [see exceptions in section II.B.2.d.(3).(c)].
   b. **Girls** present with typical secondary sexual characteristics or virilization.
3. **Etiology.** Causes may differ in boys and girls but, in general, include exposure to exogenous sex steroids (found in some skin lotions or foods), McCune–Albright syndrome, gonadal tumors, adrenal tumors, and nonclassic CAH; see section IV.C.3.a.(3). **All of these causes are independent of the HPGA.**
   a. **In boys,** consider adrenal tumors, Leydig cell tumors (presenting with asymmetric testicular enlargement), nonclassic CAH, β-human chorionic gonadotropin (β-HCG)–producing tumors, McCune–Albright syndrome, and testotoxicosis.
   b. **In girls,** consider adrenal tumors, virilizing ovarian tumors (arrhenoblastomas), feminizing ovarian tumors (juvenile granulosa tumors), nonclassic CAH, and McCune–Albright syndrome.
   c. **Specific causes of PPP in males that result in testicular enlargement**
      1. **McCune–Albright syndrome** is characterized by fracture-prone bony changes (polyostotic fibrous dysplasia), skin findings (irregularly bordered hyperpigmented macules, or **"coast of Maine"** jagged-bordered **café-au-lait spots**), and endocrinopathies (PPP or hyperthyroidism). Patients often have enlarged gonads, but their secretion of sex steroids is independent of the HPGA.
      2. **Testotoxicosis** is a rare disease in which the testes enlarge bilaterally independent of the HPGA.
      3. **β-HCG—secreting tumors** are unique to boys. These tumors are

found in the chest, pineal gland, gonad, or liver (hepatoblastoma). Because the β-HCG molecule cross-reacts with LH, it too can bind to LH receptors and enlarge the testes slightly, stimulating Leydig cells and secreting androgens.

4. **Evaluation.** A GnRH stimulation test may be warranted in addition to the following:
    a. **In boys,** check serum FSH, LH, testosterone, and β-HCG levels.
    b. **In girls,** check serum FSH, LH, and estradiol levels.
    c. Perform imaging (testicular, abdominal, CNS, etc.) studies, depending on the suspected etiology.
5. **Management.** Treatment is based on the underlying cause.

C. **Delayed puberty**

1. **Definitions**
    a. **Boys:** No testicular enlargement by 14 years of age.
    b. **Girls:** No breast tissue by 13 years of age, or no menarche by 16 years of age.
2. **Classification.** Two categories of disorders may result in delayed puberty.
    a. **Hypogonadotropic hypogonadism.** Because of the inactivity of the hypothalamus and pituitary gland, these patients have a low FSH, low LH, and, in turn, low testosterone and low estradiol, with a prepubertal (flat) GnRH stimulation test.
    b. **Hypergonadotropic hypogonadism.** Because of end-organ dysfunction (i.e., gonadal failure), these patients have high FSH and high LH levels with low testosterone or low estradiol levels. There is no abnormality in the hypothalamus or pituitary gland.
3. **Etiology of hypogonadotropic hypogonadism**
    a. **CDGP** (i.e., immature hypothalamus or "late bloomers") is much more common in **boys** than in girls. Often there is a family history in one parent (i.e., mother had late menarche or father had his growth spurt late in high school or in college). Patients with hypogonadotropic hypogonadism frequently have CDGP [see section I.D.1.b for a description of growth pattern].
    b. **Chronic diseases** can cause pubertal delay (e.g., inflammatory bowel disease, anorexia nervosa, renal failure, and heart failure).
    c. **Hypopituitarism** of any cause (e.g., brain tumors)
    d. **Primary hypothyroidism**
    e. **Prolactinoma**
    f. **Genetic syndromes**
        1. **Kallman syndrome.** Isolated gonadotropin deficiency associated with anosmia (inability to smell)
        2. **Prader–Willi syndrome** (see Chapter 5, section IV.E.2)
        3. **Bardet–Biedl syndrome.** Obesity, retinitis pigmentosa, hypogonadism, and polysyndactyly
4. **Etiology of hypergonadotropic hypogonadism**
    a. **Chromosomal disorders**
        1. **In boys,** consider **Klinefelter syndrome (XXY;** see Chapter 5, section IV.C.2).
        2. **In girls,** consider **Turner syndrome** or gonadal dysgenesis (see Chapter 5, section IV.C.1).
    b. **Autoimmune disorders** (e.g., hypogonadism in autoimmune oophoritis, which may also be associated with Hashimoto thyroiditis or Addison disease)
5. **Evaluation of delayed puberty.** A CBC, ESR, bone age, TSH and T_4, testosterone or estradiol, FSH, LH, and prolactin levels are necessary. Neuroimaging may be warranted as well.

III. Disorders of Sexual Differentiation (DSD or Formerly Known as Ambiguous Genitalia)

A. **Normal sexual differentiation (Figure 6-3)**
   1. **During the first 7 weeks of gestation,** the gonadal tissue remains undifferentiated. The final appearance of gonadal tissue is dependent on both genetic and hormonal influences.
   2. **Male sexual differentiation** is an active process, whereas **female sexual differentiation** develops by default when genetic and hormonal influences are absent.

B. **Male sexual differentiation** is initiated by the ***SRY* gene** located on the short arm of the Y chromosome. By 9 weeks' gestation, the *SRY* gene differentiates the gonads into fetal testes, which subsequently produce **testosterone** and **anti-Müllerian hormone (AMH or previously called Mullerian inhibiting substance).**
   1. **Internal ducts.** In the genetic XY male, testosterone made by fetal Leydig cells stimulates the development of the Wolffian ducts (epididymis, vas deferens, and seminal vesicles), and AMH made by fetal Sertoli cells inhibits the development of the Müllerian structures (fallopian tubes, uterus, and upper one-third of the vagina).
   2. **External genitalia.** The conversion of testosterone to dihydrotestosterone (DHT) by 5α-reductase occurs in the skin of the external genitalia. DHT is responsible for penile enlargement, scrotal fusion, and the entire masculinization of the external genitalia. By 12 weeks, this process is complete, except for penile growth, which continues to term.

C. **Female sexual differentiation.** In the absence of the *SRY* gene, the gonads become ovaries.
   1. **Internal ducts.** Because there is no testicular tissue, there is no secretion of testosterone or of AMH, resulting in the regression of the Wolffian ducts and the development of the Müllerian structures, respectively.
   2. **External genitalia.** The external genitalia do not virilize because there is a lack of testosterone and of DHT. This results in the development of the labia, the clitoris, and the lower two-thirds of the vagina.

D. **Differential diagnosis of the undervirilized male** (i.e., a neonate who usually has a 46, XY karyotype with ambiguous genitalia and one or both testes palpable; **Figure 6-4**).
   1. **Disorders of testosterone synthesis.** Many inherited enzyme deficiencies result in low testosterone levels (i.e., any enzyme deficiency in the pathway of androgen synthesis in **Figure 6-5**).
      a. **Smith–Lemli–Opitz syndrome.** This syndrome is due to defective 3β-hydroxysteroid-Δ7 reductase, the last step in cholesterol biosynthesis. Without functional cholesterol biosynthesis, steroid hormone production is defective. Patients can have microcephaly, cleft lip/palate, liver disease, syndactyly of the second and third toes and holoprosencephaly. Genital ambiguity is variable.
      b. **5α-Reductase deficiency.** Patients cannot convert testosterone to DHT, the more potent version of testosterone that binds to androgen receptors and virilizes the external genitalia. Patients may present with ambiguous genitalia, such as varying degrees of hypospadias, or as adolescents with incomplete pubertal progression. Some patients present as adolescent females who do not develop breast tissue (as opposed to patients with androgen insensitivity—see below). **A ratio of testosterone:DHT of >20:1 with β-hCG stimulation strongly supports the diagnosis. By comparison, the ratio in normal male infants is typically <10.**
   2. **Disorders of testosterone action are usually due to androgen insensitivity.** These patients have X-linked partial or complete peripheral androgen resistance resulting from defective androgen binding to the androgen receptor in the genital tissue. Presentation is

highly variable. Complete forms typically present as females with primary amenorrhea and breast development, wheras partial forms may present with some degree of impaired virilization observed in the neonate (such as cryptorchidism or hypospadias). Mullerian structures are usually absent. Patients have normal adrenal metabolites (17-OHP levels, etc.), but exaggerated levels of testosterone and DHT are seen after β-hCG stimulation.

3. **Disorders of gonad differentiation**
    a. **Gonadal dysgenesis (GD). May be complete, partial, or mixed.** Karyotypes are diverse and may include 45, XO/46, XY mosaicism. The clinical presentation is variable, as patients may have completely normal external female genitalia, to some degree of ambiguous genitalia with some internal Mullerian structures (i.e., fallopian tubes, etc.). Typically these patients have low to undetectable levels of AMH, and the gonads do not respond to stimulation with β-hCG.
    b. **True hermaphroditism (also known as ovotesticular DSD).** These patients may have ambiguous genitalia with both ovarian and testicular gonadal tissue and both Mullerian and Wolffian internal ducts. The gonads generally have some function, and levels of AMH are normal. The gonads do respond to β-hCG stimulation. Usually the karyotype is 46, XX, but it can be 46, XY.

E. **Differential diagnosis of ambiguous genitalia in the virilized female** (i.e., a **female** who is a genetic XX with ambiguous genitalia and no gonads palpable; **Figure 6-6**).
    1. **CAH caused by 21-hydroxylase (21-OH) deficiency is the most common cause of female pseudohermaphroditism** [see section IV.C]. 11β-Hydroxylase (11β-OH) deficiency and 3β-hydroxysteroid dehydrogenase deficiency are other causes of CAH.
    2. **Virilizing drug** used by mother during pregnancy
    3. **Virilizing tumor** in mother during pregnancy

F. **Evaluation of the patient with ambiguous genitalia**
    1. **Careful history.** Maternal history of drugs or virilization during pregnancy, family history of androgen insensitivity, CAH, or consanguinity.
    2. **Physical examination.** Presence or absence of gonads, labioscrotal swelling, bifid scrotum, labial fusion, urogenital sinus, or hypospadias. Palpable gonads suggest that the neonate has an XY karyotype. **(Key point: Increased blood pressure suggests CAH with 11β-OH deficiency, and decreased blood pressure suggests adrenal insufficiency;** see sections IV.B.1.a and IV.C.3.b.)
    3. **Chromosome studies (including polymerase chain reaction [PCR] or fluorescent in situ hybridization [FISH] for the *SRY* gene, and a karyotype)**
    4. **Radiographic studies** include pelvic ultrasound and genitogram to define the internal genitourinary anatomy.
    5. **Laboratory studies**
        a. **Undervirilized males. Besides the abovementioned chromosome studies, electrolytes and 17-OHP levels should be ordered.** DHT and testosterone levels (preferably after β-hCG stimulation) with LH, FSH, AMH, and androstenedione levels may be warranted. If serum testosterone is low, further evaluation for an inborn error in androgen synthesis is indicated.
        b. **Virilized females.** Serum electrolytes, testosterone level, and further studies to look for evidence of CAH (17-OHP, etc.) are indicated [see Figure 6-5 and section IV.C.4].
    6. **Management. Evaluation is complex, and gender assignment should not be rushed. Generally, these patients should be referred to centers with multidisciplinary teams of pediatric endocrinologists, geneticists, and pediatric urologists.** The **initial** focus should be on clear communication with the family regarding the process of evaluation.

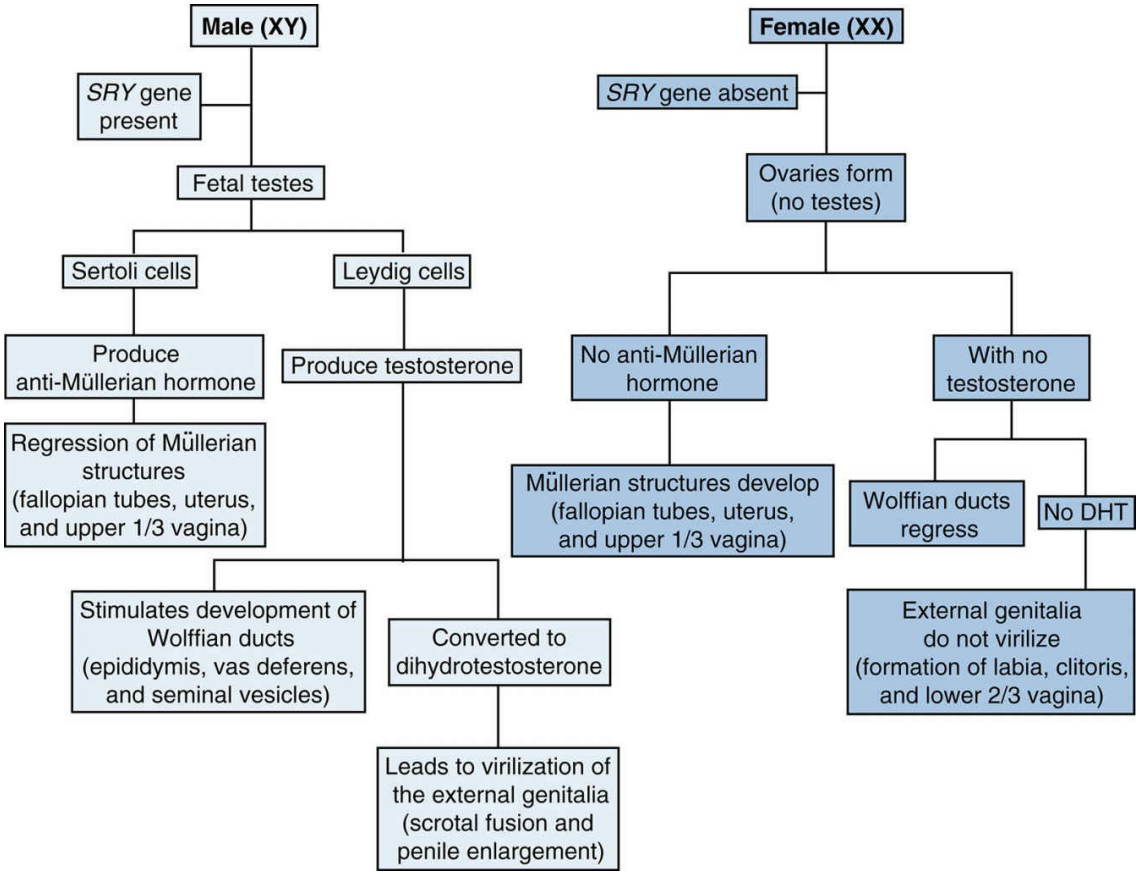

FIGURE 6.3 Normal sexual differentiation in utero. *DHT* = dihydrotestosterone.

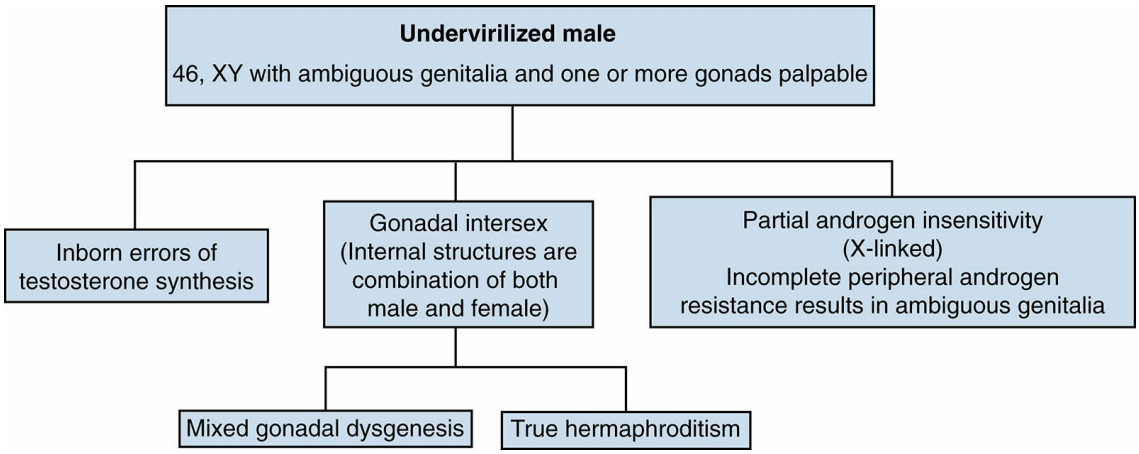

FIGURE 6.4 Differential diagnosis of ambiguous genitalia in an undervirilized male.

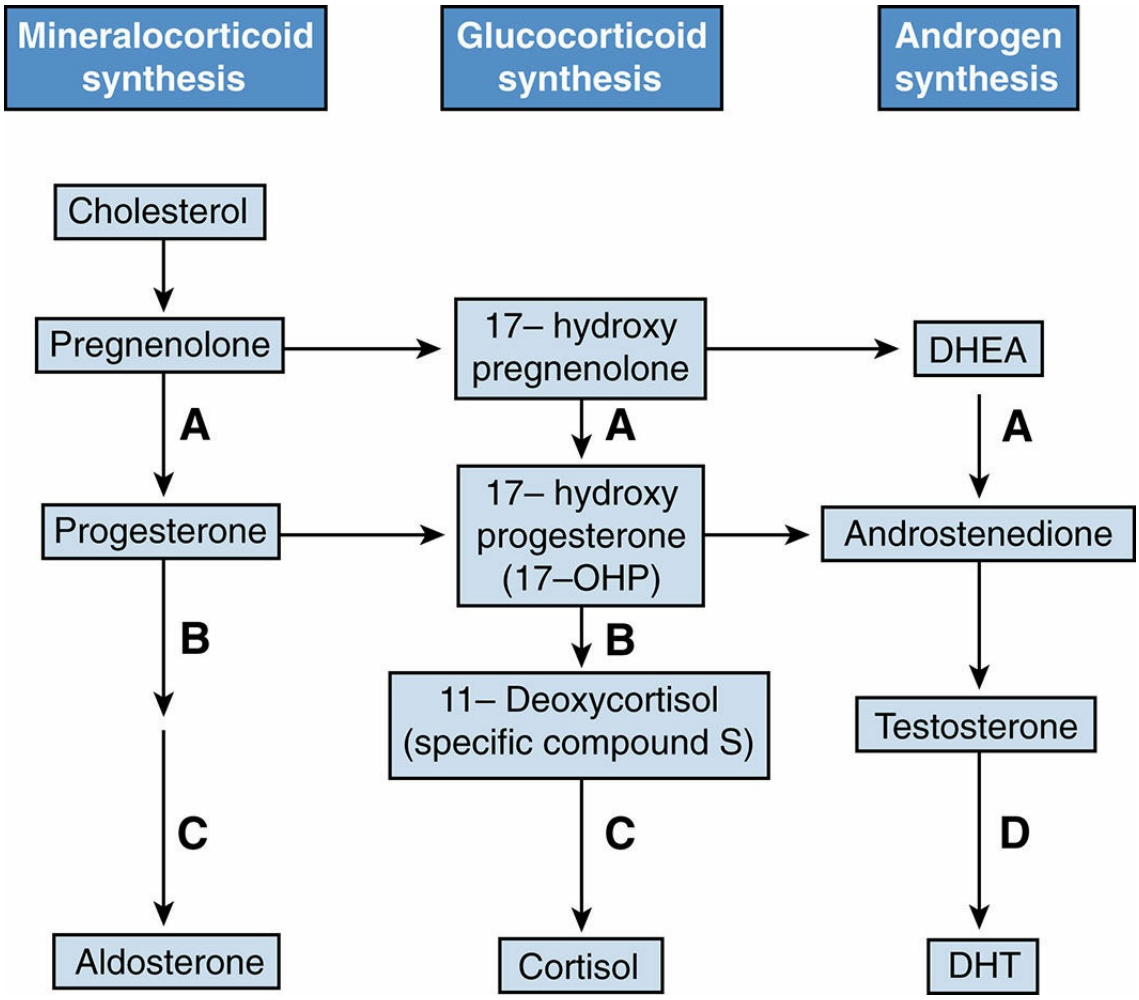

FIGURE 6.5 Steroid pathways in the adrenal cortex. *A* = 3β-hydroxysteroid dehydrogenase; *B* = 21-hydroxylase (21-OH); *C* = 11β-hydroxylase (11β-OH); *D* = 5α-reductase; *DHEA* = dehydroepiandrosterone; *DHT* = dihydrotestosterone.

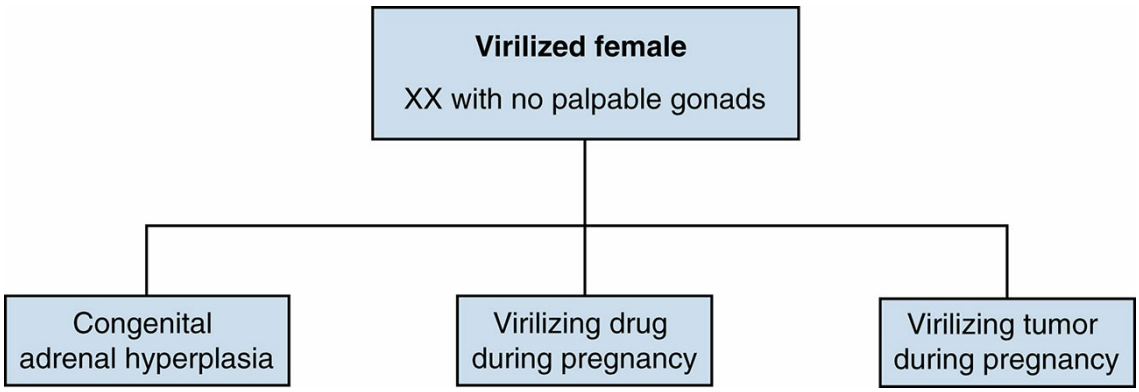

FIGURE 6.6 Differential diagnosis of ambiguous genitalia in a virilized female.

IV. Disorders of the Adrenal Gland

A. **General principles of adrenal function**
   1. The **adrenal gland** is composed of two parts, the **adrenal cortex,** which synthesizes a multitude of different steroid compounds, and the **adrenal medulla,** which produces catecholamines (i.e., epinephrine).
   2. **Three major pathways** in the adrenal cortex result in the production of **mineralocorticoids** (aldosterone), **glucocorticoids** (cortisol), and **androgens** (dehydroepiandrosterone [DHEA]), as outlined in **Figure 6-5.**
   3. **Glucocorticoid and androgen synthesis** are regulated by a negative feedback loop by the hypothalamic–pituitary–adrenal axis via adrenocorticotropin hormone (ACTH). **Mineralocorticoid synthesis,** however, is controlled by the renin–angiotensin system and is **independent** of the pituitary gland and ACTH.
   4. Children may present with disorders of adrenal insufficiency and with disorders of glucocorticoid excess.

B. **Classification of adrenal insufficiency.** Adrenal insufficiency may be **primary** or **secondary,** each with different clinical manifestations.
   1. **Primary adrenal insufficiency**
      a. This condition results from destruction of the adrenal cortex or from an enzyme deficiency **(i.e., a problem at the level of the adrenal gland).**
      b. Patients present with signs and symptoms of both **cortisol deficiency** (anorexia, weakness, hyponatremia, hypotension, and increased pigmentation over recently healed scars) and **aldosterone deficiency** (failure to thrive, salt craving, hyponatremia, and **hyperkalemia**).
      c. **Examples** include **Addison disease, CAH,** and **adrenoleukodystrophy** (rare, X-linked recessive disorder with neurologic deterioration).
   2. **Secondary adrenal insufficiency**
      a. This condition results from any process that interferes with the release of cortisol--releasing hormone (CRH) from the hypothalamus or ACTH from the pituitary **(i.e., a problem at the hypothalamic or pituitary level).**
      b. In contrast to primary adrenal insufficiency, *serum potassium may be normal* in secondary adrenal insufficiency because there is **no aldosterone deficiency,** given an intact renin–angiotensin system. However, these patients are still prone to developing acute adrenal crisis similar to that in primary adrenal insufficiency patients.
      c. **Examples** include pituitary tumors, craniopharyngioma, and Langerhans cell histiocytosis. However, **the most common cause is iatrogenic;** this occurs when the hypothalamic–pituitary axis has been suppressed by exposure to long-term dosages of glucocorticoids (usually longer than 2 weeks).

C. **CAH**
   1. This **autosomal recessive** congenital enzyme deficiency in the adrenal cortex is a classic example of primary adrenal insufficiency of childhood. **CAH** is also the **most common cause of DSD** in XX infants with no palpable gonads (i.e., virilized females).
   2. The enzyme deficiency in patients with CAH may lead to underproduction of cortisol or aldosterone and a buildup of precursors that shunt into androgen pathway leading to an **increased production of androgens** (see **Figure 6-5**).
   3. **Multiple enzyme deficiencies** may lead to CAH, and the clinical presentation varies depending on which enzyme is affected. The three main types include:
      a. **21-OH deficiency** (accounts for **>90% of cases**). Three different subtypes of 21-OH

deficiency affect the clinical presentation. There is some degree of correlation between the mutation and clinical phenotype.

1. **Classic salt-wasting CAH (i.e., both mineralocorticoid and glucocorticoid pathways are affected, resulting in both cortisol and aldosterone deficiency).** Girls present with virilization (mainly varying degrees of clitoromegaly), and at 1–2 weeks of life both boys and girls present with failure to thrive, vomiting, and electrolyte abnormalities. Boys may have no apparent genital abnormality. **(Key point: Male infants presenting with salt-wasting crisis can be confused for pyloric stenosis. Patients with salt-wasting CAH have a metabolic acidosis, whereas patients with pyloric stenosis have a metabolic alkalosis.)**
2. **Simple virilizing CAH (i.e., only the glucocorticoid pathway is affected, resulting only in cortisol deficiency).** Because there is no aldosterone deficiency, there is usually no electrolyte abnormality. Girls present with virilization at birth, and boys present later in life (1–4 years of age) with tall stature and precocious puberty.
3. **Nonclassic CAH (i.e., late-onset with mild cortisol deficiency and no mineralocorticoid involvement).** These patients usually present at 4–5 years of age. Girls present with premature adrenarche, clitoromegaly, acne, rapid growth, hirsutism, and infertility. Boys present with premature adrenarche, rapid growth, and premature acne.

b. **11β-OH deficiency** (accounts for 5% of cases). These patients present similarly to patients with the more common 21-OH deficiency, except that they are **hypertensive** and *hypokalemic. Here the enzymatic defect is further down the mineralocorticoid synthetic pathway.* The excess precursor metabolite is 11-deoxycorticosterone.

c. **3β-hydroxysteroid dehydrogenase deficiency** (rare). These patients present with salt-wasting crises, glucocorticoid deficiency, and ambiguous genitalia as a result of an early block in all three adrenal cortex steroid pathways.

4. **Diagnostic workup** varies with the type of CAH (see **Figure 6-5**):
   a. Patients with **21-OH deficiency** have increased **17-OHP levels.**
   b. Patients with *11β-OH deficiency* have increased levels of **11-deoxycortisol** and **11-deoxycorticosterone.**
   c. Patients with **3β-hydroxysteroid dehydrogenase deficiency** have increased levels of **DHEA** and **17-hydroxypregnenolone.**
5. **Management**
   a. **Hydrocortisone** is administered at a dose that sufficiently suppresses ACTH production so that androgen production decreases, but is not excessive enough to interfere with proper growth. For most patients, this will require doses of 10–20 mg/m^2 per day of hydrocortisone. This is greater than the physiologic dose of hydrocortisone of 6–8 mg/m^2 per day. See section IV.D.3 for management of adrenal crisis.
   b. If patients are also aldosterone deficient, *mineralocorticoid replacement* (fluorocortisol) in combination with salt supplements (in young children) may be given at a dosage that normalizes the plasma renin activity (PRA).
   c. **Frequent follow-up is essential**, and growth velocity, physical examination, bone age, and laboratory tests (17-OHP, PRA, androgens, etc.) should be monitored carefully. Parents should be educated and warned about the importance of compliance with medicines and how febrile episodes, vomiting, and surgical operations may require additional steroid therapy to prevent adrenal shock.

D. **Acquired adrenal insufficiency**
   1. **Etiology.** Causes are multiple.
      a. **Chronic supraphysiologic steroid use** (usually greater than 2 weeks)
      b. **Addison disease** is adrenal insufficiency resulting from **autoimmune destruction** of the adrenal cortex by lymphocytic infiltration. Antibodies to the adrenal gland may be detected (i.e., 21-OH antibodies), and there may be other associated endocrinopathies, including Hashimoto thyroiditis and type 1 diabetes mellitus (DM) (**type I polyglandular syndrome**), or hypoparathyroidism and chronic mucocutaneous candidiasis (**type II polyglandular syndrome**).
      c. **Less common causes** of acquired adrenal insufficiency are acute adrenal hemorrhage in the neonate and septicemia (especially associated with meningococcemia, known as **Waterhouse–Friderichsen syndrome**).
   2. **Evaluation**
      a. A **high index of suspicion is necessary** because the symptoms may be subtle and the conditions can be life-threatening. Patients with Addison disease can present with **unusual hyperpigmentation** due to simultaneous stimulation of melanocytes from elevated ACTH levels, resulting from lack of cortisol feedback at the level of the pituitary.
      b. History of prior steroid use or autoimmune disorders should raise clinical suspicion.
      c. Random plasma cortisol levels are usually not helpful (although a cortisol level > 20 μg/dL in the presence of stress excludes adrenal insufficiency).
      d. **ACTH stimulation test** is the **test of choice** and measures adrenal cortisol reserve by comparing the baseline cortisol level with the cortisol level 1 hour after ACTH injection. Normally, a cortisol value > 18–20 μg/dL after ACTH stimulation is considered an adequate response.
   3. **Management**
      a. **Some patients may present with adrenal crisis (hypotension, hypoglycemia, severe lethargy), and this is a medical emergency!**
      b. Prompt treatment requires **intravenous fluids** with 5% dextrose in normal saline to correct hypotension and hyponatremia, and to prevent hypoglycemia.
      c. Parenteral **steroids** (commonly referred to as "stress doses") are given in adrenal crisis until the patient is stabilized (50–100 mg/m^2 per day of hydrocortisone). Oral mineralocorticoids and dextrose-containing fluids should be given as well.
      d. For patients not in adrenal crisis, replacement with oral hydrocortisone (~8 mg/m^2 per day) and mineralocorticoids is sufficient.

E. **Glucocorticoid excess**
   1. **Clinical features** include poor growth with delayed bone age, central obesity, moon facies, nuchal fat pad, easy bruisability, purplish (hemorrhagic) striae, hypertension, and glucose intolerance.
   2. **Major causes of hypercortisolism**
      a. **Iatrogenic.** The **most common cause of glucocorticoid excess is iatrogenic,** as seen in patients who have been treated with long-term steroids for chronic diseases, such as asthma, inflammatory bowel disease, and juvenile idiopathic arthritis.
      b. **Cushing syndrome.** This is excessive glucocorticoid production caused by **benign or malignant adrenal tumors.** Note that most adrenal tumors are virilizing, but on occasion, they may also feminize.
      c. **Cushing disease.** This is excessive glucocorticoid production caused by **excessive ACTH production** by a pituitary tumor, such as a microadenoma.
   3. **Laboratory evaluation and diagnosis**

   a. **Elevated free cortisol in 24-hour urine collection.** Depression, alcohol consumption, and obesity may lead to false positives.
   b. Absence of the expected cortisol suppression seen in an **overnight dexamethasone suppression test** (i.e., dexamethasone given in the evening normally suppresses the following morning's physiologic rise in cortisol)
4. **Key point: Cortisol excess states may be confused with obesity. Hypercortisolism presents with growth impairment and delayed bone age, but obese patients have normal to fast growth and an advanced bone age.**

V. Diabetes Mellitus

A. **Epidemiology.** *Diabetes melltus (DM)* is the second most common chronic disease of childhood, affecting at least 1 of 500 children.

B. **Types of diabetes**
   1. **Type 1—insulin deficiency**
   2. **Type 2—insulin resistant**
   3. **Other types of diabetes—Cystic fibrosis–related diabetes, medication induced diabetes, and monogenic diabetes (maturity-onset diabetes of the young [MODY])**

VI. Type 1 Diabetes Mellitus (Type 1 DM)

A. **Etiology.** Type 1 DM is an **autoimmune disease** due to genetic and environmental factors.
   1. **Genetic factors**
      a. There are strong genetic influences, but inheritance has not been found to fit into classic Mendelian patterns (autosomal or X-linked). Polymorphisms in human leukocyte antigens (HLAs) (specifically DR3 and DR4 haplotypes) on chromosome 6 are responsible for most of the genetic risk in large genome-wide association studies. HLA is responsible for antigen presentation.
      b. Monozygotic twins have a >50% concordance rate, whereas dizygotic twins have only a 30% concordance rate. First-degree relatives of a patient with type 1 DM have 10-fold higher rate of developing type 1 DM.
   2. **Environmental triggers**. Viral infections including enteroviruses (coxsackie) and rubella have been implicated but not definitely proven.
   3. **Autoimmune factors**
      a. *Autoantibodies against islet antigens* (GAD65, ICA512, insulin, and ZnT8) are present in **~85% of patients.**
      b. **Autoantibodies** may be detected in asymptomatic patients years before the onset of clinical symptoms. Screening of family members of patients with type 1 DM through national screening programs is encouraged.

B. **Clinical features**
   1. The **classic presentation** includes several weeks of **polyuria, polydipsia, nocturia,** and occasionally enuresis. As symptoms progress, weight loss, vomiting, and dehydration occur.
   2. **Diabetic ketoacidosis (DKA)** may be the **initial presentation in 25% of patients** [see section VIII]. The younger the patient, the shorter the course of symptoms before DKA occurs.
   3. Girls may present with candidal vulvovaginitis.

C. **Diagnosis.** Most patients present with hyperglycemia documented by a random blood sugar above 200 mg/dL with polyuria, polydipsia, weight loss, or nocturia.

D. **Management**
   1. **Insulin**
      a. May be administered either via **multiple daily injections (MDI)** or **insulin pumps.** MDI therapy combines long-acting (basal) insulins with short-acting (bolus) insulins. Most newly diagnosed patients are started on MDI and can transition to an insulin pump, if they chose, after several months.
      b. **Monitoring**
         1. **Daily blood glucose** measurements using a glucose meter before all meals and at bedtime.
         2. **Glycosylated hemoglobin (HbA1c) level**, reflecting diabetic control for the past 2–3 months, should be checked every 3 months.
         3. **Watch for hypoglycemia.** All patients should have parenteral **glucagon** available in case of seizure or coma secondary to low blood sugar.
         4. **Watch for "honeymoon" period.** Within a few weeks after initial diagnosis, many patients exhibit a temporary progressive reduction in their daily insulin requirements. This occurs because of a transient recovery of residual β-cell function, resulting in endogenous release of insulin in response to carbohydrate exposure. This honeymoon period may last from months to 1–2 years.

5. **Watch for Somogyi phenomenon.** This occurs when the evening dose of insulin is too high, causing hypoglycemia in the early morning hours, resulting in the release of counter-regulatory hormones (epinephrine and glucagon) to counteract this insulin-induced hypoglycemia. The patient then has high blood glucose in the morning. The **treatment** is to actually *lower the bedtime insulin dose* and not to raise it.

2. **Diet. As with any child, overall carbohydrate intake should be moderate and excess simple sugars should be avoided. All patients should meet with a registered dietician.**
3. **Education and close follow-up** every 3 months.

E. **Long-term complications**

1. **Microvascular complications** include diabetic retinopathy, nephropathy, and neuropathy.
2. **Macrovascular complications are usually seen in adulthood** and include atherosclerotic disease, hypertension, heart disease, and stroke.
3. **DKA** when ill or noncompliant
4. **Autoimmune.** Type 1 DM patients are at increased risk for autoimmune thyroid conditions and celiac disease. Annual screening with TSH/T_4 and TTG IgA is recommended.

VII. Type 2 Diabetes Mellitus (Type 2 DM)

A. **Epidemiology.** *Increasingly common in the pediatric age group, especially after the age of 10, based on epidemiologic studies.*

B. **Etiology**
   1. **Strong hereditary component (stronger for type 2 than for type 1)**
   2. The cause is likely a combination of **peripheral tissue resistance to insulin** and **progressive decline in insulin secretion**, both of which result in a hyperglycemic state.

C. **Clinical features.** The clinical presentation is variable.
   1. Asymptomatic to mild DKA. **Serious DKA is uncommon** because children with type 2 DM retain some residual insulin secretion.
   2. **Obesity and obstructive sleep apnea**
   3. **Acanthosis nigricans** (velvety and hyperpigmented skin of the neck and axillary folds) is common.
   4. **Associated comorbidities may accompany type 2 DM, including hypertension, polycystic ovarian syndrome, and hyperlipidemia. Type 2 DM, along with these comorbidities, are collectively known as the metabolic syndrome.**

D. **Management**
   1. **Oral agents. Biguanides (i.e., metformin) are the preferred drugs in children and are typically used as monotherapy if HbA1c is <9%.**
   2. **Insulin therapy** may be required for those patients who fail oral agents.

VIII. Diabetic Ketoacidosis (DKA)

A. **Definition. Hyperglycemia that is usually greater than 200 mg/dL with ketonuria/ketonemia, and a serum bicarbonate level <15 mmol/L or a serum pH < 7.30.**

B. **Pathophysiology**
   1. **Insulin deficiency** creates a state of diminished glucose substrate at the cellular level, despite the high serum levels of glucose. The body's need for substrate to make energy therefore results in gluconeogenesis.
   2. **Hyperglycemia** resulting from this insulin deficiency leads to an **osmotic diuresis** with polyuria and eventual dehydration.
   3. In the face of insulin deficiency, **the counter-regulatory stress hormones** (glucagon, cortisol, GH, etc.), contribute to fat breakdown (lipolysis), gluconeogenesis and ketone formation, and eventually DKA.

C. **Clinical features**
   1. Patients with **mild DKA** may present with vomiting, polyuria, polydipsia, and mild to moderate dehydration.
   2. Patients with **severe DKA** may present with severe dehydration, severe abdominal pain that may mimic appendicitis, and deep (Kussmaul) respirations, or coma.
   3. It is the presence of ketones that gives the patient with DKA **"fruity breath."**

D. **Laboratory findings**
   1. **Anion gap metabolic acidosis**
   2. **Hyperglycemia and glucosuria**
   3. **Ketonemia and ketonuria**
   4. **Hyperkalemia** caused by metabolic acidosis (potassium moves out of the cells in the face of acidosis) or normokalemia

E. **Management**
   1. **Fluid and electrolyte therapy** and replacement of the depleted intravascular volume using isotonic saline should begin immediately. **Avoid excess fluid administration in patients with DKA, and do not administer bicarbonate to patients with DKA. Excess fluid and bicarbonate administration increases the risk of cerebral edema (see below).**
   2. A **gradual decline in serum glucose (i.e., osmolality)** is critical to minimize the risks of cerebral edema, which is a significant cause of morbidity and mortality in the treatment of DKA.
   3. **Potassium repletion** (once urine output has been established) using potassium acetate and potassium phosphate is important, because all patients are potassium depleted, even with a normal serum potassium.
   4. **Regular insulin** (usually a continuous infusion of 0.1 U/kg per hour, although younger children may need less) with careful monitoring of serum glucose levels to ensure a gradual drop in the serum glucose levels. Insulin should not be given in a bolus form to children.
   5. The **combination of intravenous fluids and insulin** should reverse the ketogenesis, stop the hepatic production of glucose, shut down the release of counter-regulatory hormones, and enhance peripheral glucose uptake.

F. **Complications**
   1. **Cerebral edema**
      a. Usually occurs 6–12 hours into therapy and rarely after 24 hours
      b. Risk factors include patients younger than 5 years, initial drops in serum glucose levels faster than 100 mg/dL per hour, bicarbonate administration, and fluid administration greater than 4 L/m^2 per 24 hours.

    c. Patients present with worsening mental status and abnormal neurologic examinations in severe cases.
2. Severe hypokalemia
3. Hypocalcemia

IX. Thyroid Disorders

A. **Thyroid physiology**
   1. **Hypothalamic–pituitary–thyroid axis** is regulated by a feedback loop between T_4, triiodothyronine (T_3), thyrotropin-releasing hormone (TRH), and thyroid-stimulating hormone (TSH).
   2. **Both T_4 and T_3** circulate bound to **thyroid-binding proteins,** including thyroid-binding globulin (TBG) and thyroid-binding prealbumin (TBPA).
   3. **The free (unbound) forms** of T_4 and of T_3 are the biologically active forms of each hormone.

B. **Hypothyroidism**
   1. **Clinical presentation in children and adolescents**
      a. **Suboptimal growth velocity** (less than 5 cm per year or 2 inches per year) with a **delayed bone age**
      b. **Goiter** may sometimes be detected on palpation of the thyroid.
      c. **Myxedema,** or "puffy skin," dry skin, or occasionally, orange-tinged skin
      d. Amenorrhea or oligomenorrhea in adolescent girls
      e. Fatigue or decreased energy levels. Sleep may be altered.
      f. Constipation
   2. **Causes** are extensive.
      a. **Congenital hypothyroidism**
         1. **Epidemiology.** This condition is **one of the most common disorders for which newborns are screened.** It is evaluated on newborn screening and has an incidence of 1 in 4000 births.
         2. **Etiology**
            a. **Thyroid dysgenesis. This is the most common cause (85%) of congenital hypothyroidism.** Ectopic thyroid gland (failure of the gland to properly descend from the base of the tongue during development) is the most common cause (~80% of cases), followed by agenesis.
            b. **Thyroid dyshormonogenesis.** This refers to multiple **inborn errors** of thyroid hormone synthesis, which account for about 10–15% of all cases of congenital hypothyroidism. These conditions are autosomal recessive and usually present with a goiter. **Pendred syndrome,** an organification defect, is the most common of these defects and is associated with **sensorineural hearing loss.**
            c. Use of **propylthiouracil (PTU)** during pregnancy for maternal Graves disease may result in transient hypothyroidism in the newborn, because PTU crosses the placenta and may temporarily block fetal thyroid hormone synthesis.
            d. **Maternal autoimmune thyroid disease** may also result in transient hypothyroidism, as maternal thyroid-blocking antibodies may cross the placenta and block TSH receptors on the newborn thyroid gland.
         3. **Clinical features.** Most newborns are asymptomatic at birth and have an unremarkable physical examination. However, *thyroid hormone is essential for normal brain growth during the first 3 years of life,* and with time, the following clinical features become more apparent if the patient goes untreated:
            a. **Classic historical features** include a history of prolonged jaundice and poor feeding.
            b. **Classic symptoms** include lethargy and constipation.

c. **Classic physical examination findings** include large anterior and posterior fontanelles, protruding tongue, umbilical hernia, myxedema, mottled skin, hypothermia, delayed neurodevelopment, and poor growth.

4. **Management**
   a. **Repeat lab testing in the context of an abnormal newborn screen should happen immediately.** Thyroid hormone replacement should begin **immediately** with l-T_4 (levothyroxine) after confirmation of hypothyroidism (elevated TSH and low-normal to low T_4 levels). Thyroid imaging (ultrasound or nuclear imaging) may be useful in distinguishing various forms of congenital hypothyroidism.
   b. If treatment is delayed until after the signs and symptoms of hypothyroidism appear, most patients will have suffered permanent neurologic sequelae.

b. **Hashimoto disease (chronic lymphocytic thyroiditis [CLT]).** This autoimmune disorder is characterized by lymphocytic infiltration of the thyroid gland, resulting in varying degrees of follicular fibrosis and atrophy and follicular hyperplasia.

1. **Epidemiology**
   a. **Most common cause of acquired hypothyroidism with or without a goiter**
   b. More common in **girls**
2. **Etiology.** Thyroid autoantibodies develop because of a disturbance in immunoregulation, resulting in a state of thyroid cell cytotoxicity or stimulation. There is often a genetic predisposition.
3. **Clinical features.** Presentation is variable.
   a. Asymptomatic
   b. Goiter, which is classically firm and pebbly in nature
   c. **Short stature**
   d. **Transient hyperthyroidism ("Hashitoxicosis")** may occur in some patients.
4. **Management.** Thyroid hormone replacement with L-*T4* to normalize the TSH level.

3. **Diagnosis of hypothyroidism**
   a. **Neonatal screening tests** for congenital hypothyroidism (TSH is measured)
   b. **Increased TSH,** which is usually the first sign of thyroid failure
   c. **Low T_4 level**
   d. **Antithyroid antibodies** (especially **thyroid antiperoxidase antibodies**) as a marker for autoimmune thyroid disease

C. **Hyperthyroidism**

1. **Clinical features**
   a. **Eye** examination may demonstrate lid lag and exophthalmos.
   b. **Thyroid gland** is enlarged and usually smooth in texture. A thyroid bruit may be appreciated in untreated patients.
   c. **Cardiac examination** demonstrates tachycardia, and patients may complain of palpitations.
   d. **Skin** is warm and flushed. **(Key point:** The presence of vitiligo or alopecia suggests the possible coexistence of other **autoimmune polyendocrinopathies,** including Addison disease and DM.)
   e. **CNS** evaluation may be remarkable for nervousness and fine tremors with a history of fatigue and difficulty concentrating in school.

f. **Pubertal** evaluation may be notable for delayed menarche and gynecomastia in boys.

2. **Graves disease (diffuse toxic goiter).** This **autoimmune disorder** is characterized by autonomous production of excessive thyroid hormone by the thyroid gland, mediated by a TSH receptor–stimulating antibody.
   a. **Epidemiology.** Graves disease is the **most common cause of hyperthyroidism** in childhood. **Females** predominate (male:female = 1:3).
   b. **Etiology**
      1. Strong genetic factors
      2. **Thyroid-stimulating immunoglobulin (TSI),** an IgG antibody, cross-reacts with the TSH receptors in the thyroid gland and stimulates T_4 production.
   c. **Laboratory findings. Increased T_3 and T_4 levels** with **suppressed TSH level** in the presence of TSI.
   d. **Management**
      1. **Antithyroid medications.** The two most commonly used antithyroid medications are **PTU** and **methimazole.** Methimazole is the preferred first-line agent given the risks of hepatotoxicity with PTU therapy.
      2. **Subtotal thyroidectomy** may be considered if antithyroid medication fails or if there is a particularly large goiter.
      3. **Radioactive iodine** can be used in older children and adolescents.

X. Bone Mineral Disorders

A. **Physiology of calcium and vitamin D metabolism**
   1. **Bone.** Both **vitamin D and parathyroid hormone (PTH)** release calcium and phosphorus from bone.
   2. **Parathyroid gland**
      a. **PTH** helps maintain a normal serum **calcium** level by releasing calcium from the bone and reabsorbing calcium from the kidneys.
      b. **PTH** also releases **phosphorus** from the bone and excretes phosphorus from the kidneys.
   3. **Kidney**
      a. **PTH** is responsible for **calcium reabsorption** and **phosphorus excretion.**
      b. The enzyme **1α-hydroxylase vitamin D** made in the kidney converts *25-(OH) vitamin D* (made by the liver) into the active vitamin D metabolite **1,25-(OH) vitamin D** (stimulated by PTH).
   4. **Gastrointestinal (GI) tract.** The main source of calcium absorption is through the intestine due to **1,25-(OH) vitamin D,** which is the **most potent form of vitamin D.**

B. **Hypocalcemia**
   1. **Definitions**
      a. **Hypocalcemia.** Serum calcium less than 8.0 mg/dL or ionized calcium less than 2.5 mg/dL.
      b. **Pseudohypocalcemia.** The lowering of total calcium levels as a result of low serum albumin levels, as seen in nephrotic syndrome. However, the active form of calcium is freely circulating. In patients with low albumin levels, the ionized calcium levels are normal. Therefore, all low total calcium levels should have an accompanying albumin level or an ionized calcium level measured to verify true hypocalcemia.
   2. **Clinical features**
      a. **Tetany** (neuromuscular hyperexcitability)
         1. **Carpopedal spasm.** Hypocalcemia causes hyperexcitability of peripheral motor nerves, resulting in painful spasms of the muscles of the wrists and ankles.
         2. **Laryngospasm.** Spasm of the laryngeal muscles
         3. **Paresthesias**
      b. **Seizures.** Younger patients with hypocalcemia tend to present with seizures or coma, whereas older patients exhibit more signs of neuromuscular hyperexcitability.
   3. **Etiology**
      a. **Early neonatal hypocalcemia (younger than 4 days)** is usually transient and may be associated with prematurity, fetal growth restriction, asphyxia, or infants of diabetic mothers. Hypomagnesemia may also result in hypocalcemia.
      b. **Late neonatal hypocalcemia (older than 4 days)**
         1. **Hypoparathyroidism.** Patients have low calcium and elevated phosphorus levels, usually caused by asymptomatic maternal hyperparathyroidism, in which the mother's high serum calcium crosses the placenta and suppresses the fetus's PTH. After delivery this creates a temporary state of hypocalcemic hypoparathyroidism.
         2. **DiGeorge syndrome** (see Chapter 5, section IV.D.1)
         3. **Hyperphosphatemia** leads to hypocalcemia by binding to calcium. It may result from **excessive phosphate intake** (found in some infant formulas) or

from **uremia.**

c. **Childhood hypocalcemia**
    1. **Hypoparathyroidism (parathyroid failure).** This condition may be autoimmune (autoimmune polyglandular syndrome) or related to DiGeorge syndrome (see Chapter 5, section IV.D.1) as above.
    2. **Pseudohypoparathyroidism (parathyroid resistance).** This rare autosomal dominant disorder results in PTH resistance. Patients present with short stature, short metacarpals, developmental delay, and low calcium despite **elevated PTH levels.**
    3. **Hypomagnesemia.** A **low magnesium** level, as seen in some renal and malabsorptive diseases, may cause hypocalcemia because it interferes with PTH release.
    4. **Vitamin D deficiency** can cause hypocalcemia with low phosphorus levels [see section X.C]. Rickets can present with hypocalcemic symptoms.

4. **Laboratory evaluation**
    a. **Serum ionized calcium and phosphorus**
    b. **Serum magnesium**
    c. **Electrocardiogram** demonstrating a **prolonged QT interval** may be found with hypocalcemia.
    d. **PTH level** to distinguish between hypoparathyroidism (low PTH) and pseudohypoparathyroidism (increased PTH)
    e. **Vitamin D level** (in an older child) if both calcium and phosphorus levels are low
    f. **Radiograph of the wrists or knees** to evaluate for **rickets** [see section X.C]
5. **Management**
    a. **Mild asymptomatic hypocalcemia may not require treatment but a search for the etiology must be done.**
    b. In newborns with serum calcium levels <7.5 mg/dL (or ionized calcium <2.5 mg/dL), or in older children with serum calcium levels < 8.0 mg/dL, calcium should be corrected to prevent CNS hyperexcitability.
    c. **Calcium supplementation**
        1. **Oral therapy** is acceptable if there are no seizures or only moderate tetany.
        2. **Intravenous calcium gluconate or calcium chloride** should be given if patients are more symptomatic.
    d. **1,25 Vitamin D analogue (calcitriol)** should be given to patients with chronic hypoparathyroidism.

C. **Rickets**
1. **Definition.** Rickets is a disorder of the growing skeleton (i.e., growth plates) that results in deficient mineralization of growing bones with a normal bone matrix.
2. **Predisposing factors**
    a. Exclusively breastfed infants with minimal sunshine exposure
    b. Use of anticonvulsant medications (phenytoin, phenobarbital), which interfere with liver metabolism
    c. Renal or hepatic failure
3. **Etiology**
    a. **Vitamin D deficiency**
    b. **GI disorders** associated with fat malabsorption resulting in vitamin D deficiency (e.g., cystic fibrosis, celiac disease)
    c. **Nutritional causes** (rare in the United States because of vitamin D supplementation)
    d. **Defective vitamin D metabolism** from renal and hepatic failure may cause a

deficiency of the important enzymes that synthesize 1,25-(OH) vitamin D, resulting in renal osteodystrophy (see Chapter 11, section XI.). Anticonvulsants may also interfere with vitamin D metabolism through their effects on liver metabolism.

e. **Vitamin D-dependent rickets**
    1. **This autosomal recessive condition is rare.**
    2. **Enzyme deficiency** in the kidneys of 1α-hydroxylase vitamin D results in the lack of 1,25-(OH) vitamin D.
    3. Patients present with increased PTH, low vitamin D levels, low calcium, low phosphorus, and increased alkaline phosphatase.
f. **Vitamin D-resistant rickets (X-linked hypophosphatemic rickets)**
    1. **X-linked dominant** disorder
    2. **Caused by a renal tubular phosphorus leak,** resulting in a low serum phosphorus level
    3. Patients present with *rickets in the face of normal calcium and low phosphorus.*
    4. Patients develop typical bowing of the legs
    5. **Treatment** includes **phosphate supplements** and 1,25 vitamin D analogues.
g. **Oncogenous rickets** is a phosphate-deficient form of rickets caused by a bone or soft tissue tumor. It should be **considered in patients who present with bone pain or a myopathy.**

4. **Clinical features**
    a. Rickets usually occurs during the **first 2 years of life** and in **adolescence,** when bone growth is most rapid.
    b. Rickets usually involves the **wrists, knees, and ribs** (at sites of growth plates), presenting with a knobby appearance.
    c. Weight-bearing bones become **bowed** once the patient begins ambulating.
    d. **Short stature**
    e. **"Rachitic rosary"** or prominent costochondral junctions
    f. **Craniotabes** or thinning of the outer skull creates a "Ping-Pong ball sensation" on palpation.
    g. **Frontal bossing** and **delayed suture closure**
5. **Radiographic findings. Wrist radiographs** show the earliest changes of rickets with the *distal end of the metaphysis appearing widened, frayed, and cupped,* instead of showing a well-demarcated zone. There is also widening of the space between the epiphysis and the end of the metaphysis.
6. **Laboratory findings.** Can vary depending on the etiology of rickets. In vitamin D–deficient rickets, a low serum phosphorus, low to normal serum calcium, elevated alkaline phosphatase, and elevated PTH levels are present. The calcium level can be normal secondary to elevated PTH, which will cause calcium release from the bone.
7. **Management.** Treatment depends on etiology.

XI. Diabetes Insipidus (DI)

A. **Definition.** Inability to maximally concentrate urine because of either low levels of antidiuretic hormone (ADH) or renal unresponsiveness to ADH.

B. **Physiology.** ADH is an octapeptide synthesized in the hypothalamic nuclei and transported via axons to the posterior pituitary. The action of ADH is to increase permeability of the renal collecting ducts to water, leading to increased water reabsorption. It is regulated by changes in volume, serum osmolality, and posture.

C. **Classification**
   1. **Central DI = ADH deficient**
   2. **Nephrogenic DI = ADH resistant** (kidney does not respond to ADH)

D. **Etiology of central DI**
   1. **Autoimmune**
   2. **Trauma** and **hypoxic–ischemic brain injury**
   3. **Hypothalamic tumors** (e.g., craniopharyngioma, glioma, germinoma)
   4. **Langerhans cell histiocytosis**
   5. **Granulomatous disease** (e.g., sarcoidosis, tuberculosis)
   6. **Vascular** (e.g., aneurysms)

E. **Etiology of nephrogenic DI.** Inherited as an **X-linked recessive** disorder

F. **Clinical features.** Children present with nocturia, enuresis, poor weight gain, polydipsia, and polyuria.

G. **Evaluation and diagnosis**
   1. If thirst mechanisms are intact and child has access to water, then serum electrolytes can be normal. Otherwise, patients present with **hypernatremic dehydration** with **inappropriately dilute urine in the face of increased serum sodium and increased serum osmolality.**
   2. **Early morning serum and urine specimens for osmolality (collected without recent fluid ingestion) are useful screening tests. A urine osmolality >600 mOsm/kg of water makes DI unlikely. A serum osmolality of >300 mOsm/kg with a urine osmolality of <300 mOsm/kg is diagnostic of DI.**
   3. **Water deprivation test** in the hospital may be used to diagnose DI. A rising serum osmolality in the presence of persistent urine output and an inappropriately low urine osmolality is diagnostic. If, at the end of the test, the patient does not respond to administered ADH, then the patient has nephrogenic DI.
   4. **Neuroimaging is mandatory for all cases of central DI.** On an **MRI of the brain** hyperintense signal normally found in the posterior pituitary is missing.
   5. A **bone scan** may be indicated to rule out Langerhans cell histiocytosis.

H. **Management.** The drug of choice for **central DI is DDAVP (synthetic ADH). Nephrogenic DI, particularly in the neonate, can be treated with low-solute formula and thiazide diuretics.**

XII. Hypoglycemia

A. General principles
   1. **Definition.** This is a controversial area, particularly in the neonate. However, at plasma glucose levels <60 mg/dL counter-regulatory responses (cortisol, GH, and glucagon secretion) designed to raise glucose levels are activated.
   2. **It is important to recognize hypoglycemia early,** especially in newborns and young infants, when the brain is dependent on glucose for proper neurodevelopment.
   3. The **symptoms of hypoglycemia** are age dependent and vary in each patient.
      a. **Newborns or infants** may have varied symptoms that include lethargy, myoclonic jerks, cyanosis, apnea, or seizures.
      b. **Older children** may have symptoms similar to adults, including tachycardia, diaphoresis, tremors, headaches, or seizures.

B. **Neonatal hypoglycemia.** This condition may be transient (most common) or persistent (less common). (See also Chapter 4, section XIII.)
   1. **Transient neonatal hypoglycemia** is usually detected by screening protocols established for high-risk infants (including prematurity, a history of perinatal asphyxia or fetal distress, sepsis, small for gestational age and large for gestational age infants, and infants of diabetic mothers).
   2. **Persistent neonatal hypoglycemia** is defined as hypoglycemia that persists for longer than 3 days. Typically, the diagnosis is based on differentiating ketotic from nonketotic hypoglycemia. Ketones (specifically β-hydroxybutarate) that are detectable at the time of an episode of hypoglycemia indicate ketotic hypoglycemia. The differential diagnosis of persistent neonatal hypoglycemia includes the following:
      a. **Nonketotic hypoglycemia**
         1. **Hyperinsulinism due to perinatal stress, genetic defects leading to islet cell hyperplasia, or Beckwith–Wiedemann syndrome:** Patients with Beckwith–Wiedemann syndrome can be LGA and present with visceromegaly, hemihypertrophy, macroglossia, umbilical hernias, and distinctive ear creases. Treatment for hyperinsulinism may involve diazoxide, octreotide, or surgical resection of the pancreas.
         2. **Fatty acid oxidation defects**
      b. **Ketotic hypoglycemia**
         1. **Hormone deficiencies**, including GH deficiency and cortisol deficiency. **(Key point: Congenital hypopituitarism should be suspected in the neonate who presents with hypoglycemia, microphallus, and midline defects such as a cleft palate.)**
         2. **Hereditary defects in carbohydrate metabolism** (e.g., glycogen storage disease type I and galactosemia) or **amino acid metabolism** (e.g., maple syrup urine disease, methylmalonic acidemia and tyrosinemia) See also Chapter 5, sections VI and VII, and Table 5-5).

C. **Hypoglycemia in infancy and childhood.** Hypoglycemia is relatively uncommon in older infants and children, but the differential diagnosis is extensive and includes the following:
   1. **Ketotic hypoglycemia** is the **most common cause of hypoglycemia in children 1–6 years of age.** This form of hypoglycemia typically occurs in the morning in the presence of ketonuria and a low insulin level. This appears to be an **inability to adapt to a fasting state.** Typically these children are thin and become hypoglycemic after intercurrent infection or prolonged fast. Treatment includes avoiding prolonged fasts and giving foods with long-acting carbohydrates at bedtime (i.e., corn starch).

2. **Ingestions** must always be considered in the differential diagnosis of hypoglycemia in the older child, especially in adolescents.
    a. **Alcohol** metabolism in the liver can deplete essential cofactors needed for adequate gluconeogenesis, resulting in hypoglycemia (especially when the child is in the fasting state).
    b. **Oral hypoglycemic agents**
3. **Inborn errors of metabolism**
4. **Hyperinsulinism,** as described in section XII.B.2.a

Review Test

1. A 7-year-old boy is brought to the office for a routine health care maintenance visit. The nurse brings to your attention that he has grown only 1 inch during the past year. A review of his growth curve during the past 2 years shows that his height percentile has fallen from the 75th to the 40th percentile. His father is 66 inches tall, and his mother is 65 inches tall. He has recently had some early morning vomiting and headache. However, physical examination is unremarkable. No striae or dorsocervical fat pads are noted. A bone age study reveals a growth delay of just over 2.5 years. Complete blood count, erythrocyte sedimentation rate, and thyroid studies are all normal. The most likely cause of this patient's short stature is which of the following?
   A. Genetic short stature
   B. Constitutional growth delay
   C. Craniopharyngioma
   D. Skeletal dysplasia
   E. Cushing disease
2. You are called to the delivery room to evaluate a newborn infant with ambiguous genitalia. The mother had an amniocentesis showing a fetus with an XX genotype. Physical examination of the neonate indicates no palpable gonads, a small phallic structure, and labial fusion with a urogenital opening. Which of the following is the most likely diagnosis?
   A. Hermaphrodite
   B. Partial androgen insensitivity
   C. Congenital adrenal hyperplasia caused by 21-hydroxylase deficiency
   D. 5α-reductase deficiency
   E. Hypopituitarism
3. An obese 12-year-old child is suspected of having the diagnosis of type 2 diabetes mellitus (DM). Which of the following statements regarding this suspected diagnosis is correct?
   A. This patient is likely to present with diabetic ketoacidosis during adolescence.
   B. Type 2 DM is more likely to occur in children <10 years of age compared with type I DM.
   C. This patient is likely to have had islet cell antibodies before the onset of clinical symptoms.
   D. Type 2 DM has a strong hereditary component.
   E. In the last decade, there has been a decline in the incidence of type 2 DM, given greater public awareness of healthy eating habits.
4. A 13-year-old girl is brought to the office by her mother because of poor attention span and deteriorating grades. She is also fidgety and cannot sit still. Her mother is also concerned because her daughter has lost 5 pounds during the past 2 months. Physical examination shows a blood pressure of 130/75 mm Hg, a heart rate of 115 beats/minute, and thyromegaly. You suspect Graves disease. Which of the following statements regarding the suspected diagnosis is correct?
   A. Thyroid-stimulating immunoglobulins (TSI) are usually present and bind to thyrotropin (TSH) receptors.
   B. Girls with Graves disease have an increased likelihood of developing precocious puberty.
   C. Subtotal thyroidotomy is the most appropriate initial management.
   D. This disease is more common in males.
   E. Radioactive iodine treatment is ineffective.
5. You have been following an 8-year-old child in your office for the past several years and have noted that during the past year, his height has remained below the third percentile. You are

concerned about his short stature and decide to begin a workup. Your workup includes a bone age determination. The patient's bone age is discovered to be 3 years younger than his chronologic age. Which of the following diagnoses should be considered?

A. Genetic short stature
B. Skeletal dysplasias
C. Intrauterine growth retardation
D. Turner syndrome
E. Growth hormone deficiency

6. You are called to the pediatric intensive care unit to evaluate a 4-year-old girl with new-onset type 1 diabetes mellitus who is in diabetic ketoacidosis (DKA). The nurse reports that she was alert and talking but over the last hour has become obtunded and listless. Which of the following conditions is the likely cause of her change in mental status?

A. Hyperglycemia
B. Cerebral edema
C. Hyperkalemia
D. Hypercalcemia
E. Hyperphosphatemia

The response options for statements 7–11 are the same. You will be required to select one answer for each statement from the following set.

A. Premature adrenarche
B. Premature thelarche
C. Central precocious puberty
D. Peripheral precocious puberty
E. Normal, no pubertal disorder

For each patient, select the most likely pubertal disorder, if present.

1. A 13-month-old girl has a several month history of breast growth with Tanner stage 2 breast development on examination, but has no pubic hair. Her growth consistently follows the 75% growth curve.
2. A 7-year-old boy presents with pubic hair, acne, and rapid growth. His bone age evaluation reveals that his bones demonstrate advanced growth equivalent to that of a 10-year-old boy. Testicular examination shows prepubertal size testes.
3. A 5-year-old girl has a 1-year history of breast development and pubic hair. She is Tanner stage 3 on breast examination and Tanner stage 2 on pubic hair examination. Today she had her first menses. Bone age determination reveals that her bone appearance is 5 years advanced, equivalent to that of a 10-year-old girl.
4. A 6-year-old girl has a strong apocrine odor, mild axillary hair, and Tanner stage 3 pubic hair. No clitoromegaly or breast development is seen. The bone age is not advanced.
5. A 5-year-old girl is referred for vaginal bleeding. Physical examination shows breast development, multiple café-au-lait spots, and thyromegaly, and cystic bony changes are apparent on the radiograph of her legs.

The response options for statements 12–15 are the same. You will be required to select one answer for each statement from the following set.

A. Hyperinsulinism
B. Hypopituitarism
C. Beckwith–Wiedemann syndrome
D. Glycogen storage disease

E. Ketotic hypoglycemia

For each patient, select the most likely diagnosis.

1. A 4-year-old thin boy with a fever and vomiting went to sleep without dinner and has a hypoglycemic seizure at 8:00 am.
2. A male newborn has a glucose level of 15 mg/dL at 6 hours of age. Physical examination reveals a cleft palate, microphallus, and undescended testes.
3. A newborn who has had hypoglycemia for 1 week is nondysmorphic and requires a high rate of dextrose infusion to maintain blood sugar. The insulin level is inappropriately high during an episode of hypoglycemia.
4. A large-for-gestational age infant has hepatomegaly, macroglossia, moderate umbilical hernia, and hypoglycemia.

Answers and Explanations

1. **The answer is C** [I.F.1.b]. The decreased rate of growth in the face of early morning emesis should make one suspect a mass lesion within the central nervous system. The workup should begin with cranial magnetic resonance imaging (MRI) scan. Both genetic short stature and constitutional growth delay are excluded from the diagnosis because patients with these conditions grow at a normal rate, at least 2 inches per year. Skeletal dysplasia may be ruled out because the delayed bone age is inconsistent with such a condition. Cushing disease may cause poor growth and bone age delay, but this patient does not seem to have physical stigmata of hypercortisolemia.
2. **The answer is C** [III.D, III.E, and III.F]. Congenital adrenal hyperplasia (CAH) as a result of 21-hydroxylase deficiency is the most common form of disorder of sex development (DSD) in XX infants. The chromosomal analysis revealing XX chromosomes and the lack of palpable gonads immediately exclude diagnoses consistent with an undervirilized male, such as those caused by partial androgen insensitivity, and inborn errors in testosterone synthesis, as in 5α-reductase deficiency. A true hermaphrodite is a possibility, but CAH is more common. Hypopituitarism in a newborn with an XX genotype would not present with ambiguous genitalia.
3. **The answer is D** [VII.A and VII.B]. There has been a significant increase in the incidence of type 2 diabetes mellitus (DM) over the last decade. There is a much stronger hereditary component in type 2 DM than in type 1 DM, and the etiology is likely a combination of peripheral tissue resistance to insulin and a progressive decline in insulin secretion. The clinical presentation of type 2 DM may be quite variable; however, most patients do not present with diabetic ketoacidosis, because type 2 DM reflects more of an insulin resistance than an insulin deficiency, and patients are not likely to present with insulin autoantibodies. In children <10 years of age, type 2 DM is much less common than type 1 DM. Patients are often asymptomatic, with only glucosuria, and physical examination may be significant for obesity and acanthosis nigricans (velvety and hyperpigmented skin of the neck and axillary folds).
4. **The answer is A** [IX.C.2]. In patients with Graves disease, thyroid-stimulating immunoglobulins are usually present because this is an autoimmune process and these antibodies are the cause of the thyrotoxic state. Girls with hyperthyroidism are more likely to have delayed menarche than to have precocious puberty. Both Graves disease and Hashimoto thyroiditis are examples of autoimmune disorders that are more common in females. First-line therapy is usually antithyroid medication, although surgery and radioactive iodine are effective and should be considered if medical treatment fails or is not tolerated.
5. **The answer is E** [I.E.2.a, I.F.1, and Table 6-1]. Bone age determination may be helpful when compared with the patient's chronologic age in the evaluation of short stature. Because of slowed growth velocity, patients with growth hormone deficiency would be expected to have their bone age less than their chronologic age, as would patients with constitutional growth delay, hypothyroidism, and hypercortisolism. Patients with genetic short stature, skeletal dysplasias, intrauterine growth retardation, and Turner syndrome would all be expected to have their bone age approximately the same as their chronologic age.
6. **The answer is B** [VIII.F]. When treating diabetic ketoacidosis (DKA), especially in children younger than 5 years, the diagnosis of cerebral edema must be entertained if there is a change in mental status. Risk factors for the development of cerebral edema include drops in serum glucose levels faster than 100 mg/dL per hour, bicarbonate administration, and excessive fluid administration. Changes in mental status can also result from hypoglycemia, hypocalcemia, and hypokalemia. Hypocalcemia can cause a seizure or change in mental status. Hypokalemia can result in an arrhythmia. Hyperphosphatemia is not a complication of DKA.

7. **The answers are B, D, C, A, and D, respectively** [II.B]. Most cases of sexual precocity are benign. Premature thelarche (question 7) is a transient state of isolated early breast development as is found in a girl younger than 7 years. Premature adrenarche is the early onset of pubic or axillary hair (question 10). Individuals with premature adrenarche present with pubic hair and an apocrine odor but no breast development or advanced bone age. Neither premature thelarche nor premature adrenarche is associated with activation of the hypothalamic–pituitary–gonadal axis.

   Central precocious puberty (CPP) is puberty directed by the hypothalamus. A girl with CPP (question 9) presents with tall stature, advanced bone age, breast development, pubic hair, and sometimes menses. A boy with CPP is tall with pubic hair and enlarged testes.
   Peripheral precocious puberty (PPP; questions 8 and 11) is sexual precocity that is not driven by the hypothalamus but rather originates from the ovaries, testes, or adrenal gland. In McCune–Albright syndrome (question 11), the girl shows breast development, café-au-lait spots, and fibrous dysplasia of the long bones. In another example of PPP (question 8), the boy's testes are prepubertal. If his androgens were driven by the hypothalamus, the testes would be enlarged.

1. **The answers are E, B, A, and C, respectively** [XII.B and XII.C]. Ketotic hypoglycemia is the most common cause of a low blood sugar in children. Patients are often thin, and symptoms develop after a prolonged fast or with infections. Congenital hypopituitarism should be considered in any newborn with a midline defect (e.g., cleft palate), hypoglycemia, and microphallus. Newborns with hypoglycemia persisting for longer than 4 days require further evaluation, and in these cases, hyperinsulinemia and Beckwith–Wiedemann syndrome should be considered. A newborn with hyperinsulinism will have no dysmorphic features but will have persistent low blood sugar due to the high amounts of circulating insulin. Beckwith–Wiedemann syndrome is characterized at birth by large for gestational age, macroglossia, umbilical hernia, and hyperinsulinemic hypoglycemia.

CHAPTER 7

Infectious Diseases

Deborah Lehman, Heather Hindo

I. General Approach to the Child With Possible Infection

A. **Detailed history and physical examination are essential.**
   1. **History** should include details about the present illness and significant past medical history. Important components of the history include chronic, recurrent, or life-threatening infections; travel; animal contact; insect (tick, mosquito, or flea) bites; medications; recent and past immunizations; unusual food ingestions (including raw meat and unpasteurized dairy products); and risk of infection with human immunodeficiency virus (HIV; e.g., intravenous drug use, remote history of blood transfusion, unprotected intercourse).
   2. **Physical examination** should be comprehensive, with special attention to general appearance and mental status rashes, skin manifestations of endocarditis (see Chapter 8, section V.C), hepatosplenomegaly, evidence of joint effusion, and lymph node enlargement.

B. **Use of the laboratory.** Pathogens may be identified by direct or indirect laboratory methods.
   1. **Direct methods**
      a. **Cultures** for bacteria and viruses
      b. **Microbiologic stains,** including **Gram stain**, **Ziehl–Neelsen stain** (acid-fast bacilli), **silver stain** (fungal elements), and **Wright stain** (stool white blood cells [WBCs])
      c. **Fluorescent antibody–antigen staining** for herpes simplex virus (HSV) 1 and 2, varicella-zoster virus (VZV), and respiratory viruses, such as respiratory syncytial virus (RSV), adenovirus, influenza A and B, parainfluenza, and *Pneumocystis jiroveci*
      d. **Direct observation,** including **wet mount** for fungal elements and *Trichomonas vaginalis* and **dark-field microscopy** for *Treponema pallidum*
      e. **Polymerase chain reaction (PCR)** is available for identification and quantification of many pathogens and has replaced fluorescent antibody–antigen staining in most centers. It can identify many respiratory pathogens, including *Mycoplasma pneumoniae*, *Bordetella pertussis* and *Bordetella parapertussis*, RSV, adenovirus, all of the herpes viruses (HSV, cytomegalovirus [CMV], Epstein–Barr virus [EBV], VZV, human herpes virus [HHV] 6), parvovirus, HIV, and rickettsial diseases, among others.
   2. **Indirect methods**
      a. **Intradermal skin testing** for *Mycobacterium tuberculosis* (TB) and *Coccidioides immitis* (Note: Skin testing for *C. immitis*, the agent of valley fever, is not widely used, and diagnosis is now more commonly made by sensitive and specific serologic testing.)
      b. **Antibody testing** for viruses (including EBV, CMV, VZV, and HIV); *Toxoplasma gondii; Bartonella henselae;* rickettsial diseases, including Rocky Mountain spotted fever and murine typhus*; Borrelia burgdorferi* (the agent of Lyme disease); and *Mycoplasma pneumoniae*
   3. **Nonspecific** laboratory indications of infection typically include elevation of acute-phase reactants, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as well as elevation of the peripheral WBC count.

II. Evaluation of the Child With Fever

A. **Fever** in children is defined as a **rectal temperature of 38°C (100.4°F) or higher**. Temperatures taken by axillary, oral, temporal, or tympanic methods may be less accurate.

B. Evaluation for serious bacterial infection (SBI) (e.g., meningitis, pneumonia, sepsis, bone and joint infections, urinary tract infection, and enteritis) should occur in the following **high-risk groups:**
   1. **Young infants,** especially those younger than 28 days, because of immaturity of their immune system
   2. **Older infants** with **high fevers** (temperature **> 39°C [102.2°F]**) **who are ill-appearing**
   3. Infants and children who are **immunodeficient**. This includes those who have **sickle cell disease (or are asplenic for another reason)** or have underlying chronic liver, renal, pulmonary, or cardiac disease. This also includes children who are receiving immunosuppressive therapy, such as chemotherapy, or immunomodulating agents for autoimmune conditions, such as inflammatory bowel disease or juvenile idiopathic arthritis (JIA).

C. **Evaluation of fever in infants < 3 months**
   1. **Epidemiology. 1–7% of infants with temperature >39°C have a SBI.** The highest risk is seen in the first 28 days of life, although the incidence of early onset neonatal sepsis (sepsis in the first week of life) has been significantly reduced as a result of maternal screening and empiric antibiotic treatment during labor and delivery for women colonized by group B streptococcus. Introduction of vaccines for *Haemophilus influenzae* type b (HIB) and *Streptococcus pneumoniae* have further decreased the incidence of SBI in infants <3 months of age.
   2. **Etiology**
      a. Infections may be acquired **in utero (i.e., transplacentally), during passage through the birth canal, or postnatally in the nursery or at home**.
      b. **Viruses are the most common organisms causing infection.**
      c. **Common bacterial organisms** causing infection in this age group are summarized in **Table 7-1**.
   3. **Clinical features** of infection in young infants are often **nonspecific** and include fever, diminished appetite, irritability, excessive sleepiness, cough, rhinorrhea, vomiting, diarrhea, and apnea.
   4. **Diagnosis. Clinical and laboratory features may be used to identify infants at low risk for SBI.**
      a. Infants who are well-appearing and previously healthy, who have had no recent antibiotic therapy, and who have no site of focal infection on examination are at low risk for SBI. Infants who are ill-appearing or toxic, and who have evidence of a focal infection on examination, are at higher risk for SBI.
      b. **Laboratory evaluation** should include complete blood count (CBC), blood culture, urinalysis, urine culture, chest radiograph if tachypnea or respiratory distress is present or if the peripheral WBC count is ≥20,000 cells/mm^3, and analysis of the cerebrospinal fluid (CSF). The following are the criteria that indicate an infant is at **low risk** for SBI:
         1. WBC >5000 and <15,000 cells/mm^3
         2. Absolute band count <1500 cells/mm^3
         3. Normal urinalysis (<10 WBCs per high-power field)
         4. If diarrhea is present, <5 WBCs per high-power field on stool Wright stain
         5. Normal CSF

5. **Management**
    a. **Hospitalization is required for:**
        1. **All infants ≤ 28 days of age**
        2. **Infants between 29 days and 3 months of age with any of the following:**
            a. **Toxic appearance on examination**
            b. Suspected **meningitis**
            c. **Pneumonia, pyelonephritis,** or **bone and soft tissue infections**, which are unresponsive to oral antibiotics
            d. Patients in social circumstances in which there is **uncertain outpatient care and follow-up**
    b. **Antibiotic management** is based on age, risk factors for infection, and etiology.
        1. Infants ≤28 days of age require intravenous antibiotics in the hospital until cultures of blood, urine, CSF, and stool (if diarrhea is present) are negative, typically after 48 hours.
        2. Infants 29 days–3 months of age who satisfy low-risk clinical and laboratory criteria [see section II.C.4] appear clinically well and who have transportation and good outpatient follow-up may be managed safely with or without outpatient parenteral antibiotic therapy (i.e., intramuscular ceftriaxone), and may not require a lumbar puncture if they are well appearing. They may also be observed in the hospital without antibiotic administration and discharged when cultures are negative. If antibiotics are to be administered, a full evaluation (blood, urine, and CSF cultures) should be obtained before the initiation of antibiotics.
        3. Infants 29 days–3 months of age who do not meet low-risk clinical and laboratory criteria, but appear clinically well, can also be managed as outpatients but should receive parenteral empiric antibiotic therapy (i.e., intramuscular ceftriaxone) following collection of blood, urine, and CSF cultures.
        4. Infants who appear ill, irrespective of laboratory data, should be hospitalized for parenteral therapy while cultures are pending.
        5. Recommended parenteral antibiotic therapy for hospitalized infants is presented in **Table 7-1**.

D. **Evaluation of fever in children aged 3–36 months**
1. **Epidemiology.** Before the widespread immunization with vaccines for HIB and pneumococcal conjugate vaccine (PCV13), the risk of SBI was 3–10%. The likelihood of bacteremia was as high as 5–10% in well-appearing children with temperature >39°C and a peripheral WBC count >20,000 cells/mm^3. With the introduction of these vaccinations, the risk has decreased to less than 1% in a well-appearing child with fever. This reduction has changed the recommendations for management of immunized infants without a source on examination. Infants who have not received the primary booster series of immunizations, including PCV13 and HIB, should be considered incompletely immunized and at higher risk for SBI.
2. **Etiology** (see Table 7-1). ***S. pneumoniae*** is the **most common** organism. **HIB** is **less common** as a result of the introduction of HIB vaccine. Other pathogens include *Escherichia coli*, particularly in the setting of a probable urinary tract infection, and *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) in the setting of skin and soft tissue infection.
3. **Diagnostic evaluation** and **management** are based on the degree of the fever and whether the child appears toxic.
    a. If the child is toxic or ill-appearing, a complete evaluation for sepsis, intravenous

antibiotics, and hospitalization are required.

b. If the child is nontoxic-appearing and the temperature is <39°C (<102.2°F), and immunizations are up to date, no laboratory tests are required and the child may be observed closely at home.
c. If the child is nontoxic-appearing and has persistent fever (>3 days) with a temperature ≥ 39°C (>102.2°F), the following studies are suggested:
    1. Urine culture for male children <12 months of age and female children <2 years of age
    2. CBC with differential, and blood culture if WBC count is >15,000 cells/mm^3
    3. Chest radiograph if respiratory distress, rales, or tachypnea is present, or if the peripheral WBC count is ≥20,000 cells/mm^3
    4. Stool culture if there is blood or mucus in the stool, or if there are ≥5 WBCs per high-power field on Wright stain
    5. Empiric antibiotics for all children or only for those whose WBC count is >15,000 cells/mm^3, with re-evaluation in 24–48 hours
d. Recommended parenteral antibiotic therapy for hospitalized infants and children is presented in **Table 7-1**.

Table 7-1
Typical Bacterial Pathogens and Empiric Antibiotics for Infants and Children with Suspected Sepsis or Meningitis

Age	Bacterial Pathogens	Empiric Intravenous Antibiotics
0–1 month	Group B streptococcus	Ampicillin + gentamicin or ampicillin + cefotaxime
	Escherichia coli	
	Listeria monocytogenes	
1–3 months	Group B streptococcus	Ampicillin + cefotaxime (add vancomycin* if bacterial meningitis is suspected)
	Streptococcus pneumoniae	
	Listeria monocytogenes	
3 months–3 years	*Streptococcus pneumoniae*	Cefotaxime (add vancomycin*if bacterial meningitis is suspected)
	Neisseria meningitidis Haemophilus influenzae type b	
3 years–adult	*Streptococcus pneumoniae*	Cefotaxime (add vancomycin*if bacterial meningitis is suspected)
	Neisseria meningitidis	

*Vancomycin is added to empiric coverage if bacterial meningitis is suspected to cover for highly resistant *S. pneumoniae*.

III. Fever of Unknown Origin (FUO)

A. **Definition.** Fever of unknown origin (FUO) is a term used to describe a **fever lasting longer than 8 days to 3 weeks** (experts disagree about the length of time of fever necessary to diagnose fever as FUO). With current diagnostic advances, the most accepted definition of FUO is a fever for at least 8 days in a child when **prior history, physical examination, and preliminary laboratory evaluation have all failed to lead to a diagnosis**.

B. **Etiology**
   1. **Most children with FUO do not have a rare illness** but rather a common infection with an unusual presentation.
   2. The **differential diagnosis** is extensive (**Table 7-2**).
   3. **One-fourth of cases of FUO resolve spontaneously** without a diagnosis having been made.
   4. **Noninfectious causes such as connective tissue disease, autoimmune disease, and malignancy should also be considered.**

C. **Evaluation** should include the following:
   1. **Comprehensive history,** focusing on a thorough **review of systems** (especially weight loss; rashes; stool patterns; and the height, duration, and pattern of fever), **past medical and surgical history** (including prior blood transfusions), **travel history, animal exposure,** and **family and social history**.
   2. **Detailed physical examination,** focusing on general appearance and growth curves, skin and mucous membrane findings, presence of lymphadenopathy and hepatosplenomegaly, and evaluation of joints and bones.
   3. **Laboratory studies** are based on the history and physical examination, and the initial evaluation often includes the following:
      a. **CBC with differential** to evaluate for infection or leukemia
      b. **ESR or CRP,** which are nonspecific indicators of tissue inflammation
      c. **Serum transaminases** to evaluate for hepatitis
      d. **Urinalysis and urine culture** to evaluate for infection
      e. **Blood cultures** to evaluate for bacteremia, including endocarditis
      f. **Antistreptolysin O (ASO) titer** to evaluate for recent streptococcal infection, as seen in rheumatic fever
      g. **Antinuclear antibody (ANA) and rheumatoid factor (RF)** to screen for rheumatic diseases
      h. **Stool** for fecal leukocytes, culture, ova and parasites, and PCR for *Clostridium difficile* toxin if diarrhea is present
      i. **Tuberculosis skin test or IGRA (interferon gamma release assay) testing**
      j. **HIV testing** (enzyme-linked immunoassay [EIA] and/or PCR)
   4. **Imaging options** may include chest radiography, echocardiography to evaluate for bacterial endocarditis, bone scanning to evaluate for osteomyelitis, gallium scanning to assess for sites of inflammation, and computed tomography (CT) and magnetic resonance imaging (MRI) of specific areas of concern. Abdominal, pelvic, and chest CT scans are frequently performed as part of an extended workup for FUO to localize occult abscesses, to identify lesions in the liver or spleen, and to detect pulmonary infiltrates which are not visualized on a plain chest x-ray.
   5. **Management.** Hospitalization is generally recommended for children with fever for more than 2 weeks to facilitate evaluation and to document fever and coexisting symptoms. Hospitalization can also be helpful to document the fever pattern and associated vital sign changes with fever, and to coordinate the workup. Specific

management is based on the identified cause of the FUO.

Table 7-2
Differential Diagnosis of Fever of Unknown Origin

Infectious disorders (most common cause of FUO)
Occult infection (e.g., pyelonephritis, sinusitis, mastoiditis, or otitis media)
Viral syndromes (e.g., Epstein–Barr, cytomegalovirus, enterovirus, hepatitis B, HIV, or parvovirus B19)
Occult bacteremia (e.g., salmonellosis, tularemia, brucellosis, or gonococcemia)
Bacterial endocarditis
Tuberculosis
Occult abscess (e.g., liver, intra-abdominal, or perinephric)
Musculoskeletal infections (e.g., diskitis, osteomyelitis, or septic arthritis)
Spirochete infections (e.g., Lyme disease, or leptospirosis)
Parasitic infections (e.g., malaria, or toxoplasmosis)
Cat scratch disease (*Bartonella henselae*) Rickettsial disease (murine typhus, or Rocky Mountain spotted fever)
Rheumatologic disorders (second most common cause of FUO)
Juvenile idiopathic arthritis (JIA) (including systemic JIA, which is termed Still's disease)
Kawasaki disease
Systemic lupus erythematosus
Acute rheumatic fever
Polyarteritis nodosum
Malignancy (third most common cause of FUO)
Lymphoma
Leukemia
Periodic fever disorders characterized by spiking fevers at regular monthly intervals. Although these are commonly considered as FUO, they are more typically of shorter duration (3–5 days) and recur at regular intervals.
Familial Mediterranean fever: fever, peritonitis, pleuritis, and monoarthritis
Periodic fever syndrome or periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome (PFAPA): typically presenting in early childhood with regularly occurring monthly fevers and associated symptoms. This syndrome is self-limited and usually resolves by 5 or 6 years of age.
Cyclic neutropenia: neutropenia at time of fever occurring at regular 21-day intervals

Miscellaneous causes
Inflammatory bowel disease
Sarcoidosis
Drug fever
Factitious disorder

FUO = fever of unknown origin; *HIV* = human immunodeficiency virus.

IV. Meningitis

A. **Definition.** Meningitis is the **inflammation of the meninges** and is classified as **bacterial** or **aseptic (nonbacterial)**.

B. **Bacterial meningitis**

1. **Epidemiology**
   a. Highest incidence of bacterial meningitis is during the **first month of life**.
   b. Overall incidence during childhood has declined dramatically owing to the introduction of conjugate vaccines for *S. pneumoniae* and HIB. Before vaccination, HIB was the leading cause of bacterial meningitis outside the newborn period.
   c. **Risk factors** for bacterial meningitis include the following:
      1. **Young age**
      2. **Immunodeficiency** (e.g., asplenia, humoral-mediated immunodeficiency, and **terminal complement deficiency,** which predisposes individuals to infections with *Neisseria meningitidis*)
      3. **Anatomic defects** (e.g., basilar skull fracture, ventriculoperitoneal shunt, cochlear implants), which increase the risk of meningitis caused by *S. pneumoniae* owing to direct extension from the nasopharynx and ear.
2. **Etiology.** Causes of infection are based on the age of the child (see Table 7-1).
3. **Clinical features**
   a. Infants and young children often have minimal and **nonspecific signs and symptoms** (e.g., poor feeding, irritability, lethargy, respiratory distress). **Fever may be absent or minimal.** A bulging fontanelle may be found on physical examination.
   b. Older children often present with **fever** and **signs suggestive of meningeal irritation**.
      1. **Alteration in level of consciousness,** with irritability, somnolence, or obtundation
      2. **Nuchal rigidity** and positive **Kernig** (inability to extend the knee when the thigh is flexed 90° at the hip) **and Brudzinski** (the thighs and legs involuntarily flex when the neck is flexed) **signs**. These signs indicate inflammation of sensory nerves and are less reliably present in infants and young children.
      3. **Seizures** (20–30% of children have a seizure before or at the time of admission)
      4. **Photophobia**
      5. **Emesis**
      6. **Headache.** Both emesis and headache are symptoms of increased intracranial pressure.
4. **Diagnosis. Index of suspicion for bacterial meningitis should be especially high in febrile, irritable infants.** Evaluation of all children with suspected bacterial meningitis should include the following:
   a. **Lumbar puncture,** which may demonstrate
      1. **Pleocytosis** with a predominance of **neutrophils**. The CSF WBC count often exceeds 5000 cells/mm^3, but early in the course the cell count may be lower.
      2. **Hypoglycorrhachia** (low CSF glucose)—ratio of CSF glucose to serum glucose <0.40 and CSF glucose typically <40 mg/dL.
      3. **Increased protein**-typically 100–500 mg/dL
      4. **Increased intracranial pressure** (in older children)
      5. **Positive Gram stain and/or culture**
      6. Bacterial antigens may be tested but have a low sensitivity and are not

recommended on a routine basis.

7. Pretreatment with antibiotics may sterilize the CSF culture but should not alter the aforementioned CSF cellular and biochemical profile.
8. See **Table 7-3** for a comparison of the CSF profile in bacterial, viral, tuberculous, and fungal meningitis.
9. **Interpretation of a traumatic lumbar puncture:** Lumbar punctures that contain a large number of red blood cells (RBCs) are difficult to interpret, but a correction can be calculated that accounts for the ratio of WBCs and RBCs in the serum from the patient's CBC. For patients with a normal peripheral WBC count, a rough estimation is that one WBC in the CSF may account for every 500 RBCs in the CSF.

b. **Blood culture** is positive in most cases of bacterial meningitis.
c. **CT scan with contrast** to evaluate for brain abscess is often recommended, especially for patients with focal neurologic findings or altered mental status.

5. **Management. Early, empiric treatment of bacterial meningitis is critical.**
   a. **Antibiotic therapy** varies based on age of child and the most likely pathogens, as follows:
      1. **Newborns** (0–28 days): Ampicillin plus aminoglycoside or a third-generation cephalosporin. Intravenous acyclovir for possible HSV infection should also be considered for ill neonates, especially those presenting with apnea, seizures, or cutaneous vesicles.
      2. **Young infants** (1–3 months): Ampicillin (for *Listeria monocytogenes* coverage) plus a third-generation cephalosporin. Vancomycin should be added if bacterial meningitis is highly suspected, to cover for highly resistant *S. pneumoniae*.
      3. **Older infants and children** (>3 months): Third-generation cephalosporin. Vancomycin should be added if bacterial meningitis is highly suspected, to cover for highly resistant *S. pneumoniae*.
   b. **Corticosteroids** given before or with the first dose of antibiotics have been shown to be effective at reducing the incidence of hearing loss in HIB meningitis. Efficacy in other causes of bacterial meningitis has not been as clearly demonstrated. If corticosteroids are given, they should be administered before or with the first dose of antibiotics for maximum benefit, and should only be administered to children outside the neonatal period. Dexamethasone is given for a 2–4-day regimen (0.6 mg/kg per day) divided into four daily doses.
   c. **Supportive care.** Children presenting with meningitis typically have been ill for a few days and may be moderately dehydrated. Management should include attention to fluids with rehydration to normovolemic status, followed by administration of maintenance fluids with close attention to vital signs, urine output, specific gravity, and serum sodium to monitor for the development of the syndrome of inappropriate release of antidiuretic hormone (SIADH).
6. **Complications.** Complication rates are highest following meningitis caused by Gram-negative organisms, followed by *S. pneumoniae,* HIB, and finally, *Neisseria meningitidis.* Mortality rates range from 5 to 50% depending on the infecting bacterial species.
   a. **Hearing loss** is the **most common** complication, occurring in up to 25% of patients.
   b. **Global brain injury** occurs in 5–10% of patients.
   c. Other complications include **SIADH, seizures, hydrocephalus, brain abscess, cranial nerve palsy, learning disability, and focal neurologic deficits**.

C. **Aseptic meningitis**

1. **Definition.** Aseptic meningitis is the **inflammation of the meninges with a CSF**

lymphocytic pleocytosis and, if caused by a virus, **normal CSF glucose and normal to minimally elevated CSF protein**.

2. **Etiology (Table 7-4).** Most causes of aseptic meningitis are viral.
3. **Clinical features** may be similar to those found in bacterial meningitis.
    a. Symptoms of viral meningitis may be mild with fever, headache, and emesis, or severe with altered level of consciousness and seizures.
    b. Symptoms in aseptic meningitis caused by ***M. tuberculosis*** **(TB)** may be nonspecific initially, with lethargy or irritability. During the second week of illness, signs and symptoms progress rapidly and may include cranial nerve deficits, altered level of consciousness, coma, paraplegia, and eventually death if untreated.
4. **Diagnosis** (see Table 7-3 for the CSF findings commonly seen in viral, fungal, tuberculous, and bacterial meningitis)
    a. **Viral meningitis**
        1. Viral culture of the CSF may be performed; however, the virus may not grow for 10–14 days, if it grows at all.
        2. PCR technology is available for the detection of EBV, CMV, HSV, VZV, and enteroviruses.
        3. Positive surface cultures for enterovirus from throat and/or rectum may be suggestive in cases of enteroviral meningitis.
    b. **TB meningitis.** CSF findings include lymphocytic pleocytosis, hypoglycorrhachia, and dramatically elevated protein. Brain imaging shows a characteristic **basilar enhancement.** Positive CSF acid-fast bacilli (AFB) stains (although rarely positive in TB meningitis), positive culture (may take as long as 6 weeks for growth), or positive PCR findings are diagnostic. **Fifty percent of patients have a negative chest radiograph and tuberculin skin test at the time of presentation.**
    c. **Diagnostic studies that may identify other causes of aseptic meningitis** include CSF rapid plasma reagent (RPR) for syphilis; India ink for fungus (cryptococcus) and cryptococcal antigen tests; and CSF and serum antibody testing for coccidioidomycosis, Lyme disease, rickettsial disease, and cysticercosis.
5. **Management**
    a. Most causes of viral meningitis are self-limited.
    b. TB meningitis is treated with four medications, including isoniazid, rifampin, pyrazinamide, and streptomycin or a fluoroquinolone (levofloxacin). Corticosteroids are also commonly used to manage brain inflammation and elevated intracranial pressure.
6. **Prognosis** of aseptic meningitis is dependent on the causative agent, and ranges from excellent in enteroviral meningitis to poor in TB meningitis (20% mortality in young children).

Table 7-3
Cerebrospinal Fluid Profiles in Meningitis

Pathogen	WBC Differential (cells/mm^3)	Protein	Glucose	Gram Stain, Culture, and Other Definitive Tests
Acute bacterial	100–50,000	High	Low	Positive culture and Gram stain
	PMNs predominate			
Partially treated bacterial	1000–10,000Monos predominate	Normal to high	Low normal	Negative culture and usually negative Gram stain
				(+) CSF bacterial antigens
Viral	10–1000PMNs early, then monos + lymphsHSV encephalitis may show RBCs	Normal to minimally elevated	Normal	Enterovirus may be recovered by culture
				Enterovirus and HSV may be identified by PCR

Tuberculosis	10–500Lymphs predominate	Very high	Low to very low	AFB smear and culture rarely positive PCR may be positive
Fungal	25–500Lymphs predominate	Normal to high	Low	Culture may be positive For cryptococcal meningitis, India ink and cryptococcal antigen are positive For coccidioidal meningitis, cocci antibody is positive
Parameningeal focus (brain abscess)	10–200 PMNs or monos predominate	High	Normal	Negative culture

AFB = acid-fast bacilli; *PMNs* = polymorphonuclear cells; *monos* = mononuclear cells; *lymphs* = lymphocytes; *CSF* = cerebrospinal fluid; *PCR* = polymerase chain reaction; *RBCs* = red blood cells; *HSV* = herpes simplex virus; *WBC* = white blood cell.

Table 7-4

Causes of Aseptic Meningitis

Viral meningitis (**most common cause of aseptic meningitis**). If infection also involves the brain, it is termed a meningoencephalitis.
Enteroviruses (**most common cause of viral meningitis in the United States;** most common in the summer and fall)
Mumps
Lymphocytic choriomeningitis
Herpes viruses (herpes simplex virus, Epstein–Barr virus, cytomegalovirus, varicella zoster virus, human herpes viruses 6 and 7) Human immunodeficiency virus Parechoviruses
Viruses that commonly cause encephalitis include arboviruses (St. Louis, Western equine, Eastern equine, and West Nile virus), **influenza, and the herpes viruses**
Bacterial causes (some bacteria may cause an aseptic picture)
Mycobacterium tuberculosis (most commonly seen in children younger than 5 years of age)
Borrelia burgdorferi (Lyme disease)
Treponema pallidum (syphilis) *Brucella* spp.
Fungal causes
Coccidioides immitis
Cryptococcus neoformans
Histoplasmosis capsulatum
Parasitic causes
Taenia solium (etiologic agent of cysticercosis)
Toxoplasma gondii (in immunocompromised patients) Roundworms: *Baylisascaris procyonis* causes an eosinophilic meningitis *Naegleria fowleri*
Noninfectious causes
Kawasaki disease

Medications (sulfa, intravenous immune globulin [IVIG])
Autoimmune conditions (systemic lupus erythematosus [SLE])

V. Upper Respiratory Infections

A. **General concepts.** Upper respiratory infections (URIs) account for most pediatric acute illness visits. Although generally benign illnesses, they may cause significant morbidity and parental anxiety.

B. **Simple URI (common cold)**
   1. **Etiology.** More than 100 viruses have been implicated and include **rhinovirus, parainfluenza virus, coronavirus, and RSV**.
   2. **Clinical features**
      a. Presenting symptoms include low-grade fever, rhinorrhea, cough, and sore throat. Symptoms resolve within 7–10 days.
      b. **Color of nasal discharge alone does not predict the presence of concurrent sinusitis** because purulent nasal discharge may occur early in the course of a URI.
      c. **Persistent symptoms** (>10 days) **or persistent fever should prompt the clinician to evaluate for bacterial superinfection** (e.g., sinusitis, acute otitis media).
   3. **Diagnosis** is based on clinical features. The viral agent is rarely identified.
   4. **Management.** The **most important step is to ensure adequate hydration, particularly in young children,** and to exclude more serious disorders, such as sinusitis and acute otitis media. Over-the-counter medications (e.g., antihistamines, mucolytics, cough suppressants, and decongestants) have minimal effectiveness and may cause side effects. **Antibiotics have no role in the management.**

C. **Sinusitis**
   1. **Development of the sinuses.** Ethmoid and maxillary sinuses form in the third to fourth month of gestation and are present at birth. The sphenoid sinuses develop between 3 and 5 years of age, and frontal sinuses between 7 and 10 years of age.
   2. **Categories of sinusitis.** Sinusitis is divided into **acute, subacute, and chronic forms** on the basis of **duration of symptoms**.
   3. **Diagnosis** is based on clinical features. Note that physical examination (particularly sinus transillumination) is unreliable for diagnosis and that **imaging is not useful for the initial diagnosis or management of uncomplicated sinusitis**.
   4. **Management** of uncomplicated acute bacterial sinusitis includes empiric antibiotic therapy (for example, with amoxicillin-clavulanate) to cover likely pathogens, including *S. pneumoniae, H. influenzae, and M. catarrhalis.*

D. **Pharyngitis**
   1. **Etiology**
      a. **Viral causes** include those viruses associated with simple URIs, as well as **coxsackievirus, EBV, and CMV**.
      b. **Bacterial causes** include ***Streptococcus pyogenes*** (group A β-hemolytic streptococcus [**GABHS**] or "**strep throat**"), *Arcanobacterium hemolyticum,* and *Corynebacterium diphtheriae* (diphtheria).
   2. **Clinical features.** The **clinical features of viral pharyngitis and GABHS pharyngitis overlap,** resulting in difficulty differentiating between the two conditions solely on the basis of history and physical examination.
      a. **Viral pharyngitis** may present with simple URI symptoms. Tonsillar exudates may also be present. Certain viral infections may have the following specific findings:
         1. Children with **EBV pharyngitis** may present with *enlarged posterior cervical lymph nodes, malaise, and hepatosplenomegaly*.
         2. Children with **coxsackievirus pharyngitis** may present with **painful vesicles or ulcers** on the posterior pharynx and soft palate (**herpangina**). Blisters may

also be present on the palms and soles (**hand-foot-mouth disease**).

b. **Bacterial pharyngitis**

1. **GABHS pharyngitis** (strep throat) is usually seen in school aged children (5–15 years of age) and most commonly in the winter and spring. Although it is difficult to distinguish GABHS pharyngitis from viral pharyngitis on the basis of signs and symptoms, GABHS infection has the following characteristics:
   a. **Lack of other URI symptoms** (e.g., rhinorrhea, cough)
   b. **Exudates on the tonsils, petechiae on the soft palate, strawberry tongue, and enlarged tender anterior cervical lymph nodes**
   c. **Fever**
   d. **Scarlatiniform rash** in some patients [see section IX.A.5]
   e. Complications of GABHS infection are described in section IX.A.5.g.
2. **Diphtheria** is extremely rare in developed nations because of universal vaccination. Patients present with low-grade fever and a **gray, adherent tonsillar membrane**. Toxin-mediated cardiac and neurologic complications may also develop.

3. **Diagnosis**
   a. Patients with suspected GABHS pharyngitis should undergo culture (gold standard) or antigen testing ("rapid strep test") to confirm GABHS pharyngitis and to avoid the overuse of antibiotics.
   b. Because 5% of the population carries GABHS in the pharynx (GABHS carriers), culture or rapid antigen testing should be limited to symptomatic patients who lack concomitant viral symptoms.
4. **Management**
   a. Management of viral pharyngitis is supportive and includes analgesics and the maintenance of adequate hydration.
   b. Management of GABHS pharyngitis includes oral penicillin VK or amoxicillin, a single dose of intramuscular benzathine penicillin, or for penicillin-allergic patients, a macrolide.
   c. Management of severe EBV pharyngitis, with pending airway obstruction, may sometimes include corticosteroids.
   d. Diphtheria is treated with oral erythromycin or parenteral penicillin, and a specific antitoxin that is available from the Centers for Disease Control and Prevention. Respiratory isolation is very important to prevent spread of infection.

E. **Acute otitis media**

1. **Definitions**
   a. **Acute otitis media (AOM)** is defined as an **acute infection of the middle ear space**.
   b. **Otitis media with effusion (OME)** is defined as fluid within the middle ear space without signs or symptoms of infection.
2. **Etiology.** Bacterial pathogens include ***S. pneumoniae*, nontypeable *H. influenzae*,** and ***Moraxella catarrhalis***. Viruses causing URIs also commonly cause AOM.
3. **Clinical features of AOM**
   a. AOM usually develops during or after a URI.
   b. Symptoms may include **fever, ear pain, and decreased hearing**. Symptoms are less reliably present in young children.
   c. If the tympanic membrane perforates, patients may report pus or fluid draining from the ear.
4. **Diagnosis**
   a. **Proper diagnosis of AOM depends on the identification of fluid within the middle ear space in the presence of symptoms of infection.**

1. **Pneumatic otoscopy** to identify abnormal movement of the tympanic membrane, and therefore fluid within the middle ear, is an essential component of the physical examination and is the **most reliable method of detecting middle ear fluid.**
2. **Erythema and loss of tympanic membrane landmarks are unreliable methods of identifying fluid within the middle ear space.**

b. Although not routine, identification of the bacterial etiology may be made by tympanocentesis.
c. A perforated tympanic membrane with purulent discharge within the external auditory canal is also consistent with the diagnosis of AOM.

5. **Management**
   a. Antibiotics are often prescribed for AOM; however, they are not always indicated, especially in older children, because most cases of AOM resolve spontaneously without complications.
   b. Initial antibiotic therapy, if used, is usually **amoxicillin**. If the patient attends a day care facility or has received antibiotics within the previous 1–2 months, then the likelihood of infection with penicillin-resistant *S. pneumoniae* increases. Initial therapy may then include high-dose amoxicillin, amoxicillin–clavulanic acid, or a cephalosporin. Macrolides may be used in penicillin-allergic patients.
   c. Antibiotics are not indicated for OME.

F. **Otitis externa**
1. **Definition.** Otitis externa (OE) is defined as an **infection of the external auditory canal** (EAC).
2. **Pathogenesis.** Factors that interfere with the EAC-protective mechanisms (e.g., cerumen removal, trauma, maceration of the skin from swimming, or excessive moisture or humidity) predispose to OE.
3. **Etiology.** Pathogens are most commonly *Pseudomonas aeruginosa*, *S. aureus,* or *Candida albicans.* OE can also develop in a patient with a perforated tympanic membrane secondary to AOM.
4. **Clinical features.** Pain, itching, and drainage from the ear are usually present. Systemic symptoms are usually absent. A history consistent with AOM is helpful in determining whether there has been a tympanic membrane perforation.
5. **Diagnosis.** Findings on physical examination are the basis of diagnosis. **Erythema and edema of the EAC** may be present, sometimes with purulent or whitish material within the canal. There may also be tenderness on palpation or movement of the tragus. Visualization of the tympanic membrane is important to exclude perforation. In refractory cases, cultures of infected material may identify the etiologic agent.
6. **Management**
   a. The **key to successful management is to restore the EAC to its natural acidic environment**.
   b. For mild cases of OE (minimal pain and discharge), acetic acid solution may be sufficient to relieve the discomfort and to restore the natural environment of the EAC.
   c. For more severe cases, topical antibiotics (sometimes combined with a topical corticosteroid) are prescribed.
   d. Perforated AOM complicated by OE is treated with both oral and topical antibiotics.

VI. Middle and Lower Respiratory Infections

Middle and lower respiratory infections, including pneumonia, bronchiolitis, epiglottitis, croup, and bacterial tracheitis, are described in Chapter 9, section III.

VII. Cervical Lymphadenitis

A. **Definition.** Cervical lymphadenitis is defined as an enlarged, inflamed, tender lymph node or nodes in the cervical area.

B. **Etiology and differential diagnosis**

1. **Localized bacterial infection**
    a. ***S. aureus*** is the **most common bacterial agent**.
    b. ***S. pyogenes*** is also common.
    c. **Mycobacterial infections,** including *M. tuberculosis* and atypical mycobacterium (*Mycobacterium avium* complex)
    d. ***B. henselae,*** which causes cat scratch disease [see section XVII.B]
2. **Reactive lymphadenitis** occurs in response to infections in the pharynx, teeth, and soft tissues of the head and neck.
3. **Viral infections,** such as EBV, CMV, and HIV, can also cause reactive lymphadenitis in the cervical area.
4. **Kawasaki disease** may present with unilateral cervical lymphadenitis. A unilateral enlarged cervical lymph node (>1.5 cm in diameter) is one of the diagnostic criteria of Kawasaki disease. [see chapter 16, section II]
5. ***T. gondii*** infection may cause a mononucleosis-like illness with cervical lymphadenopathy.
6. **Structural lesions in the neck** (e.g., branchial cleft cyst, cystic hygroma) can become secondarily infected and may present similarly to cervical lymphadenitis.

C. **Clinical Features of Lymphadenitis**

1. The infected node is **mobile, tender, warm,** and enlarged, and the overlying skin is erythematous. Fluctuance may be present.
2. Nodes may be single, or multiple nodes may be clumped together in a mass.
3. Systemic symptoms (e.g., fever) may be present.

D. **Diagnosis** is based on clinical features.

1. Tests, such as placement of a tuberculin skin test, a CBC with differential, and antibody titers for *B. henselae* and *T. gondii,* may be indicated for infected nodes **unresponsive to therapy**.
2. **Antibody titers** for EBV, CMV, and HIV serology may be indicated if **lymphadenopathy is diffuse and persistent**.
3. **Imaging studies** may help define the anatomy of the cervical area and identify areas of suppuration or abscess that might require surgical drainage. Imaging is essential if there is concern about airway compromise resulting from a deep infection.

E. **Management** includes empiric antibiotics directed toward the most common organisms (*S. aureus* and *S. pyogenes*). Initial treatment may include a first-generation cephalosporin or an antistaphylococcal penicillin for 7–10 days. Intravenous antibiotics are indicated for the toxic-appearing child with lymph adenitis, or for the child who remains symptomatic despite appropriate oral therapy.

VIII. Parotitis

A. **Definition.** Parotitis is defined as inflammation of the parotid salivary glands.

B. **Etiology**

1. **Mumps and other viruses** (e.g., CMV, EBV, HIV, influenza) usually cause **bilateral involvement** of the parotid gland. **Before universal vaccination, mumps was the most common cause of parotitis.**
2. **Bacterial parotitis (acute suppurative parotitis)** is caused by *S. aureus* and *S. pyogenes,* and usually results in **unilateral parotid involvement**. Bacterial parotitis is uncommon during childhood, although children with decreased salivary flow or stone formation are at increased risk.

C. **Clinical features** include swelling centered above the angle of the jaw with fever. Physical examination of the oropharynx may reveal pus that can be expressed from Stensen's duct.

D. **Diagnosis** is based on clinical features and may be confirmed by CT scan.

1. Culture of the drainage from Stensen's duct may reveal the microbiologic cause of bacterial parotitis.
2. Viral parotitis may be diagnosed by viral serology. Mumps virus may also be detected in the urine.

E. **Management**

1. Viral parotitis is treated with supportive care and analgesics.
2. Acute suppurative parotitis is treated with antibiotics directed against *S. aureus* and *S. pyogenes.* Rarely, surgical excision and drainage are required.

F. **Complications**

1. Mumps may also result in meningoencephalitis, orchitis and epididymitis, and pancreatitis.
2. Acute suppurative parotitis may result in formation of an abscess and osteomyelitis of the jaw.

IX. Skin and Soft Tissue Infections

A. **Bacterial infections**

1. **Impetigo**
    a. **Definition.** Impetigo is a superficial skin infection involving the *upper dermis*.
    b. **Etiology. *S. aureus* is the most common agent, but GABHS (or *S. pyogenes*)** may also cause infection.
    c. **Clinical features. Honey-colored crusted** or bullous lesions are present, commonly on the face, especially around the nares. Fever is generally absent. **Infection is easily transmitted.**
    d. **Diagnosis.** Visual inspection is the basis of diagnosis. Cultures are not required.
    e. **Management.** Treatment may include topical mupirocin or oral antibiotics, such as dicloxacillin, a first-generation cephalosporin, or clindamycin.
    f. **Complications.** Bacteremia, poststreptococcal glomerulonephritis (treatment of impetigo does not prevent this complication), and staphylococcal scalded skin syndrome (SSSS) are possible complications.
2. **Erysipelas**
    a. **Definition.** Erysipelas is a skin infection that involves the *dermal lymphatics*.
    b. **Etiology** is usually **GABHS**.
    c. **Clinical features** include **tender, erythematous skin with a distinct border**. The face and scalp are common locations.
    d. **Diagnosis** is by visual inspection.
    e. **Management** includes systemic therapy with antibiotics targeted against GABHS.
    f. **Complications** include bacteremia, poststreptococcal glomerulonephritis, and necrotizing fasciitis.
3. **Cellulitis**
    a. **Definition.** Cellulitis is a skin infection that occurs *within the dermis*.
    b. **Etiology.** Causes include **GABHS** and ***S. aureus***. Infection is usually caused by a break in the skin barrier, allowing bacteria to gain td class="id" beyond the protective layer of the epidermis.
    c. **Clinical features.** Cellulitis is characterized by erythema, warmth, and tenderness. The infected skin border is **indistinct**.
    d. **Diagnosis** is by visual inspection. Blood cultures are seldom positive. In more aggressive forms of cellulitis, biopsy and culture of the leading edge of infection may be useful to identify the pathogenic organism.
    e. **Management** includes oral or intravenous antibiotics directed against the typical causative agents, including first-generation cephalosporins or antistaphylococcal penicillins.
4. **Important variants of cellulitis**
    a. **Buccal cellulitis** is now an uncommon form of cellulitis that presents as a **unilateral bluish discoloration on the cheek of a young unimmunized child**. Patients are often febrile and may appear toxic. The causative agent is **HIB**, and blood cultures are often positive. Management includes intravenous antibiotics directed against *H. influenzae*, usually a second- or third-generation cephalosporin (e.g., cefuroxime or cefotaxime). Patients with buccal cellulitis caused by HIB have a high rate of concomitant bacteremia and meningitis, and therefore blood cultures and CSF cultures should be obtained.
    b. **Perianal cellulitis** occurs as **well-demarcated erythema involving the skin around the anus**. Children may also present with constipation. The cause is usually

GABHS. Diagnosis is by visual inspection or a positive rectal swab culture for GABHS. Management includes oral antibiotics (e.g., first-generation cephalosporin, dicloxacillin).

c. **Necrotizing fasciitis** is a **potentially fatal form of deep cellulitis**. Patients present with **pain and systemic symptoms out of proportion to physical findings**. Infection extends beyond the underlying fascia into the muscle. Examination may reveal crepitus and hemorrhagic bullae. The cause is polymicrobial and may involve GABHS and anaerobic bacteria. **Intravenous antibiotics and surgical debridement are essential components of therapy.**

d. **Staphylococcal Scalded Skin Syndrome (SSSS)** is caused by strains of *S. aureus* that produce an exfoliative toxin. Presentation includes fever, **tender skin,** and bullae. Large sheets of skin slough several days after the illness begins, and the **Nikolsky sign is present** (extension of bullae when pressure is applied to the skin). Management includes good wound care and intravenous antibiotics directed against *S. aureus.*

5. **Scarlet fever**

a. **Definition.** Scarlet fever is a *toxin-mediated* bacterial illness that results in a characteristic skin rash.

b. **Etiology.** The infection is caused by strains of *GABHS* that produce an erythrogenic toxin.

c. **Epidemiology**

1. Peak incidence is in the winter and spring.
2. Transmission is by large respiratory droplets or by infected nasal secretions.

d. **Clinical features**

1. The exanthem may develop during any GABHS infection (e.g., impetigo, cellulitis, pharyngitis).
2. Before or during the exanthem, fever, chills, malaise, and often an exudative pharyngitis [see also section V.D] may occur.
3. The **exanthem is characterized by the following:**
   a. **Begins on the trunk** and moves peripherally
   b. The skin is **erythematous** *with tiny skin-colored papules* (scarlatiniform appearance) with the texture of sandpaper (**sandpaper rash**). The rash blanches with pressure.
   c. Petechiae are often localized within skin creases in a linear distribution ("**Pastia lines**").
   d. **Desquamation** of dry skin occurs as the infection resolves.

e. **Diagnosis.** The basis of diagnosis is clinical features and a positive throat culture for *S. pyogenes* (gold standard), or a positive rapid streptococcal tests that detect the GABHS antigen.

f. **Management**

1. The **goal is to prevent development of rheumatic fever**.
2. **Appropriate antibiotics** include oral penicillin VK or amoxicillin, intramuscular benzathine penicillin, or, for penicillin-allergic patients, erythromycin or macrolides.

g. **Complications of GABHS infections**

1. **Poststreptococcal glomerulonephritis** may occur several weeks after streptococcal pharyngitis. Patients present with hypertension and cola-colored urine. **Antibiotic therapy does not prevent this complication** (see Chapter 11, section V.F.1).
2. **Rheumatic fever** (see Chapter 16, section VI)

3. **Poststreptococcal arthritis** is characterized by joint symptoms (without other features of rheumatic fever) that may last for weeks. **Antibiotic therapy does not prevent this complication.**

6. **Toxic shock syndrome (TSS)**
   a. **Definition.** TSS is a **toxin-mediated** illness characterized by fever, shock, desquamating skin rash, and multiorgan dysfunction.
   b. **Etiology and pathogenesis**
      1. ***S. aureus*** is the most common organism associated with TSS, although an increase in **GABHS**-associated TSS has been reported. In the early 1980s, the majority of TSS cases caused by *S. aureus* were in young women using **tampons.** However, only 50% of TSS cases are now related to tampon use.
      2. Organisms produce toxins (exotoxins and TSS toxin) that result in the clinical features of TSS.
   c. **Clinical features and diagnostic criteria (Table 7-5).** Patients with TSS may present with a wide variety of signs and symptoms.
   d. **Management.** Treatment includes supportive measures to reverse shock, antistaphylococcal antibiotics, and removal of the nidus of infection (tampon) if present. Intravenous immune globulin (IVIG) may have some benefit.
7. **Infection caused by animal and human bites (see Chapter 20, sections IX.B–D)**

B. **Fungal infections of the skin** (Chapter 19, section V.A)
C. **Viral infections of the skin** (see Chapter 19, section V.C)
D. **Ectoparasitic infections of the skin** (see Chapter 19, section V.D)

TABLE 7-5
Diagnostic Criteria for Toxic Shock Syndrome Due to *Staphylococcus aureus*

Diagnostic criteria
(Probable case = five of six criteria; confirmed case = six of six criteria)
1. **Temperature >3**8.9°C
1. **Hypotension** (SBP <90 mm Hg or < 5th percentile for age for children)
1. Diffuse macular **erythroderma** (appears similar to sunburn)
1. **Desquamation**, particularly of the extremities including the palms, soles, fingers, and toes, occurs 10–14 days after onset of illness
1. **Multisystem involvement,** including three or more of the following: a. Gastrointestinal—vomiting, diarrhea, and abdominal pain at onset of illness b. Myalgias or elevated creatine kinase levels > twice the upper limit of normal c. Hyperemia of the mucous membranes (vaginal, oropharyngeal, or conjunctival hyperemia) d. Pyuria in the presence of negative urine cultures, or elevated blood urea nitrogen and creatinine to twice normal limit e. Thrombocytopenia—platelet count < 100,000 mm^3 f. Central nervous system—altered level of consciousness, without focal neurologic signs when fever and hypotension are absent.
1. **Negative cultures of blood, cerebrospinal fluid, and pharynx** (except for positive blood culture for *S. aureus*) and negative serologic tests for Rocky Mountain spotted fever (RMSF), leptospirosis, or measles.

Other clinical findings may include oral ulcers, acute respiratory distress syndrome, headache, edema, conjunctivitis, disseminated intravascular coagulation, elevated transaminases, hypocalcemia, and hypoalbuminemia.

SBP = systolic blood pressure.

X. Bone and Joint Infections (see Chapter 17, section III.B)

XI. Diarrhea

A. **Etiology. Diarrheal diseases and resulting dehydration are among the most common causes of childhood morbidity and mortality worldwide.** Specific infectious causes of diarrhea include the following:
   1. **Viral causes** most commonly include **rotavirus and norovirus**.
      a. **Rotavirus**
         1. **Epidemiology.** Worldwide, rotavirus is the **most common infectious agent causing gastroenteritis**. This RNA virus is usually seen in the **winter months** and is easily spread by the fecal–oral route. Incidence has significantly decreased following implementation of routine rotavirus vaccine for infants in the first 6 months of life.
         2. **Clinical features.** Incubation period is 1–3 days. Patients may be asymptomatic or may have **vomiting, diarrhea,** and **dehydration**. Diarrhea is usually self-limited and lasts 4–7 days. Symptoms of URI may sometimes be present.
         3. **Diagnosis.** A positive stool enzyme-linked immunosorbent assay (ELISA) test is used to make the diagnosis. WBCs and blood are typically absent from the stool.
         4. **Management.** Treatment is **supportive** with particular attention to fluid management and early institution of feedings to prevent gut atrophy. Some children may develop transient lactose intolerance.
      b. **Norovirus**
         1. **Epidemiology.** Norovirus is an RNA virus, which also is very efficiently spread by the fecal–oral route and through contact with infected fomites. **Outbreaks of gastroenteritis occur in all age groups, particularly in closed populations** (e.g., day care centers, schools, cruise ships).
         2. **Clinical features** are similar to those caused by rotavirus with **vomiting as a prominent symptom**. Duration of illness is only 48–72 hours, a **shorter duration** as compared with the other viral causes.
         3. **Diagnosis** is confirmed by enzyme immunoassays for stool antigen detection, as well as norovirus-specific PCR.
         4. **Management** is supportive with close attention to hydration status and electrolytes.
   2. **Bacterial causes,** associated clinical features, and management (see **Table 7-6**)
   3. **Parasitic causes** [see section XV]

B. **Evaluation** should include a detailed history, complete physical examination, and selective laboratory studies.
   1. **Specific historical features** include the following:
      a. Presence of fever, rash, abdominal pain, vomiting, and blood or mucus in the stool
      b. Recent antibiotic use (e.g., may result in *C. difficile* infection)
      c. **Day care attendance or travel**
      d. Pets (e.g., lizards and turtles as well as domesticated fowl may transmit *Salmonella* species)
      e. Unusual foods or recently consumed recalled foods (e.g., raw dairy product consumption has been associated with outbreaks of *Salmonella* and *E. coli*, and well-publicized outbreaks of gastroenteritis have been linked to some packaged fruits, vegetables, nuts, and prepared foods).
   2. **Physical examination** should be detailed and focused, especially on assessment of

hydration, particularly in young children.

3. **Laboratory studies** may include CBC, serum electrolytes, and assessment of stool for gross or occult blood (i.e., stool guaiac or immunoassay), WBCs (i.e., Wright stain), ova and parasite evaluation (three separate ova and parasite stool specimens increase the yield), and culture. Specific and rapid testing (ELISA or PCR) are useful in the detection of rotavirus, norovirus, *Giardia lamblia, Cryptosporidium,* and *C. difficile* infection. Bacterial multiplex PCR testing is now widely available to screen for bacterial diarrheal pathogens (Table 7-6).
    a. The **classic electrolyte finding** is a **non–anion gap hyperchloremic metabolic acidosis** as a result of bicarbonate loss in the stool.
    b. In general, the presence of either gross or occult blood in stools predicts the presence of stool WBCs.
    c. The **utility of a stool culture when WBCs are absent in the stool is low**.

C. **Management principles**

1. **Fluid management is the cornerstone of therapy.**
2. **Antibiotics** are indicated for only a few causes of infectious diarrhea (**Table 7-6**) and should be avoided in cases of bloody diarrhea when enterohemorrhagic *E. coli* is suspected as antibiotics may increase the risk of hemolytic uremic syndrome.

Table 7-6
Characteristics of Bacterial Causes of Infectious Diarrhea

Bacterium	Clinical Features	Diagnosis	Management
Enterotoxigenic *Escherichia coli*	**Major cause of traveler's diarrhea**Generally noninvasive with watery diarrhea	Stool WBCs and RBCs **absent**Diagnosis is made clinically but can be confirmed on culture	Antibiotics (fluoroquinolones or azithromycin in children) may shorten duration of symptoms
			Hydration is essential
Enteropathogenic *E. coli* (EPEC)	Noninvasive watery diarrhea seen in infants and preschoolers	Stool WBCs **absent**Diagnosis made on stool culture	Oral sulfonamides or fluoroquinolones are indicated
			Hydration is essential
Enterohemorrhagic *E. coli* (EHEC)	**Strain 0157:H7 is responsible for hemolytic uremic syndrome (HUS)** via endotoxin release	Stool WBCs **present**	**If suspected or confirmed, antibiotic therapy is avoided** (antibiotics may increase risk for or worsen the course of HUS as a result of enhanced endotoxin release)
		Diagnosis confirmed by culture and multiplex PCR	
		HUS: renal failure, thrombocytopenia, and microangiopathic hemolytic anemia	
Shigella sonnei	**Bloody diarrhea predominatesChildren may develop seizures** secondary to neurotoxin release	Stool WBCs **present**	Third-generation cephalosporins, macrolide (azithromycin), or fluoroquinolones are indicated
		Culture is diagnostic and important for organism susceptibilities	
		Multiplex PCRs available for multiple organism detection	
***Salmonella* species**	May cause **bloody or nonbloody diarrhea**	Stool WBCs may be **present or absent**	Treatment is not indicated for uncomplicated gastroenteritis in immunocompetent hosts >3 months of age because it may increase carriage time
	Spread by fecal–oral route, **poultry, milk, eggs, and exposure to reptiles**	Culture is usually diagnostic and important for organism susceptibilities	
	Patients, especially those with sickle cell disease, may develop bacteremia or osteomyelitis	Multiplex PCRs available for multiple organism detection	Treatment for invasive disease or in high risk host includes a third- generation cephalosporin
Campylobacter jejuni	**Most common cause of bacterial bloody diarrhea in the United States**	Stool WBCs are usually *present* if blood is presentStool culture is diagnostic as is multiplex	Oral macrolide (azithromycin and erythromycin) is indicated and leads to improved symptoms and decreased risk for relapse, but symptoms commonly resolve
	Disease is often self-		

	limited and is spread by contaminated food (usually poultry)	PCR	without antimicrobial intervention
Yersinia enterocolitica	May cause **mesenteric adenitis** along with gastroenteritis **that may mimic acute appendicitis**	Stool culture or mesenteric node culture grows the organism	Antibiotics may benefit patients; third-generation cephalosporins are commonly used
Clostridium difficile	A normal component of gut flora that may cause colitis if it overgrows the rest of the gut flora, as is seen **after antibiotic use**	Diagnosis is made by identifying toxin in the stool	Oral or intravenous metronidazole is effective
		Endoscopy may demonstrate **pseudomembranes**	Oral vancomycin is reserved for resistant cases
Vibrio cholerae	Seen in developing countriesCharacterized by watery diarrhea with **massive water loss**	Diagnosis is based on history of massive watery diarrhea in a patient returning from, or residing in, an endemic area	**Fluid replacement is critical**Antibiotics (macrolides, fluoroquinolones, and tetracyclines) are recommended in conjunction with fluid replacement to shorten the duration of diarrhea and reduce viral shedding.
		V. cholerae may be cultured from stool, but this is not routinely performed in the United States	
		Detection of cholera toxin gene by EIA and serologic testing is available at the Centers for Disease Control and Prevention.	

WBCs = white blood cells; *EIA* = enzyme-linked immunoassay; *PCR* = polymerase chain reaction; *RBCs* = red blood cells.

XII. Urinary Tract Infections (see Chapter 11, section XIV)

XIII. Specific Viral Infections

A. **HIV (Human Immunodeficiency Virus)**

1. **Epidemiology.** The number of children less than 13 years of age infected with HIV significantly declined with the introduction of interventions to prevent mother-to-infant transmission. Half of all new HIV infections in the United States occur in people less than 25 years of age; thousands of teens acquire new HIV infections each year. Worldwide, over 3 million children are living with HIV, the majority of whom were infected perinatally or through breastfeeding. The highest incidence of pediatric HIV is in sub-Saharan Africa.
2. **Transmission**
    a. Perinatal transmission in the United States and other developed countries has decreased dramatically due to interventions that prevent mother-to-child transmission.
        1. **In utero, intrapartum, or postpartum** (through breastfeeding) **transmission** of HIV from an infected mother to her infant may occur. Transmission rates range from <2% in the United States, because of the common use of antiretroviral therapy during pregnancy, to 50% in the developing world where access to antiretroviral therapy may be limited.
        2. Factors that **increase the risk of transmission**:
            a. High maternal viral load (as measured by number of RNA copies)
            b. Advanced maternal HIV disease
            c. Primary maternal HIV infection
            d. Concomitant maternal genital infections, including chorioamnionitis
            e. Premature birth
            f. Prolonged rupture of membranes
        3. Factors that **decrease the risk of transmission**:
            a. Undetectable maternal viral load
            b. Cesarean section
            c. Adherence to maternal highly active antiretroviral therapy (HAART) and infant postexposure prophylaxis with antiretroviral therapy (zidovudine)
    b. Other modes of HIV transmission are as follows:
        1. **Sexual contact,** an important mode of infection in adolescents and young adults
        2. **Blood product** transmission, which is now exceptionally rare owing to very sensitive mandatory blood product screening
        3. **Sharing intravenous and tattoo needles**
3. **Clinical features**
    a. Most infants with perinatally-acquired HIV infection are **asymptomatic** for the first year of life.
    b. The following are the **early symptoms of HIV infection in children:**
        1. **Failure to thrive**
        2. **Thrombocytopenia**
        3. **Recurrent infections,** such as otitis media, pneumonia, and sinusitis
        4. **Lymphadenopathy**
        5. **Parotitis**
        6. **Recurrent, difficult-to-treat thrush**
        7. **Loss of developmental milestones**
        8. **Severe varicella infection or zoster**

4. **Diagnosis**
    a. **All infants born to HIV-infected mothers will have transplacentally acquired maternal antibody that may persist for as long as 18–24 months.**
    b. **HIV-specific DNA PCR** is performed at birth, 2 weeks, and between 2 and 4 months of age to detect infants who are infected perinatally.
    c. **Negative HIV-specific DNA PCR at 4 months is consistent with an infant who has not been infected.** If the DNA PCR is negative for HIV, infants are followed for the next year and tested for HIV by EIA after they have lost transplacentally acquired maternal antibody (by age 18–24 months).
5. **Management**
    a. Infants born to HIV-infected mothers should be tested for the presence of virus, as outlined earlier in section XIII.A.4, in addition to the following:
        1. **Zidovudine** administered orally for 6 weeks for postexposure prophylaxis.
        2. **Trimethoprim/sulfamethoxazole** (TMP/SMX) for *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis is started at 6 weeks of age until HIV DNA PCR at age 4 months is negative.
        3. **No breastfeeding** if safe water supply is available (developed countries)
        4. **Urine CMV culture** to detect coinfection with CMV (occurs in 5%)
        5. **CBC with differential** to monitor for zidovudine toxicity (bone marrow suppression)
    b. **HIV-infected children** should be managed at an institution experienced in the care of children with HIV. Management includes administration of medications, nutritional counseling, social work services, and regular neurodevelopmental testing.
        1. All HIV-infected children should receive **antiretroviral agents** that may include nucleoside reverse transcriptase inhibitors (NRTIs), non–nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors, as well as newer agents that include integrase strand transfer inhibitors and CCR5 (chemokine receptor 5) antagonists. **Combination therapy is the cornerstone of treatment to avoid selection of resistant viruses.** Close monitoring is essential because medications may cause bone marrow suppression, hepatitis, and pancreatitis.
        2. **Prophylaxis for opportunistic infections is important.** The decision to begin prophylaxis is based on the patient's age, CD4 count, and history of prior opportunistic infections.
        3. **Immunizations** and usual **well-child care are critical**. HIV-infected children should receive all routine childhood vaccines except the live varicella vaccine. The measles, mumps, and rubella (MMR) vaccine, although a live viral vaccine, is currently recommended for all but the most severely immunocompromised HIV-infected children. Annual influenza vaccine, pneumococcal vaccine (both conjugate, PCV-13, and polysaccharide, PPSV-23), as well as annual testing for tuberculosis are all recommended. All family members should receive influenza immunization to protect immunocompromised household members.
        4. Regular monitoring of T-cell subsets and HIV RNA PCR to assess viral load are used to monitor response to therapy, typically every 3 months.
        5. Ophthalmologic examination to assess for CMV retinitis in HIV-infected children who are CMV antibody positive should occur annually.
6. **Complications of HIV infection**
    a. **Opportunistic infections**

1. **PCP**
    a. **Epidemiology**
        1. *Most common opportunistic infection in HIV-infected children*
        2. Risk of infection correlates with CD4 cell number and percentage: for children <5 years of age, a CD4 count <500 cells/μL or percentage <15% and for children ≥5 years of age, a CD4 count <200 cells/μL or percentage <15%.
    b. **Clinical features.** Fever, hypoxia, and interstitial pulmonary infiltrates are present.
    c. **Management.** Prophylaxis against PCP infection is with oral **TMP/SMX** and is based on the patient's age and CD4 cell count and percentage. Treatment of PCP infection may include TMP/SMX, dapsone, pentamidine, or atovaquone. Moderate to severe infections are also treated with systemic corticosteroids.
2. ***M. avium* complex (MAC).** MAC is characterized by fever, weight loss, night sweats, abdominal pain, bone marrow suppression, and elevated transaminases. Risk is highest when the CD4 count falls less than 50 cells/mm^3.
3. **Fungal infections.** Candidal infections (e.g., thrush, esophagitis), cryptococcal infections (e.g., meningitis, pneumonia), histoplasmosis, coccidioidomycosis, and aspergillosis may occur.
4. **Viral infections.** CMV (e.g., retinitis, esophagitis, colitis), HSV, and VZV infections may occur.
5. **Parasitic infections.** Toxoplasmosis and infections caused by *Cryptosporidium* and *Isospora belli* may occur.

b. **Lymphoma,** caused by primary or reactivation of EBV infection

7. **Prognosis.** The expanded testing of pregnant women for HIV, coupled with aggressive prenatal antiretroviral therapy, has dramatically reduced and almost eliminated perinatal HIV transmission in the United States. Morbidity and mortality of HIV-infected children have also declined, correlating with the licensure of highly active antiretroviral agents and more sensitive testing for better evaluation of response to therapy.

B. **Infectious mononucleosis**

1. **Etiology and epidemiology**
    a. **EBV,** a member of the herpes virus family, is the **major etiologic agent.** EBV is commonly acquired during adolescence, although infection also occurs often in young children. EBV is **transmitted primarily by saliva** and infects the B lymphocytes.
    b. Other agents, including **toxoplasmosis, CMV, and HIV,** may cause a similar clinical syndrome.
2. **Clinical features**
    a. **Young children may be asymptomatic.**
    b. Older children develop **typical signs and symptoms**.
        1. **Fever,** which may last up to 3 weeks
        2. **Malaise and fatigue**
        3. **Tonsillopharyngitis** (typically exudative, **resembling GABHS pharyngitis**)
        4. **Cervical lymphadenopathy** (lymphadenopathy may also be diffuse)
        5. **Hepatosplenomegaly.** The spleen is enlarged in 80% of patients.
        6. A minority of patients may also develop a **macular rash**.
        7. **Symptoms self-resolve in weeks to months.**
3. **Diagnosis**
    a. **CBC** may demonstrate **atypical lymphocytes**. Other laboratory abnormalities

include neutropenia, thrombocytopenia, and elevated transaminases.

b. **Monospot** is a **first-line test in diagnosing EBV infectious mononucleosis**. A monospot measures the presence of heterophile antibody, which has the ability to agglutinate sheep RBCs. It has an overall sensitivity of 85% but is **less sensitive in children under 4 years of age** because these antibodies do not reliably form in younger children. CMV causes most monospot-negative cases of infectious mononucleosis in older children.

c. **EBV antibody titers are the preferred method of diagnosing EBV infection in children younger than 4 years of age.**
    1. To diagnose EBV, antibodies to **viral capsid antigen (VCA), early antigen (EA), and Epstein–Barr nuclear antigen (EBNA)** are tested.
    2. Acute infection is diagnosed by finding **elevated levels of IgM–VCA** and absent antibodies to EBNA. Antibodies to EBNA are detected 2–3 months after acute infection. If EBNA is positive at the time of evaluation, the symptoms are not due to EBV (a way to remember this is EBNA = Epstein–Barr Not Active).

d. **PCR** testing is the test of choice for evaluating immunocompromised patients suspected of having complications of EBV primary disease or reactivation, but should not be used in healthy children to make an acute EBV diagnosis.

4. **Management.** Therapy for most cases of EBV infection is supportive. Corticosteroids are sometimes used for severe tonsillopharyngitis causing airway compromise. Antivirals are not used to treat EBV in immunocompetent patients, as they are not active against the latent form of the virus.
5. **Complications**
    a. **Neurologic complications,** including cranial nerve palsies and encephalitis
    b. Severe tonsillopharyngitis, which may cause **upper airway obstruction**
    c. **Ampicillin-associated rash.** Patients with EBV infection who are misdiagnosed with GABHS pharyngitis and prescribed ampicillin (or amoxicillin or other beta-lactam antibiotics) often develop a **diffuse pruritic maculopapular rash** one week after starting the antibiotic. This is not an allergic reaction but is idiosyncratic.
    d. **Splenic rupture.** Children with infectious mononucleosis with splenomegaly should be restricted from contact sports until the spleen has returned to normal size, typically after 3–4 weeks.
    e. **Hemophagocytic lymphocytosis** or hemophagocytosis, a condition in which bone marrow cells are consumed by activate macrophages, can result following primary infection with EBV. Clinical features of this serious condition include fever with multiple organ involvement. Hallmark laboratory findings include extremely elevated ferritin, transaminitis, and coagulopathy.
    f. **Malignancy.** EBV has been isolated from nasopharyngeal carcinoma and Burkitt lymphoma. Patients who have received organ transplants are at risk for EBV-associated posttransplant lymphoproliferative diseases.

C. **Measles**

1. **Etiology.** Measles is also known as rubeola or "10-day measles" (in contrast to rubella or "3-day measles") and is caused by an RNA virus of the **Paramyxoviridae family**.
2. **Epidemiology**
    a. Routine measles vaccination has significantly decreased and almost eliminated the incidence of measles in the United States over the past 50 years. Before the vaccination program, there were millions of cases of measles annually. Widespread immunization has led to eradication in the United States. Approximately 50–100 cases per year in the United States are due to importations from measles endemic

countries leading to outbreaks among unimmunized individuals.
   b. Measles is **highly infectious** and spreads easily among susceptible individuals in households and schools.
3. **Clinical features.** Manifestations develop after an **8- to 12-day incubation period**. Clinical features include a classic clinical prodrome, followed by a transient enanthem (rash on mucous membranes) and then a characteristic exanthem (rash on the skin).
   a. The **three Cs (cough, conjunctivitis, and coryza)** is a mnemonic to help remember the **classic prodrome**. Other early symptoms include photophobia and low-grade fever.
   b. The **enanthem** (**Koplik spots)** is characterized as small gray papules on an erythematous base, located on the buccal mucosa. **Koplik spots are pathognomonic of measles and are present before the generalized exanthem.** They are transient and may be absent by the time the other typical clinical features develop.
   c. The **exanthem** is characterized as an erythematous macular eruption that **begins around the neck and ears and spreads down the chest and upper extremities during the subsequent 24 hours**. The exanthem covers the lower extremities by the second day, becomes confluent by the third day, and lasts for 4–7 days.
   d. **Temperature** usually >101°F (>38.3°C) accompanies the onset of symptoms.
4. **Complications**
   a. **Pneumonia is the most common complication and the most common cause of mortality.**
   b. **Otitis media** is also common.
   c. **Laryngitis and laryngotracheobronchitis (croup)**
   d. **Encephalomyelitis** (i.e., inflammation of both the brain and spinal cord)
   e. **Subacute sclerosing panencephalitis** is a rare **late** complication of measles infection that occurs years after the primary infection. Children infected in the first two years of life are at greatest risk for developing this debilitating and often fatal disease.
5. **Diagnosis.** The basis of diagnosis is clinical features and confirmation of measles infection by PCR testing of samples from the urine, throat, or nasopharynx, or by detection of measles-specific IgM.
6. **Management**
   a. Supportive care is most important.
   b. **Vitamin A** has been shown to improve outcomes of children in developing countries, and it is recommended that all hospitalized infants and children with measles be treated with vitamin A.
   c. Immunoglobulin can be used for postexposure prophylaxis in high-risk individuals (e.g., children with HIV and other immunodeficiency states, or infants under 12 months of age) who are exposed to measles.

D. **Rubella**
1. **Etiology.** Rubella, which is also known as German measles or "3-day measles," is caused by an RNA virus in the **togavirus family**.
2. **Epidemiology.** Like measles, the incidence of rubella has declined during the past 50 years as a result of routine immunization during childhood and is no longer circulating in the United States. Rubella is also **highly infectious**.
3. **Clinical features.** Unlike measles, rubella is a mild disease and is often **asymptomatic**. Incubation period is 14–21 days.
   a. The **prodrome** includes mild upper respiratory symptoms and low-grade fever.
   b. **Painful lymphadenopathy,** especially of the suboccipital, posterior auricular, and cervical nodes

c. The **exanthem** follows the adenopathy and is characteristically **nonpruritic, maculopapular, and confluent**. It begins on the face, spreads to the trunk and extremities, and lasts 3–4 days.
d. The **fever is usually mild** (<101°F or <38.3°C) and accompanies the other clinical symptoms.

4. **Complications**
   a. **Meningoencephalitis**
   b. **Polyarthropathy,** involving mostly the fingers, knees and wrists, is seen primarily in teenage girls and young women, and may last several weeks.
   c. **Congenital rubella syndrome (CRS)** is the **most serious complication of an otherwise relatively benign disease**. Owing to vaccination, CRS has been successfully eliminated from the Americas.
      1. **CRS occurs after primary maternal infection during the first trimester. Fetal anomalies occur in 30–50% of infected fetuses.**
      2. **Presenting clinical features** include thrombocytopenia, hepatosplenomegaly, jaundice, and purpura ("**blueberry muffin baby**").
      3. **Structural abnormalities** include **congenital cataracts** and **a patent ductus arteriosus**. Other findings include **sensorineural hearing loss** and meningoencephalitis.
      4. **Late complications** may include mental retardation, hypertension, type 1 diabetes mellitus, and autoimmune thyroid disease.
5. **Diagnosis** is by viral culture or PCR or by serology. Because of transplacental passage of IgG antibody, diagnosis of an infant with CRS is made by viral isolation or by PCR.
6. **Management** is supportive.

E. **Hepatitis** (see Chapter 10, section XI.F)
F. **Varicella** (see Chapter 19, section V.C.6)

XIV. Specific Fungal Infections

A. **Aspergillosis.** ***Aspergillus*** **species are ubiquitous molds that cause both invasive disease and noninvasive allergic disease.**
   1. **Invasive disease** occurs in severely immunocompromised patients, such as recipients of bone marrow or solid organ transplant. Management includes high-dose systemic antifungal therapy with amphotericin B and often surgery to resect the aspergilloma, a tumor-like mass formed by the fungus. Prognosis is poor.
   2. **Allergic bronchopulmonary aspergillosis** is characterized by **wheezing, eosinophilia, and pulmonary infiltrates.** It occurs most commonly in patients with chronic lung disease (e.g., cystic fibrosis). Patients have elevated aspergillus-specific immunoglobulin E levels, and management includes corticosteroids and, in some cases, antifungal therapy.

B. **Candidiasis**
   1. **Epidemiology and etiology.** *Candida* species, especially *C. albicans*, are present on the skin and throughout the gastrointestinal tract.
      a. In immunocompetent individuals, overgrowth of yeast may occur normally, or under the influence of systemic antibiotics, causing mild superficial infection.
      b. In immunocompromised individuals, overgrowth of yeast may occur readily, causing severe invasive infection.
   2. **Clinical features and management**
      a. Overgrowth of *Candida* on the skin or mucous membranes may lead to diaper dermatitis, **oral thrush,** or vulvovaginal candidiasis. Treatment includes topical antifungal therapy.
      b. Invasive candidal infections in immunocompromised patients may include fungemia, meningitis (see Table 7-3 for CSF profile), osteomyelitis, and endophthalmitis. Treatment includes systemic antifungal therapy.

C. **Coccidioidomycosis**
   1. **Etiology.** *C. immitis* is a fungus found in the soil in the southwestern United States and in Mexico.
   2. **Clinical features**
      a. Infection occurs when *Coccidioides* is inhaled into the lungs.
      b. Most infections are **asymptomatic** or cause a **mild pneumonia**.
      c. African Americans, Filipinos, pregnant women, neonates, and immunocompromised individuals are at highest risk for **disseminated disease,** which may include severe pneumonia, meningitis, and osteomyelitis.
   3. **Management.** Mild pulmonary disease in immunocompetent patients generally does not require treatment. Disseminated disease and illness in immunocompromised hosts are treated with systemic antifungal therapy.

D. **Cryptococcal infection**
   1. **Etiology.** *Cryptococcus neoformans* is a yeast found in the soil.
   2. **Clinical features**
      a. Infection is acquired when *Cryptococcus* is inhaled into the lungs.
      b. **Most infections are asymptomatic.**
      c. Spread to the central nervous system (CNS) occurs primarily in immunocompromised patients. Cryptococcal meningitis is one of the AIDS-defining illnesses.
      d. Disseminated infection, including infection of the bones, joints, and skin, may also occur in immunocompromised hosts but is rare in children.

3. **Management.** Treatment of disseminated and CNS cryptococcal infection includes systemic antifungal therapy.

XV. Specific Parasitic Infections

A. **Amebiasis**
   1. **Etiology.** Infection is by the protozoan ***Entamoeba histolytica***. Infection is acquired by **ingestion of the cyst in contaminated food or water**. Symptoms begin 1–4 weeks later as the trophozoite form emerges from the cyst and invades the colonic mucosa.
   2. **Epidemiology.** Amebiasis is present worldwide with the highest incidence in developing nations.
   3. **Clinical features**
      a. **Most patients are asymptomatic.**
      b. **Symptomatic intestinal disease** ranges from **mild colitis to severe dysentery**. Young children, pregnant women, and immunocompromised patients have more severe disease.
         1. **Symptoms** include **cramping abdominal pain, tenesmus, and diarrhea** that may contain blood or mucus. Weight loss, fever, tender hepatomegaly, chest pain, right shoulder pain, respiratory distress, and jaundice may also occur.
         2. **Abdominal complications** include intestinal perforation, hemorrhage, strictures, and a local inflammatory mass or **ameboma**.
      c. **Extraintestinal amebiasis** manifests as an **abscess,** most commonly in the liver, although it may form in the brain, lung, or other organs.
   4. **Diagnosis.** Identification of the trophozoites or cysts in the stool is diagnostic. Colonoscopy with biopsy or **serum antibody assays** may also be helpful. Ultrasound or CT scan can identify an abscess in the liver or other organs.
   5. **Management.** Treatment is based on the site of involvement and includes elimination of both the invading organism and those within the intestinal lumen. **Metronidazole** is the **mainstay of therapy** and is recommended along with a luminal amebicide, such as iodoquinol.

B. **Giardiasis**
   1. **Etiology.** Infection is by the protozoan ***G. intestinalis***. Infection occurs by fecal–oral contamination when the cyst is accidentally ingested.
   2. **Epidemiology.** Giardiasis occurs worldwide, and it is the **most common intestinal parasitic infection of humans**. Individuals who **drink contaminated mountain water in the western United States are at higher risk,** but giardiasis is an endemic disease and can occur as large waterborne or **day care center** outbreaks. Humans are the primary reservoirs, and transmission is commonly person-to-person, but can also be from animals, such as dogs and cats.
   3. **Clinical features.** Signs and symptoms are variable and range from asymptomatic disease to explosive diarrhea. Symptoms occur 1–2 weeks after ingestion of the cyst and may persist for 2–6 weeks.
      a. Infection **localizes within the small bowel,** causing **diarrhea** that is typically described as **voluminous, watery, and foul smelling**.
      b. Abdominal pain, cramping, **bloating, flatulence,** weight loss, and low-grade fever may also occur.
   4. **Diagnosis. Direct examination** of stool for **cysts and trophozoites** or **stool ELISA tests** are used to make the diagnosis. Small bowel biopsy is sometimes indicated in difficult-to-diagnose cases.
   5. **Management.** Treatment includes **metronidazole**, tinidazole, or nitazoxanide.

C. **Malaria**
   1. **Etiology.** Malaria is an obligate intracellular blood-borne parasitic infection caused by

four species of ***Plasmodium*: *Plasmodium falciparum*** (responsible for the most severe disease), *Plasmodium vivax, Plasmodium malariae,* and *Plasmodium ovale*.

2. **Epidemiology**
    a. **Malaria is the most important parasitic cause of morbidity and mortality in the world,** responsible for 2–3 million deaths each year, mostly in young children.
    b. Malaria is endemic in tropical and subtropical regions of the world. The risk of malaria is high for travelers to these endemic areas.
    c. **Transmission** of *Plasmodium* occurs via the bite of the infected female ***Anopheles* mosquito,** a night-biting mosquito.
3. **Clinical features**
    a. **Initial findings** include vague flulike symptoms that typically include headache, malaise, anorexia, and fever.
    b. **Cyclical fevers** follow the flulike prodrome and occur every 48–72 hours, which **correlate with RBC rupture and subsequent parasitemia**. Chills, vomiting, headache, and abdominal pain may also occur.
    c. **Other features** include **hemolytic anemia,** splenomegaly, jaundice, and hypoglycemia. Cerebral malaria, renal failure, shock, and respiratory failure may all occur.
4. **Diagnosis.** Identification of the parasite on **thin and thick Giemsa-stained peripheral blood smears** is diagnostic. The thick smear is for malarial screening, and the thin smear is for malarial identification and staging (determination of the level of parasitemia) of the particular *Plasmodium* species. Rapid diagnostic testing is becoming increasingly more available, and is particularly important in resource poor areas. Molecular (PCR) tests are also available in reference laboratories. The U.S. Centers for Disease Control and Prevention has consultants available who can assist with diagnosis of patients with suspected malaria.
5. **Management.** Choice of antimalarial therapy is based on resistance patterns, species type, and severity of illness. Medications include chloroquine, atovaquone-proguanil, quinine, quinidine gluconate, mefloquine, doxycycline, and clindamycin used in combination with quinine.
6. **Prevention**
    a. **Avoidance of mosquito bites is the mainstay of prevention.** DEET (*N,N*-diethyl-*m*-toluamide)-containing repellants, insecticide-impregnated bed nets, and protective clothing are essential.
    b. **Chemoprophylaxis,** which may include oral chloroquine, mefloquine, doxycycline, or atovaquone and proguanil hydrochloride (depending on the area visited and its *Plasmodium* species and resistance patterns).
    c. **Control of the *Anopheles* mosquito** is important for individuals living in endemic areas.

D. **Toxoplasmosis**

1. **Etiology.** Infection is by the intracellular parasite ***T. gondii***.
2. **Epidemiology. Transmission** occurs through **direct contact with cat feces** (the cat is the definitive host for the parasite); ingestion of undercooked meat, fruits, or vegetables contaminated with cysts; transplacental passage; exposure to contaminated blood products; or organ transplantation.
3. **Clinical features**
    a. **Most patients are asymptomatic.**
    b. **Symptoms,** if present, include a **mononucleosis-like illness** consisting of malaise, fever, sore throat, myalgias, and lymphadenopathy. Rash and hepatosplenomegaly may be present. Symptoms are self-limited and generally benign.

c. **Reactivation of disease may occur if patients become immunosuppressed.** In this case the presentation is often more severe and may include encephalitis, focal brain lesions, pneumonitis, or, rarely, disseminated disease. Toxoplasmosis is an important opportunistic infection in HIV-infected patients who **commonly present with focal seizures**.
d. **Ocular toxoplasmosis** may occur. ***T. gondii* is the most common cause of infectious chorioretinitis**.
e. **Congenital toxoplasmosis** is characterized by the **triad of hydrocephalus, intracranial calcifications, and chorioretinitis**.

4. **Diagnosis.** Serologic testing, PCR, or identification of the organism in cultures of amniotic fluid, CSF, or blood are used for diagnosis.
5. **Management.** Most infections do not require specific therapy. Treatment is indicated for infants with congenital toxoplasmosis, pregnant women with acute toxoplasmosis, and immunocompromised individuals with reactivation resulting in toxoplasma encephalitis. Treatment includes the use of sulfadiazine and pyrimethamine.
6. **Prevention. Pregnant women and immunocompromised individuals are at highest risk.** Therefore, they should avoid cat feces and undercooked meats and should clean all fruits and vegetables before consumption. Gloves should be used when gardening or preparing meat.

XVI. Specific Helminth Infections

A. **General concepts (characteristics of specific infections are noted in Table 7-7)**
   1. **Groups at highest risk** include immigrants, travelers, and homeless individuals.
   2. **Common clinical features**
      a. **Most infections are asymptomatic.**
      b. **Abdominal symptoms** include pain, anorexia, nausea, rectal prolapse, and obstruction.
   3. **Diagnosis** is usually made by **three separate stool examinations for ova and parasites**. To detect **pinworms,** a **cellulose tape test** may be performed; the tape is placed sticky side down on the perianal region before sleep and is removed immediately on awakening, and then examined for eggs.

B. **Cysticercosis**
   1. **Epidemiology**
      a. **Worldwide distribution** with high incidence in **Mexico** and Central America
      b. In endemic areas, **20–50% of cases of epilepsy are caused by cysticercosis**.
   2. **Etiology.** Infection occurs via the **fecal–oral route** when the eggs of ***Taenia solium*,** the pork tapeworm, are accidentally ingested.
   3. **Clinical features**
      a. No symptoms are present until the tapeworm **encysts in the muscle, subcutaneous tissue, or brain**.
      b. **Subcutaneous nodules** may be palpated or seen as calcifications on radiography.
      c. **Neurocysticercosis**
         1. The **fourth ventricle** is the **most common site of involvement,** although the brain parenchyma, meninges, spine, or eyes may be affected.
         2. **Signs and symptoms** include **seizures (presenting symptom in 70% of cases),** hydrocephalus, and stroke.
   4. **Diagnosis**
      a. **Ova and parasite stool evaluation** detects the *Taenia* eggs in only 25% of cases.
      b. Serology is available in some laboratories.
      c. **Head CT or MRI scans** may show a solitary parenchymal cyst, or single or multiple calcifications. Calcified lesions represent areas of old, nonviable parasitic infection.
   5. **Management.** Antiparasitic medications are reserved for individuals infected with the adult tapeworm. Those with neurocysticercosis with brain imaging that shows only calcified lesions require only anticonvulsant therapy.

Table 7-7
Characteristics of Specific Helminth Infections

Infection	Epidemiology	Clinical Features	Management
Enterobius vermicularis (pinworm)	**Common helminthic infection in the United States**	**Anal or, less commonly, vulvar pruritus**Insomnia, anorexia, enuresis, nighttime teeth-grinding	Single dose of pyrantel pamoate or albendazole; repeat in 2 weeksTreat all close contacts
	Fecal–oral transmission of eggs		
	Preschool and school-age children		
Ascaris lumbricoides (roundworms)	Largest and most common intestinal roundwormFecal–oral transmission of eggs	*Löffler syndrome*—transient pneumonitis as larvae migrate through the lungs causing fever, cough, wheezing, and eosinophilia	Single dose of albendazole or ivermectin, or 3-day treatment with mebendazole or nitazoxanide
		Small bowel obstruction	Screen all close contacts
Trichuris trichiura (whipworm)	Worldwide distributionOften seen in association with ***Ascaris***	Most are asymptomaticAbdominal pain, tenesmus, bloody diarrhea, and	Ivermectin or mebendazole for 3 days

	infection	rectal prolapse	Screen all close contacts
Necator americanus and ***Ancylostoma duodenale*** (hookworm)	Rural, tropical, and subtropical areas where soil is contaminated with human feces	**Rash and pruritus at site of penetration**	Albendazole, mebendazole, or pyrantel pamoate
			Iron supplementation
	Percutaneous infection through a bare foot; larvae migrate to the lungs and are coughed up and then swallowed	**Iron-deficiency anemia** with fatigue, pallor, and failure to thrive	Screen close contacts
Strongyloides stercoralis	Tropics, subtropics, and southern and southwestern United States	**Transient pruritic papules** at site of penetration	Ivermectin is the drug of choice; albendazole is associated with lower cure rates
		Pneumonitis	
	Life cycle same as hookworm	**Gastrointestinal symptoms**	
		Eosinophilia	
Cutaneous larva migrans	Intradermal migration of dog or cat hookworms	**Migrating, pruritic, serpiginous, erythematous tracks on the skin**	Resolves without treatment in most cases
	Contact with feces-contaminated soil	Self-limited, lasting weeks to months	Ivermectin or albendazole for severe disease
Toxocara canis **or** ***cati*** **(toxocariasis or visceral larva migrans; VLM)**	Most common in children 1–4 years of age who have pica	**Generalized VLM:** fever, eosinophilia, leukocytosis, and hepatomegaly; may have malaise, anemia, cough, or myocarditis	Albendazole
	Ingestion of eggs in contaminated soil or dog fur		
	Larvae released from eggs and migrate through tissues	**Ocular larva migrans:** retinal granulomas or endophthalmitis	Steroids may also be used for severe cases of myocarditis or CNS or ocular involvement

CNS = central nervous system.

XVII. Miscellaneous Infections

A. **Rickettsial infections**
   1. **Lyme disease** (see Chapter 16, section VII)
   2. **Rocky Mountain Spotted Fever (RMSF)**
      a. **Etiology.** RMSF is caused by ***Rickettsia rickettsii,*** a Gram-negative intracellular coccobacillus that is transmitted by the bite of a tick.
      b. **Epidemiology**
         1. RMSF is endemic across the United States, but occurs primarily in the **southeastern regions of the United States**.
         2. Incidence is highest in school-age children, and infection usually occurs in the spring and summer.
         3. Fewer than 50% of patients recall a tick bite.
      c. **Clinical features.** Symptoms and signs range from mild to life-threatening, and may include:
         1. **Fever**
         2. **Petechial rash** that **begins on the extremities** (ankles and feet) and moves in a caudal and centripetal direction (i.e., wrists and hands first, and then to trunk and head)
         3. **Myalgias**
         4. **Hepatosplenomegaly and jaundice**
         5. **CNS symptoms,** such as **headache,** coma, and seizures
         6. **Hypotension**
      d. **Laboratory findings. Thrombocytopenia,** elevated transaminases, and **hyponatremia** may occur. CSF findings may show an aseptic meningitis picture (see Table 7-3).
      e. **Diagnosis.** The diagnosis is made clinically but should be confirmed with serologic tests for *Rickettsia.*
      f. **Management.** Treatment includes oral or intravenous doxycycline and supportive care. Antibiotics are usually started empirically on the basis of clinical presentation before the results of diagnostic testing, given the risk of significant morbidity and mortality in untreated infection. Although doxycycline is not used in children <8 years of age, given the life-threatening complications of this infection, doxycycline is administered to all children when RMSF is suspected.
      g. **Prevention.** Prevention methods include tick avoidance and prompt tick removal. Prophylactic antibiotics after tick bites are not indicated.
   3. ***Ehrlichia* and *anaplasma***
      a. **Etiology.** Human monocytic ehrlichiosis (HME) is caused by multiple organisms (***Ehrlichia chaffeensis*** is the most prevalent) and is transmitted by the bites of several tick species. Human granulocytic anaplasmosis (HGA), also transmitted by tick bite, is caused by *Anaplasma phagocytophilum.*
      b. **Epidemiology.** Most cases occur in the spring and summer, and the epidemiology follows the location of the transmitting tick. HME is found in the Southern and Southeastern United States, and HGA is primarily seen in the Northeast and the Midwest.
      c. **Clinical features.** Ehrlichiosis and anaplasmosis are often referred to as **"spotless RMSF"** because they have many of the same presenting findings as RMSF but usually no rash. Signs and symptoms include fever, headache, myalgias, and lymphadenopathy.

d. **Laboratory findings.** These are similar to those seen in RMSF and other rickettsial diseases [see section XVII.A.2.d].
e. **Diagnosis.** The diagnosis is confirmed by serology as well as specific PCR.
f. **Management.** Treatment includes the use of doxycycline and supportive care.

B. **Cat scratch disease**
1. **Etiology.** Cat scratch disease is caused by the Gram-negative bacteria ***B. henselae***.
2. **Clinical features**
a. **Regional lymphadenopathy** (especially in the axillary, cervical, or inguinal region), **typically distal to the site of a cat scratch, or more commonly a kitten scratch,** is the **most common presentation**. Kittens with fleas are thought to be at highest risk for transmission of this species of bacteria.
b. The initial scratch results in a papule along the line of the scratch, followed by lymphadenopathy 1–2 weeks later.
c. The involved lymph node is commonly erythematous, warm, and tender. Suppuration occurs in approximately 10%.
d. **Fever** may occur in one-third of patients.
e. **Less common findings** include **Parinaud oculoglandular syndrome** (conjunctivitis and preauricular lymphadenitis associated with *B. henselae infection*), encephalitis, osteomyelitis, hepatitis, and pneumonia.
f. Patients with **FUO** with hepatosplenic lesions should be evaluated for cat scratch disease.
3. **Diagnosis.** Histopathologic examination of tissue will demonstrate granulomas with microabscesses. *Bartonella* can be cultured from tissue as well, but most cases are diagnosed with *Bartonella*-specific antibodies and/or PCR, which is much more sensitive than serology.
4. **Management.** Treatment usually consists of **supportive care** as the lymphadenitis self-resolves**.** Antibiotics are generally reserved for patients with systemic disease or immunodeficiency. Antibiotics used include oral azithromycin, TMP/SMX, and ciprofloxacin.

C. **Tuberculosis (TB)**
1. **Etiology.** The cause of TB is ***M. tuberculosis***.
2. **Categories**
a. **Exposed person** is the term used to describe an individual who has been in **recent contact** with an individual with **contagious pulmonary TB**. Physical examination, tuberculin skin test or interferon gamma release assay (IGRA), and chest radiograph are all normal.
b. **Latent tuberculosis infection (LTBI)** is the term used to describe an asymptomatic individual with a positive tuberculin skin test or IGRA, normal physical examination, and a chest radiograph that either is negative or shows healed infection.
c. **Tuberculosis disease** is the term used to describe an individual with **signs and symptoms of TB** with or without positive findings on chest radiograph [see section XVII.C.5]. Disease may be pulmonary or extrapulmonary, or both.
3. **Epidemiology**
a. TB is most common among urban, low-income, and nonwhite racial and ethnic groups, although it may be seen in children of any socioeconomic status.
b. Those at **highest risk** include **immigrants** from highly endemic regions of the world, health care personnel, **homeless** individuals, residents of institutions or **correctional facilities,** and individuals with **immunodeficiency conditions** (e.g., HIV, chronic disease, immunosuppressive medications, including TNF alpha

receptor antagonists or blockers).

c. **Transmission** of TB occurs by inhalation of small airborne droplets from an individual with contagious pulmonary TB. **Children younger than 10 years of age are generally not contagious** because their cough is minimal and their pulmonary lesions are usually small.

4. **Clinical features**
   a. **In LTBI, most children with a positive tuberculin skin test or IGRA result are asymptomatic and do not progress to TB disease. Infants younger than 12 months of age and postpubertal adolescents are at the greatest risk of developing disease.**
   b. **Symptoms of TB disease** include **fever, chills, weight loss, cough, and night sweats**.
   c. **Extrapulmonary TB disease** may include the following:
      1. **Cervical lymphadenitis (scrofula), the most common form of extrapulmonary TB disease in children**
      2. **Meningitis** (for CSF findings, see Table 7-3)
      3. Abdominal involvement (ileitis)
      4. Skin and joint involvement
      5. **Skeletal disease,** which may involve the vertebrae (**Pott disease**)
      6. **Disseminated or miliary disease**
      7. **Renal involvement**
5. **Radiographic features of TB disease**
   a. **Hilar or mediastinal lymphadenopathy**
   b. **Lobar involvement, pleural effusion, or cavitary disease,** which typically affects the upper lung segments.
6. **Diagnosis.** Diagnosis and categorization of TB infection are based on an individual's risk for infection, *Mantoux skin test (Tuberculin skin test, or TST)*, chest radiographic findings, and culture.
   a. **Tuberculin skin test (TST) or Mantoux skin test** contains five tuberculin units of purified protein derivative **(PPD)**.
      1. It is administered intradermally and read 48–72 hours later by health care personnel trained in interpretation.
      2. The tuberculin skin test becomes positive **2–12 weeks after exposure to TB.**
      3. A positive tuberculin skin test is identified by measuring the area of **induration** (not erythema), and is interpreted on the basis of clinical and individual risk factors, which include the following:
         a. **≥5 mm** is considered positive in children who have had close contact with an individual with TB, who have clinical or chest radiographic findings consistent with TB, or who are immunocompromised, including those with HIV.
         b. **≥10 mm** is considered positive if children are younger than 4 years of age, have a chronic medical condition, or live in an area endemic for TB.
         c. **≥15 mm** is considered positive in children older than 4 years of age who do not have other risk factors.
   b. *IGRAs* can be used in children 2 years and older, and is preferred to TST for children 2 years of age and older who have been vaccinated with bacillus Calmette–Guérin (BCG).
      1. Two IGRAs are available: QuantiFERON Gold In-Tube test measures total interferon gamma produced and T-SPOT TB test measures the number of cells that produce interferon gamma. Both require one blood test and measure ex vivo interferon gamma production from T lymphocytes in response to

stimulation with antigens specific to *M. tuberculosis* complex, which includes *M. tuberculosis* and *M. bovis.* These antigens are not found in BCG and so IGRA testing can be useful in the evaluation of children older than 2 years of age who have received a BCG and may have a cross reactive TST. IGRAs have comparable sensitivity to TST but increased specificity.

2. IGRA results can be positive, negative, or indeterminate.
    a. Positive: Patient should be considered infected with *M. tuberculosis* complex.
    b. Negative
    c. Indeterminate: Result can be indeterminate due to issues with collection, the specific assay, or the patient's immune response.

c. **Definitive diagnosis** involves the following:
    1. **Positive culture** for *M. tuberculosis* from **early morning gastric aspirates** obtained by a nasogastric tube (gastric aspirate samples are preferred for diagnosis in children because children are generally unable to cough up sputum for culture, but instead swallow the sputum into the stomach), pleural fluid, CSF, or other body fluids.
    2. **Positive staining of fluid for acid-fast bacilli (AFB)**
    3. **Positive histology** (caseating granulomas) from a biopsy specimen

7. **Management.** Treatment is based on the TB category.
    a. Patients with **LTBI** are treated with **isoniazid** (INH) for 9 months. Older adolescents, pregnant adolescents, and adults are also given daily pyridoxine (vitamin B_6) to prevent neurologic complications of INH therapy.
    b. Patients with TB are treated on the basis of the location of TB and the susceptibility pattern of the organism. Treatment generally includes 2 months of INH, rifampin, pyrazinamide, and ethambutol, followed by 4 months of INH and rifampin.

Review Test

1. A 13-day-old male infant presents with a fever (temperature up to 100.6°F [38.1°C]), mild irritability, and diminished appetite. His parents report no change in the number of wet diapers. Which of the following statements regarding this patient's management or prognosis is correct?
   A. Careful observation at home is appropriate because of the relatively low fever and normal urine output.
   B. The risk of bacteremia in this patient is approximately 25%.
   C. Intramuscular ceftriaxone and close home monitoring are appropriate after evaluation with a complete blood count, blood culture, urinalysis, and urine culture.
   D. Irrespective of the results of initial laboratory testing, management should include intravenous antibiotics and hospitalization.
   E. Bacteria likely to cause fever in this patient include *Streptococcus pneumoniae* and *Haemophilus influenzae* type b.
2. A 10-month-old female infant with up-to-date immunizations presents with a fever (temperature up to 103.5°F [39.7°C]) for the past 3 days. She was previously healthy. Her parents report no symptoms other than the fever. On examination, she is well hydrated and appears nontoxic, and no focus of infection is identified. Which of the following is the next appropriate management step?
   A. Complete blood count (CBC) and blood culture, and empiric oral antibiotics to cover likely causes of bacteremia
   B. Urine culture and urinalysis, and if suggestive of a urinary tract infection, empiric antibiotics to cover likely urinary pathogens
   C. No laboratory studies are indicated because the patient appears nontoxic.
   D. Hospitalization and empiric intravenous cefotaxime
   E. CBC, blood culture, urinalysis, urine culture, lumbar puncture, and chest radiograph; intramuscular ceftriaxone should be given because of the high risk of bacteremia.
3. A 2-year-old girl presents with fever. On examination, she has exudative pharyngitis, enlarged posterior cervical lymph nodes, and splenomegaly. Which of the following statements regarding her evaluation and management is correct?
   A. Amoxicillin should be prescribed after performing a throat culture for suspected "strep throat."
   B. Monospot testing is highly sensitive and is the best test to make a diagnosis in this case.
   C. Human immunodeficiency virus is the most likely cause of this infection.
   D. Amoxicillin may result in a pruritic rash in this patient.
   E. The patient should be administered corticosteroids that will lead to rapid improvement and resumption of full activity.
4. A 6-year-old girl is sent home from summer camp with a temperature of 101.3°F (38.5°C), stiff neck, photophobia, and headache. Lumbar puncture in the emergency department reveals the following results: white blood count 380 cells/mm^3, with 65% polymorphonuclear cells and 35% lymphocytes; normal protein and glucose; and negative Gram stain. Which of the following pathogens is the most likely cause of her meningitis?
   A. *Neisseria meningitidis*
   B. *Streptococcus pneumoniae*
   C. Enterovirus
   D. *Borrelia burgdorferi*
   E. *Mycobacterium tuberculosis*
5. A previously healthy 18-month-old girl is admitted to the hospital with fever (temperature up

to 102.8°F [39.3°C]), vomiting, and lethargy. She was well until 2 days ago, when she was diagnosed with a viral upper respiratory infection. Lumbar puncture to evaluate the cerebrospinal fluid shows the following results: white blood cells 3050 cells/mm^3, with 98% polymorphonuclear cells; very low glucose; and elevated protein. Gram stain shows Gram-positive diplococci. Initial management should include which of the following?

A. Vancomycin and third-generation cephalosporin
B. Third-generation cephalosporin alone
C. Ampicillin and third-generation cephalosporin
D. Third-generation cephalosporin and acyclovir
E. Third-generation cephalosporin and corticosteroids

6. A 25-year-old woman is pregnant with her first child. The woman has human immunodeficiency virus (HIV) infection that was diagnosed 2 years before this pregnancy. Which of the following has been shown to *increase* her risk of transmitting HIV to her infant?
   A. Treatment with highly active antiretroviral therapy during pregnancy and before delivery
   B. Exclusive bottle formula feeding
   C. Prolonged rupture of membranes
   D. Birth by cesarean section
   E. Orally administered zidovudine given to the infant after birth
7. An 8-year-old girl presents with sore throat, fever, and a rough sandpaper-like rash over her trunk and extremities. A throat culture is positive for group A β-hemolytic streptococcus. Treatment of her infection with antibiotics will prevent which of the following complications?
   A. Reactive arthritis
   B. Rheumatic fever
   C. Poststreptococcal glomerulonephritis
   D. Guillain–Barré syndrome
8. A 1-year-old girl presents with weight loss and a 2-week history of large, bulky, nonbloody, foul-smelling stools. She has been attending day care and recently received amoxicillin for an ear infection. Which of the following is the most likely cause of her diarrhea?
   A. *Entamoeba histolytica*
   B. Enterotoxigenic *Escherichia coli*
   C. *Clostridium difficile*
   D. *Giardia lamblia*
   E. Norwalk virus
9. A 19-year-old boy, a college sophomore, presents with high fever, headache, cough, conjunctivitis, and a diffuse macular rash over his trunk and face. He is unsure of his immunization status. You suspect measles infection. Which of the following is correct regarding this diagnosis?
   A. Vitamin A may improve his outcome.
   B. Koplik spots would likely be present on examination of his mouth.
   C. Mortality is most commonly caused by measles encephalitis.
   D. Diagnosis is based on culture and direct fluorescent antigen testing.
   E. Corticosteroids will decrease symptoms and improve outcome.

The response options for statements 10–14 are the same. You will be required to select one answer for each statement in the set.

A. Malaria *Plasmodium* species
B. *Toxoplasma gondii*
C. *Giardia lamblia*
D. *Entamoeba histolytica*

E. *Coccidioides immitis*
F. *Cryptococcus neoformans*
G. *Aspergillus fumigatus*
H. *Candida albicans*

For each clinical description, select the most likely cause.

1. At birth, a term infant is noted to have hydrocephalus and intracranial calcifications on computed tomography of the head. Eye examination reveals bilateral chorioretinitis.
2. A 5-year-old boy is admitted with a fever of unknown origin. An abdominal computed tomographic scan reveals a large hepatic abscess.
3. A 12-year-old girl with cystic fibrosis has an exacerbation of her disease and presents with wheezing, pulmonary infiltrates, and eosinophilia.
4. A 16-year-old boy is admitted to the hospital for a workup of cyclical fevers after a trip to India. His illness began with flulike symptoms.
5. An 18-month-old girl and three of her day care classmates present with 2 weeks of watery diarrhea and some weight loss.
6. A 2-year-old boy has a positive tuberculin skin test that measures 12 mm. It was placed during a routine well-child care visit. He is well, without fever, chills, cough, weight loss, or night sweats. No known tuberculosis contacts are identified. Which of the following statements regarding this patient's management is correct?
   A. A chest radiograph should be ordered because the tuberculin test is positive.
   B. He should be placed into respiratory isolation immediately because he is likely to spread tuberculosis to others.
   C. Isoniazid is not indicated because this tuberculin skin test is negative.
   D. Triple drug therapy for tuberculosis should be started immediately.
   E. Gastric aspirates should be ordered.

The response options for statements 16–20 are the same. You will be required to select one answer for each statement in the set.

A. *Salmonella* species
B. *Shigella sonnei*
C. *Yersinia enterocolitica*
D. *Clostridium difficile*
E. *Campylobacter jejuni*
F. *Vibrio cholerae*
G. Enterotoxigenic *Escherichia coli*
H. *E. coli* 0157:H7

Match the clinical description with the likely causative organism.

1. While visiting Monterey, Mexico, a 16-year-old boy develops watery, nonbloody diarrhea, without fever.
2. A 3-year-old boy presents with an acute onset of high fevers, bloody diarrhea, and a generalized tonic-clonic seizure. The stool Wright stain reveals sheets of white blood cells.
3. An 8-year-old girl presents with a 1-week history of diarrhea and low-grade fever. The family reports that they have recently acquired a pet turtle.
4. A 10-year-old boy is admitted to the hospital and taken directly to the operating room for suspected acute appendicitis. Surgeons discover a normal appendix but enlarged mesenteric lymph nodes.
5. A group of travelers to Bangladesh suddenly develop massive, watery, nonbloody diarrhea

that results in severe dehydration and electrolyte imbalance.

The response options for statements 21–24 are the same. You will be required to select one answer for each statement in the set.

A. Buccal cellulitis
B. Impetigo
C. Necrotizing fasciitis
D. Erysipelas
E. Staphylococcal scalded skin syndrome
F. Toxic shock syndrome

Match the clinical description with the likely diagnosis.

1. A 9-month-old girl with mild facial eczema has fever and a facial skin rash. The skin lesion is weepy with a honey-colored crust.
2. An unvaccinated 4-month-old boy has a blue color to his cheeks and a positive blood culture for *Haemophilus influenzae* type b.
3. An infant boy has fever, an erythematous skin rash, and a positive Nikolsky sign.
4. A 7-year-old girl develops fever and a rapidly expanding tender skin rash with a well-demarcated border.

Answers and Explanations

1. **The answer is D** [II.C.5 and Table 7-1]. Fever in an infant younger than 28 days of age must be taken very seriously because the neonate's immune system is immature. As a result, the current appropriate management for any neonate with fever (temperature >100.4°F [>38°C]) includes a complete workup for serious bacterial infection (SBI) that includes evaluation of the blood, urine, and cerebrospinal fluid for evidence of bacterial infection; administration of empiric intravenous antibiotics; and hospitalization. The risk of SBI in a nontoxic infant younger than 3 months of age is approximately 1–7%. Usual bacteria resulting in infection in this age group include group B streptococcus, *Escherichia coli,* and *Listeria monocytogenes.*
2. **The answer is B** [II.D.3 and Table 7-1]. Because of the patient's elevated fever, evaluation for a urinary tract infection, including urine culture and urinalysis, is indicated. Because the infant is completely immunized, risk of bacteremia is low enough *not* to warrant blood tests. If she were incompletely immunized (had not received her 2-, 4-, and 6-month vaccinations), a complete blood count and blood culture would be indicated and intramuscular ceftriaxone may be given either empirically, or only if the white blood count is ≥15,000 cells/mm^3. Hospitalization is generally not required unless the patient is toxic in appearance, is dehydrated, or has poor ability to return to the physician for follow-up. Neither evaluation of spinal fluid nor a chest radiograph is indicated in this nontoxic patient without respiratory signs or symptoms. Neither intravenous antibiotics nor hospitalization is indicated because the infant is nontoxic and well hydrated.
3. **The answer is D** [XIII.B]. This patient's clinical presentation with fever, lymphadenopathy, pharyngitis, and splenomegaly is most consistent with infectious mononucleosis. If a child with infectious mononucleosis is given amoxicillin, a diffuse pruritic rash may develop. Monospot testing is highly sensitive in older children, but heterophile antibodies do not reliably form in children younger than 4 years of age. Antibody titers are therefore the preferred diagnostic test in such young children. The most common cause of infectious mononucleosis is Epstein–Barr virus. Although supportive care is most appropriate, corticosteroids may be indicated for treatment of infectious mononucleosis complicated by airway compromise, but are not routinely recommended. Splenomegaly is not consistent with the diagnosis of streptococcal pharyngitis.
4. **The answer is C** [IV.C.3 and Tables 7-3 and 7-4]. This cerebrospinal fluid (CSF) evaluation is most consistent with aseptic meningitis, specifically viral meningitis. Enteroviruses are the most common cause of viral meningitis and most often occur during the summer and fall. Early in viral meningitis, the white blood cell (WBC) count in the CSF may demonstrate a polymorphonuclear cell predominance that shifts to a lymphocyte predominance within 24–48 hours. The normal protein and glucose and negative Gram stain are also consistent with viral meningitis. Meningitis caused by *Neisseria meningitidis* or *Streptococcus pneumoniae* would be reflected by a higher CSF WBC count, lower glucose, and higher protein. Although patients with Lyme meningitis, which is caused by *Borrelia burgdorferi,* may present with an aseptic CSF profile, the onset is not as acute as in this patient. Patients with *Mycobacterium tuberculosis* present with a low to very low glucose and elevated protein level in the CSF.
5. **The answer is A** [IV.B.5]. Empiric therapy of presumed bacterial meningitis should include a third-generation cephalosporin and the addition of vancomycin until sensitivities are available, because of the high level of pneumococcal antibiotic resistance in many communities. Ampicillin is not indicated because this child is out of the age range at which *Listeria* infection occurs. Acyclovir is not indicated because the cerebrospinal fluid profile is most consistent with bacterial meningitis, not viral meningitis. Acyclovir is used to treat neonates with presumed herpes simplex meningitis, or encephalitis or in older children with

encephalitis. Corticosteroids are effective in reducing the incidence of hearing loss in *Haemophilus influenzae* type b meningitis but have not been shown to be effective for other bacterial pathogens.

6. **The answer is C** [XIII.A.2]. Factors that increase the risk of HIV transmission from mother to infant include high maternal viral load (measured by RNA copy number) at delivery, concomitant chorioamnionitis or other genital tract infections, primary or advanced maternal HIV infection, premature birth, and prolonged rupture of membranes. Transmission may also occur through breast milk. Transmission is decreased through the use of maternal antiretroviral therapy, newborn prophylaxis with antiretroviral agents (e.g., zidovudine), birth by cesarean section, and low maternal viral load.
7. **The answer is B** [IX.A.5.f]. This patient's clinical presentation of a sandpaper-like rash associated with pharyngitis and fever is consistent with scarlet fever, caused by erythrogenic toxin–producing strains of group A β–hemolytic streptococcus (GABHS). Although there are multiple complications of GABHS infection, including rheumatic fever, glomerulonephritis, and reactive arthritis, only rheumatic fever will be prevented by treatment with antibiotics.
8. **The answer is D** [Tables 7-6 and 7-7, XV.B.3]. Infection with the protozoan *Giardia lamblia* is associated with bulky, foul-smelling stools, weight loss, and day care attendance. *Entamoeba histolytica* and *Clostridium difficile* generally cause bloody diarrhea. *Escherichia coli* infection generally results in short-term watery diarrhea. Day care attendance is also associated with Norwalk virus; however, symptoms of Norwalk virus infection generally last only 48–72 hours.
9. **The answer is A** [XIII.C.3, XIII.C.4, XIII.C.5]. This patient's presentation is most consistent with measles infection. Management includes supportive care, and vitamin A therapy may also be beneficial. Koplik spots are transient, and by the time the rash is present, Koplik spots are no longer appreciated. Bacterial pneumonia is the most common complication of measles infection and is the most common cause of mortality. Diagnosis is based on confirmation by serologic testing in the presence of typical clinical features. Corticosteroids do not play a role in the therapy of measles.
10. **The answers are B, D, G, A, and C, respectively** [XV.D.3, XV.A.3, XIV.A.2, XV.C.3, and XV.B.3]. The triad of intracranial calcification, hydrocephalus, and chorioretinitis is consistent with congenital toxoplasmosis, which is caused by *Toxoplasma gondii. Entamoeba histolytica* may result in asymptomatic infection or colitis. The most common extraintestinal complication is a liver abscess. *Aspergillus* infection may result in invasive disease or in noninvasive allergic disease characterized by wheezing, eosinophilia, and pulmonary infiltrates. This can occur in patients with severe asthma or with cystic fibrosis. Malaria classically presents with a flulike illness followed by the development of high fevers that cycle in 48- to 72-hour paroxysms. *Giardia lamblia* typically presents with bulky, large-volume, watery stools that eventually lead to weight loss. Outbreaks can occur in day care settings where children are in diapers.
11. **The answer is A** [XVII.C]. A tuberculin skin test is considered positive depending on a patient's specific risk factors for acquisition of tuberculosis. A tuberculin skin test ≥10 mm is considered positive if the patient is younger than 4 years of age or if the patient resides or has lived in an area endemic for tuberculosis. Therefore, given that the tuberculin skin test is positive in this patient, a chest radiograph to evaluate for pulmonary tuberculosis is indicated. Children younger than 10 years of age with tuberculosis are unlikely to be contagious because of minimal cough and pulmonary involvement. Medications for tuberculosis disease (e.g., rifampin, isoniazid, pyrazinamide, ethambutol regimen) are indicated if the patient has signs and symptoms of tuberculosis. Gastric aspirates are indicated only if the chest radiograph reveals pulmonary disease.
12. **The answers are G, B, A, C, and F, respectively** [Table 7-6]. Enterotoxigenic *Escherichia coli* is the major cause of traveler's diarrhea and results in nonbloody watery stools. Bloody stools

may result from infection with *Salmonella, Shigella, Yersinia, Campylobacter,* enterohemorrhagic *E. coli,* and *Clostridium difficile. Shigella* may be associated with seizures caused by the release of a neurotoxin. *Salmonella* may be acquired by ingestion of contaminated poultry or by exposure to turtles and lizards that carry the organism. *Yersinia* may result in mesenteric adenitis that causes pain mimicking acute appendicitis. Infection with *Vibrio cholerae* generally occurs in developing countries and causes massive fluid loss from the gut. *E. coli* 0157:H7 causes bloody diarrhea and is the causative agent in hemolytic uremic syndrome.

13. **The answers are B, A, E, and D, respectively** [IX.A]. Impetigo typically presents with honey-crusted lesions on the face; it is caused by infection with *Staphylococcus aureus* and group A β-hemolytic streptococcus (GABHS). Buccal cellulitis is characterized by a bluish color to the cheeks of a young child; this condition is typically caused by infection with *Haemophilus influenzae* type b, which is identified on blood culture. Staphylococcal scalded skin syndrome is manifested by Nikolsky sign or the extension of bullae with lateral pressure applied to the skin. Fever, tender skin, and widespread bullae are present. Erysipelas is characterized by tender, erythematous skin, but the border is well demarcated. Necrotizing fasciitis and toxic shock syndrome are complications of infection with GABHS. Necrotizing fasciitis is a severe skin infection that involves multiple layers of tissue. Toxic shock presents with fever, sunburn rash, and multiorgan failure. Both of these complications are a result of toxin produced by the GABHS.

CHAPTER 8

Cardiology

David A. Ferry, Leigh Christopher Reardon

I. Congestive Heart Failure (CHF)

A. **Definition.** Congestive heart failure (CHF) is a clinical syndrome defined as **inadequate oxygen delivery** by the myocardium to meet the metabolic demands of the body.

B. **Pathophysiology.** Signs and symptoms of CHF often result from compensatory mechanisms that lead to increased demand on an already compromised myocardium.
   1. **Hypoperfusion of end organs** stimulates the heart to maximize contractility and heart rate in an attempt to increase cardiac output.
   2. **Hypoperfusion** also signals the kidneys to **retain salt and water** through the renin–angiotensin system in an attempt to increase blood volume.
   3. **Catecholamines** released by the sympathetic nervous system also increase heart rate and myocardial contractility.

C. **Etiology.** CHF may result from congenital heart disease (CHD), acquired heart disease, and a variety of miscellaneous disorders.
   1. **CHD** may result in CHF.
      a. **Increased pulmonary blood flow** may cause CHF. Examples of congenital lesions that cause increased pulmonary blood flow include a large ventricular septal defect (VSD), a large patent ductus arteriosus (PDA), transposition of the great arteries (TGA), truncus arteriosus, and total anomalous pulmonary venous return (TAPVR).
      b. **Obstructive lesions** may also cause CHF. Examples include severe aortic, pulmonary, and mitral valve stenosis, coarctation of the aorta, interrupted aortic arch, and hypoplastic left heart syndrome.
      c. **Other causes** include arteriovenous malformations and mitral or tricuspid regurgitation, which all lead to volume overload in the heart.
   2. **Acquired heart disease** may also lead to CHF.
      a. **Viral myocarditis is a common cause of CHF** in older children and adolescents.
      b. Other cardiac infections (e.g., endocarditis, pericarditis), metabolic diseases (e.g., hyperthyroidism), medications (e.g., doxorubicin, a chemotherapeutic agent), cardiomyopathies, and ischemic diseases (e.g., coronary artery disease)
      c. Dysrhythmias, including certain types of tachycardia and bradycardia
   3. **Miscellaneous** causes of CHF include the following:
      a. **Severe anemia** may cause **high-output CHF.**
      b. Rapid infusion of intravenous fluids, especially in premature infants
      c. Obstructive processes of the airway, such as enlarged tonsils or adenoids, laryngomalacia, and cystic fibrosis may cause CHF as a result of chronic hypoxemia that results in pulmonary hypertension and right-sided heart failure.

D. **Clinical features**
   1. **Tachypnea, cough, wheezing, and rales** on examination and **pulmonary edema** on chest radiograph (CXR) are evidence of pulmonary congestion.
   2. **Tachycardia, sweating, pale or ashen skin color, diminished urine output, and enlarged cardiac silhouette** on CXR are evidence of impaired myocardial performance and therefore poor cardiac output.
   3. **Hepatomegaly and peripheral edema** are evidence of systemic venous congestion.
   4. Other signs and symptoms include **failure to thrive, poor feeding (common symptom in newborns)**, and **exercise intolerance (common symptom in older children and adolescents)**.
   5. **Cyanosis and shock** are **late manifestations**.

E. **Management**
   1. **Goals of medical management** are to improve myocardial function and relieve

pulmonary and systemic congestion.

   a. **Cardiac glycosides** (e.g., digoxin) may increase the efficiency of myocardial contractions and relieve tachycardia.
   b. **Loop diuretics** (e.g., furosemide, ethacrynic acid) reduce intravascular volume by maximizing sodium loss, which in turn leads to diminished ventricular dilation and improved cardiac function.
   c. **Inotropic medications** (e.g., dobutamine, dopamine, epinephrine) are administered intravenously to augment cardiac contractility, thereby increasing the force of the heart's contraction. They may be used to treat severe CHF.
   d. Other medications, such as amrinone and milrinone (phosphodiesterase inhibitors) improve contractility and reduce afterload (the pressure in the aorta that the left ventricle must overcome to eject blood).

2. **Interventional catheterization** procedures can address some of the underlying causes of CHF (e.g., **balloon valvuloplasty** for critical aortic and pulmonary valve stenosis).
3. **Surgical repair** is often the definitive treatment of CHF secondary to CHD.
4. **Cardiac transplant** is reserved for the most severe cases of CHF that are refractory to medical management.

II. Innocent Cardiac Murmurs

A. **Definition.** Innocent murmurs result from turbulent but normal blood flow, are **not caused by structural heart disease,** and have no hemodynamic significance.

B. **Epidemiology.** Approximately **50%** of children have an innocent heart murmur at some point during childhood.

C. **Clinical features.** The most common innocent heart murmurs are presented in **Table 8-1**.

Table 8-1
Clinical Features of Innocent Heart Murmurs

Murmur	Age	Location	Characteristics
Still's murmur (left ventricular outflow tract)	Ages 2–7 years	Mid-left sternal border	Grade 1–3, systolic
			Vibratory, twanging, or buzzing
			Loudest supine
			Louder with exercise and expiration
Pulmonic systolic murmur (systolic ejection murmur)	Any age	Upper left sternal border	Grade 1–2, peaks early in systole
			Blowing, high-pitched
			Loudest supine
			Louder with exercise and inspiration
Venous hum	Any age, especially school age	Neck and below the clavicles	Continuous murmur
			Heard only sitting or standing
			Disappears if supine; changes with compression of the jugular vein or with neck flexion or extension

III. Acyanotic Congenital Heart Disease

A. Normal cardiac anatomy is depicted in Figure 8-1.

B. **Clinical and diagnostic features.** Physical examination, CXR, and electrocardiographic (ECG) findings of acyanotic CHD are presented in **Table 8-2**. **Echocardiography confirms the specific anatomic lesions.**

C. **Atrial septal defect (ASD)** (**Figure 8-2**)

1. **Classification**
   a. **Ostium primum.** This type of ASD is a defect in the lower portion of the atrial septum. A cleft, or division, in the anterior mitral valve leaflet is almost always present and may cause mitral regurgitation. Ostium primum ASD is a common congenital heart lesion in **Down syndrome**.
   b. **Ostium secundum.** This type of ASD is a defect in the middle portion of the atrial septum. Ostium secundum is the **most common type** of ASD.
   c. **Sinus venosus.** This type of ASD is a defect superiorly and posteriorly in the septum near the junction of the right atrium and superior vena cava (SVC). In sinus venosus ASD, the right pulmonary veins usually drain anomalously into the right atrium or SVC instead of draining into the left atrium.
2. **Pathophysiology.** Blood flows across the ASD **from the left atrium to the right atrium** (i.e., **left-to-right shunt**). The direction of the blood flow is determined by the relative diastolic compliances of the right and left ventricles (which in turn are determined by systemic and pulmonary vascular resistances [SVR and PVR]). **Blood therefore flows from areas of higher resistance to areas of lower resistance.** Increased blood flow across the ASD leads to an increase in size of the right atrium and right ventricle and to increased pulmonary blood flow.
3. **Clinical features**
   a. **Symptoms are minimal,** if any, except in patients with an ostium primum defect who develop mitral regurgitation that results in CHF.
   b. **Physical examination** findings include the following:
      1. **Increased right ventricular impulse** (manifesting as a stronger point of maximal impulse) as a result of right ventricular volume and pressure overload.
      2. **Systolic ejection murmur** (from excessive pulmonary blood flow) best heard at the **mid and upper left sternal borders**. A mid diastolic filling rumble representing increased blood flow through the tricuspid valve may also be heard.
      3. **Fixed-split second heart sound.** With blood shunting across the ASD from the left atrium to the right atrium to the right ventricle, the **second heart sound is widely split** because of the increased volume of blood that must be ejected from the right ventricle, leading to later closure of the pulmonic valve compared with the aortic valve (i.e., a wider split of the A2 and P2 components of the second heart sound). **The splitting is fixed**, and does not vary with respiration, because the blood shunting across the ASD ensures that the right ventricle receives a fixed volume of blood, by balancing the increased volume reaching the right ventricle with inspiration and the decreased volume of blood reaching the right ventricle with expiration (i.e., the normal physiologic variation in timing of aortic and pulmonic valve closure with respiration is absent).
4. **Management.** Treatment of primum and sinus venosus ASDs is **closure by open heart**

surgery to prevent right-sided heart failure, pulmonary hypertension, atrial dysrhythmias, and paradoxical embolism (a stroke caused by a blood clot traveling from the right atrium to the left atrium via the ASD). Most **secundum ASDs can be successfully closed using interventional catheterization procedures** with implantation of atrial septal occlusion devices.

D. **Ventricular septal defect (VSD)**

1. **Classification.** VSDs are classified by location as **inlet, trabecular (muscular), membranous,** and **outlet (supracristal)** (**Figure 8-3**).
2. **Pathophysiology.** After birth, as pulmonary vascular pressure decreases, blood flows across the VSD *from the left ventricle to the right ventricle,* owing to the lower resistance within the pulmonary circulation compared to the resistance within the systemic circulation. However, with time, the pulmonary vessels hypertrophy in response to this increased pulmonary flow. This hypertrophy may lead to increased PVR (pulmonary hypertension). If treated early, the increased PVR is usually reversible. If increased pulmonary blood flow persists, the pulmonary hypertension may become irreversible and even progress to *Eisenmenger syndrome* [see section III.D.3.d.(2)].
3. **Clinical features and course** vary greatly depending on the magnitude of the left-to-right shunting across the VSD. **The amount of blood flow directed from one side of the heart to the other side (i.e., the shunt) is determined by both the size of the VSD and the degree of PVR.** For example, the larger the VSD and the lower the PVR, the greater the blood flow across the VSD and into the pulmonary vessels. *The greater the pulmonary blood flow, the more symptomatic the patient.* Typical clinical presentations include the following:
    a. **Small VSDs** have little to no shunt across the VSD and **may close spontaneously**. On examination, small VSDs typically have a *high-pitched holosystolic murmur* ranging from a grade 3 to grade 4 murmur. A thrill at the lower left sternal border and a grade 4 high-pitched holosystolic murmur is indicative of a very restrictive defect with a high flow velocity across the VSD. Key point: **As the size of the VSD decreases, the intensity of the murmur increases.**
    b. **Moderate VSDs** may have a large shunt across the VSD that may result in signs and symptoms of CHF. A **holosystolic murmur** is usually present, and its intensity depends on the size of the shunt. If the left-to-right shunt across the VSD is large (2:1 pulmonary-to-systemic flow—i.e., twice as much blood flows to the lungs as to the systemic circulation), then a diastolic murmur of mitral turbulence may also be heard at the apex (mitral filling rumble representing the excess blood from the lungs now passing through the mitral valve).
    c. **Large VSDs** often cause signs and symptoms of CHF. They have less turbulence across the VSD, so the *systolic murmur is shorter and lower in pitch.* A mitral filling rumble may be heard at the apex. The S_2 tends to be loud and more narrowly split than usual, with P_2 (pulmonary closure sound) being accentuated due to high pulmonary artery pressure.
    d. **PVR may eventually become elevated in moderate or large VSDs in response to chronically high pulmonary flow.** When this occurs, clinical features change.
        1. **When PVR becomes elevated,** the right ventricular impulse is noticeably increased and the second heart sound may be single and loud. The mitral filling rumble disappears because of diminished pulmonary blood flow as a result of decreased left-to-right shunting. Symptoms of CHF also diminish as PVR increases, because of the decrease in pulmonary blood flow.
        2. **If PVR remains elevated, pulmonary hypertension may become irreversible, even if the VSD is surgically closed.** In the extreme situation in which PVR

increases and exceeds SVR, shunting changes from left-to-right to right-to-left (a condition termed **Eisenmenger syndrome**). The **right-to-left shunt is manifested by cyanosis**.

4. **Management**
    a. **Medical management** of CHF is indicated in a symptomatic child. Large shunts are also associated with a high incidence of pulmonary infections from excessive blood flow.
    b. **Surgical closure** is indicated in the following circumstances:
        1. **Heart failure refractory to medical management**
        2. **Large VSDs with pulmonary hypertension** are usually surgically closed at 3–6 months of age.
        3. **Small to moderate VSDs** with persistent left ventricular (LV) volume overload are usually surgically closed between 2 and 6 years of age. Some small VSDs may be left alone if there is no LV volume overload in childhood. Sometimes, transcatheter closure of smaller VSDs can be done with excellent results.

E. **Patent ductus arteriosus (PDA)**

1. **Definition.** In the fetus, the ductus arteriosus connects the pulmonary artery to the aorta. After birth, as the Pa_{O_2} rises, the ductus arteriosus normally fibroses. If it remains open, it is termed a **PDA**. The incidence of PDA is especially high in preterm infants.
2. **Postnatal pathophysiology.** In healthy infants the SVR exceeds PVR, and blood therefore flows through the PDA from the aorta to the pulmonary artery (left-to-right shunt). This leads to increased pulmonary blood flow (**Figure 8-4**).
3. **Clinical features.** Signs and symptoms depend on the size of the PDA and on the relationship between SVR and PVR.
    a. **Small PDAs** usually produce **no symptoms,** but **moderate or large PDAs** almost always result in signs and symptoms of **CHF** due to increased pulmonary blood flow.
    b. **Physical examination findings**
        1. The classic murmur is a **"machinery-like" continuous murmur** at the **upper left sternal border**.
        2. **If the left-to-right shunt is large,** there may also be a **diastolic rumble** of blood flow across the mitral valve at the apex, a **widened pulse pressure** ($^{>}$30 mm Hg) and **bounding pulses**.
    c. **Risk of pulmonary hypertension** caused by excessive pulmonary blood flow through a large PDA over time.
4. **Management**
    a. **Indomethacin** is often used in premature infants to close a PDA medically.
    b. PDAs in the nonneonate are usually closed surgically by transcatheter insertion of a device.

F. **Coarctation of the aorta**

1. **Definition.** Coarctation of the aorta is narrowing of the aortic arch, just below the origin of the left subclavian artery and typically at, or just proximal to, the origin of the ductus arteriosus. It may be a discrete narrowing (hourglass) or a long-segment obstruction.
2. **Pathophysiology.** The narrowed segment obstructs or diminishes flow from the proximal to the distal aorta (**Figure 8-5**).
3. **Clinical features.** Signs and symptoms depend on the severity of the obstruction and on the presence of any other associated cardiac abnormalities.
    a. **Neonates or infants with severe coarctation** may **depend on a right-to-left shunt through the PDA** for perfusion of the lower thoracic and descending aorta. Such

infants may be **minimally symptomatic initially,** but **as the PDA closes, symptoms of CHF develop and progress**.

1. Blood pressure may be elevated in the upper extremities and low in the lower extremities before the onset of CHF (before the PDA becomes narrower or closes).
2. Once the neonate or infant develops CHF, pulses in all four extremities are poor due to low cardiac output.

b. **Older children or adolescents** may have no symptoms and may have only hypertension or a heart murmur. **Hypertension** is typically noted in the **right arm,** and commonly in the left arm as well, with *reduced blood pressure in the lower extremities*.

1. **Femoral pulse,** which normally precedes the radial pulse, is **dampened and delayed** until after the radial pulse (**radiofemoral delay**).
2. **Blood pressure and pulse findings** may be less prominent if collateral vessels (intercostal arteries) develop, which allow the ascending aortic pressure and flow to circumvent the coarctation.
3. **Bicuspid aortic valve or aortic stenosis** is present in *50% of patients with coarctation* of the aorta. If either of these conditions is present, a systolic murmur of aortic stenosis may be heard [see section III.G.3].
4. **Bruit of turbulence** through the coarctation may be audible at the left upper back near the left scapula.

4. **Management**

a. **Initial management** in the **symptomatic neonate** is directed at improving circulation to the lower body.

1. **Intravenous prostaglandin E** (PGE) is given urgently to open the ductus arteriosus.
2. **Inotropic medications** are given to overcome myocardial depression, and low-dose dopamine is used to maximize renal perfusion and function.

b. **Corrective repair**

1. **Surgery** is the usual approach in newborns and infants and involves excision of the narrowed segment followed by end-to-end anastomosis. Late recurrence of narrowing may occur in up to 50% of patients.
2. **Balloon angioplasty with or without endovascular stent placement** is the treatment of choice for short segment coarctations in school-age children and teens who have not undergone surgical correction. It is also the primary intervention for **recurrent coarctation after surgical correction**.

5. **Prognosis** is excellent, but long-term concerns include recurrence of coarctation and upper extremity hypertension with exercise.

G. **Aortic stenosis**

1. **Definition.** Aortic stenosis is narrowing of the aortic valve. Pathologically, aortic stenosis typically appears as commissural fusion of the three normal leaflets, leading to a bicuspid or unicuspid valve.
2. **Pathophysiology.** Aortic stenosis results in reduced LV output. At the myocardial level, aortic stenosis results in an imbalance between myocardial oxygen demand (which is higher than usual owing to the increased ventricular work as a result of outflow obstruction) and supply. This may lead to myocardial ischemia. In the neonate, severe aortic stenosis may be associated with hypoplasia of the left ventricle as a result of impaired fetal LV development.
3. **Clinical features.** Signs and symptoms depend on the severity of the stenosis and age. **Physical examination** findings are presented in Table 8-2.

a. **Neonates with severe stenosis ("critical aortic stenosis")** appear normal at birth but develop signs and symptoms of CHF at 12–24 hours of age. Once the PDA closes, all systemic flow must be ejected through the aortic valve. However, in critical aortic stenosis this is not possible and adequate perfusion to the body cannot be maintained.
b. **Older children** generally have **no symptoms** until the stenosis becomes severe. Once severe, symptoms include **exercise intolerance, chest pain, syncope,** and even **sudden death**.

4. **Management. Indications for intervention** include CHF, symptoms such as chest pain or syncope, and documentation of a high resting pressure gradient across the aortic valve (>50–70 mm Hg).
   a. **Balloon valvuloplasty** is often the initial management approach for aortic stenosis without associated significant regurgitation.
   b. **Surgery** is often required for aortic stenosis with regurgitation and for recurrent stenosis. The aortic valve is replaced with either the patient's own pulmonary valve (**Ross procedure**) or a prosthetic valve.

H. **Pulmonary stenosis**

1. **Definition.** Pulmonary stenosis is narrowing of the pulmonary valve. Pathologically, fusion of the valve commissures is typically seen.
2. **Pathophysiology.** Pulmonary stenosis results in increased right ventricular pressure and reduced right ventricular output.
3. **Clinical features. Physical examination** findings are presented in Table 8-2.
   a. **Severe pulmonary stenosis in the neonate** may be manifested by **cyanosis** as a result of **right-to-left shunting** at the atrial level through a patent foramen ovale (PFO).
   b. For most children, outflow obstruction is **mild to moderate** and **symptoms are absent**.
4. **Management.** Treatment is **balloon valvuloplasty** for symptomatic infants with critical pulmonary stenosis, and for older children with significant gradients across the pulmonary valve (>35–40 mm Hg) or high right ventricular pressures.

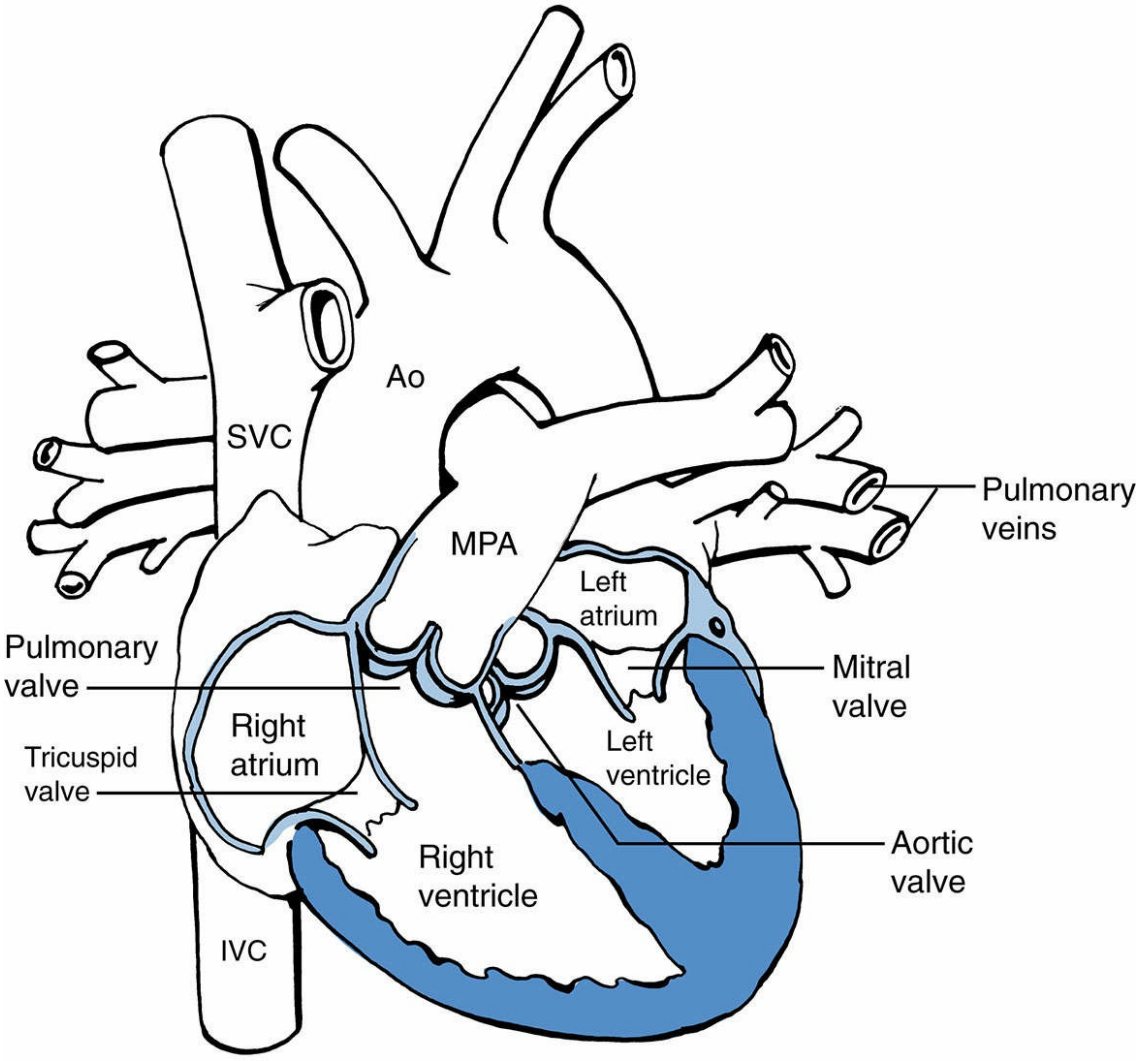

FIGURE 8.1 Anatomy of the normal heart. *Ao* = aorta; *MPA* = main pulmonary artery; *SVC* = superior vena cava; *IVC* = inferior vena cava.

Table 8-2
Key Differentiating Clinical Features of Acyanotic Congenital Heart Disease

Heart Lesion	Physical Examination Findings	ECG	Chest Radiograph
Atrial septal defect	Systolic ejection murmur mid-left sternal border and ULSB	RAD, RVH, and RAE	Right atrial and ventricular enlargement
	Fixed split S_2		Increased PVM
	Diastolic rumble LLSB		
Ventricular septal defect	High-pitched holosystolic murmur at LLSB, with or without a thrillDiastolic rumble at apex if pulmonary blood flow is high	If small: normal or mild LVH	If small: normal
		If moderate: LVHRVH if pulmonary hypertension present	If moderate or large: cardiomegaly and increased PVM
			If elevated PVR: normal or decreased PVM
Patent ductus arteriosus	Continuous murmur at ULSB; "machinery-like"	LVHRVH if pulmonary hypertension present	Cardiomegaly with increased PVM
	Brisk pulses		
Coarctation of the aorta (older child)	Elevated BP in right arm	Normal or LVH	Normal heart sizeRib notching (evidence of collateral flow)
	Reduced BP in legs		
	Dampened and delayed femoral pulse		
	Bruit left upper back		
Aortic	Ejection click at base and apex (fixed with	Normal or LVH	Normal or mild

stenosis	respiratory cycle)		cardiomegalyProminent ascending aorta (poststenotic dilation)
	Systolic ejection murmur at base with radiation to URSB, apex, suprasternal notch, and carotids		
	Thrill at URSB and suprasternal notch		
Pulmonary stenosis	Ejection click at apex (variable with respiratory cycle)	RVH	NormalProminent main pulmonary artery due to poststenotic dilation
	Systolic ejection murmur at ULSB		

ECG = electrocardiogram; *ULSB* = upper left sternal border; *LLSB* = lower left sternal border; *URSB* = upper right sternal border; S_2 = second heart sound; *LVH* = left ventricular hypertrophy; *RVH* = right ventricular hypertrophy; *BP* = blood pressure; *RAE* = right atrial enlargement; *RAD* = right axis deviation; *PVM* = pulmonary vascular markings; *PVR* = pulmonary vascular resistance.

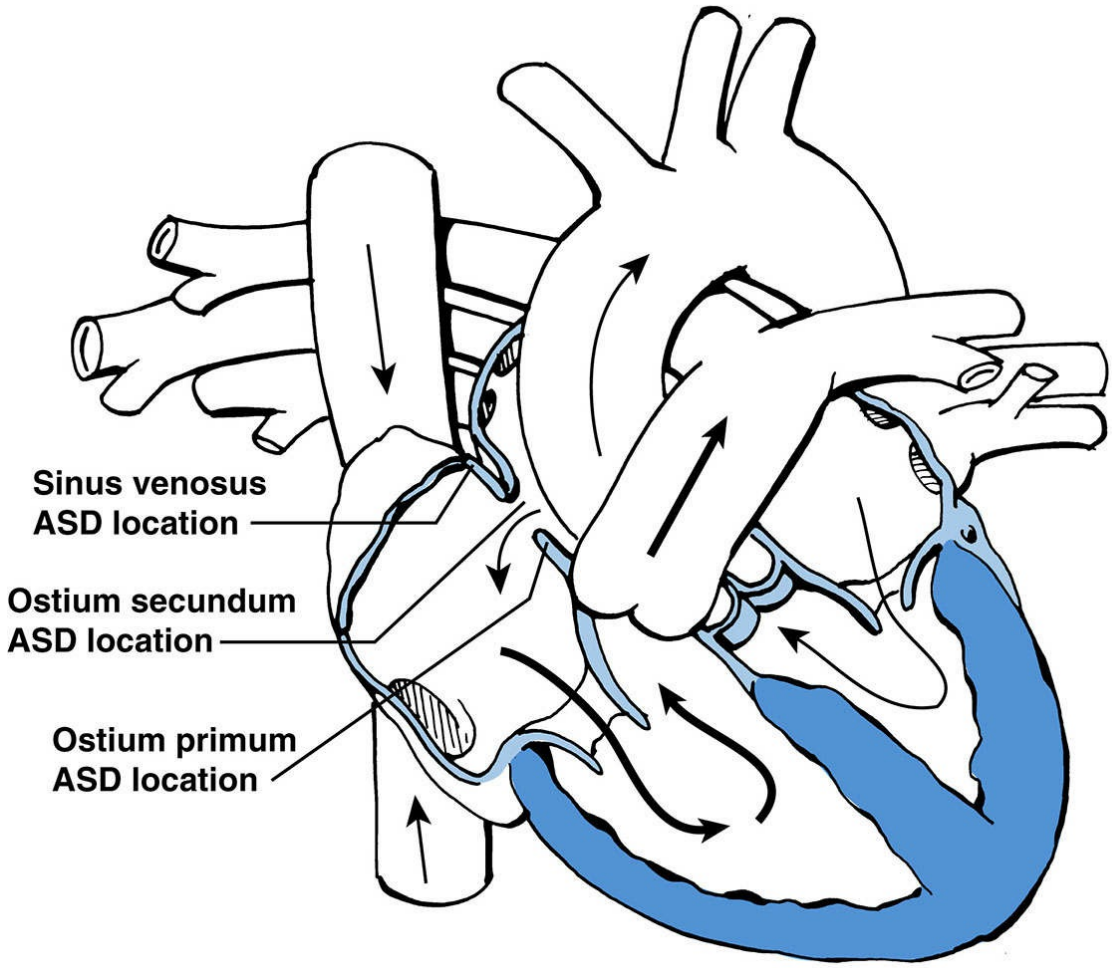

FIGURE 8.2 Location of atrial septal defects (ASDs). Arrows designate the direction of blood flow. Thick arrows designate increased blood flow. The right atrium and the right ventricle are enlarged. The location of the sinus venosus ASD is the posterior–superior aspect of the atrial septum.

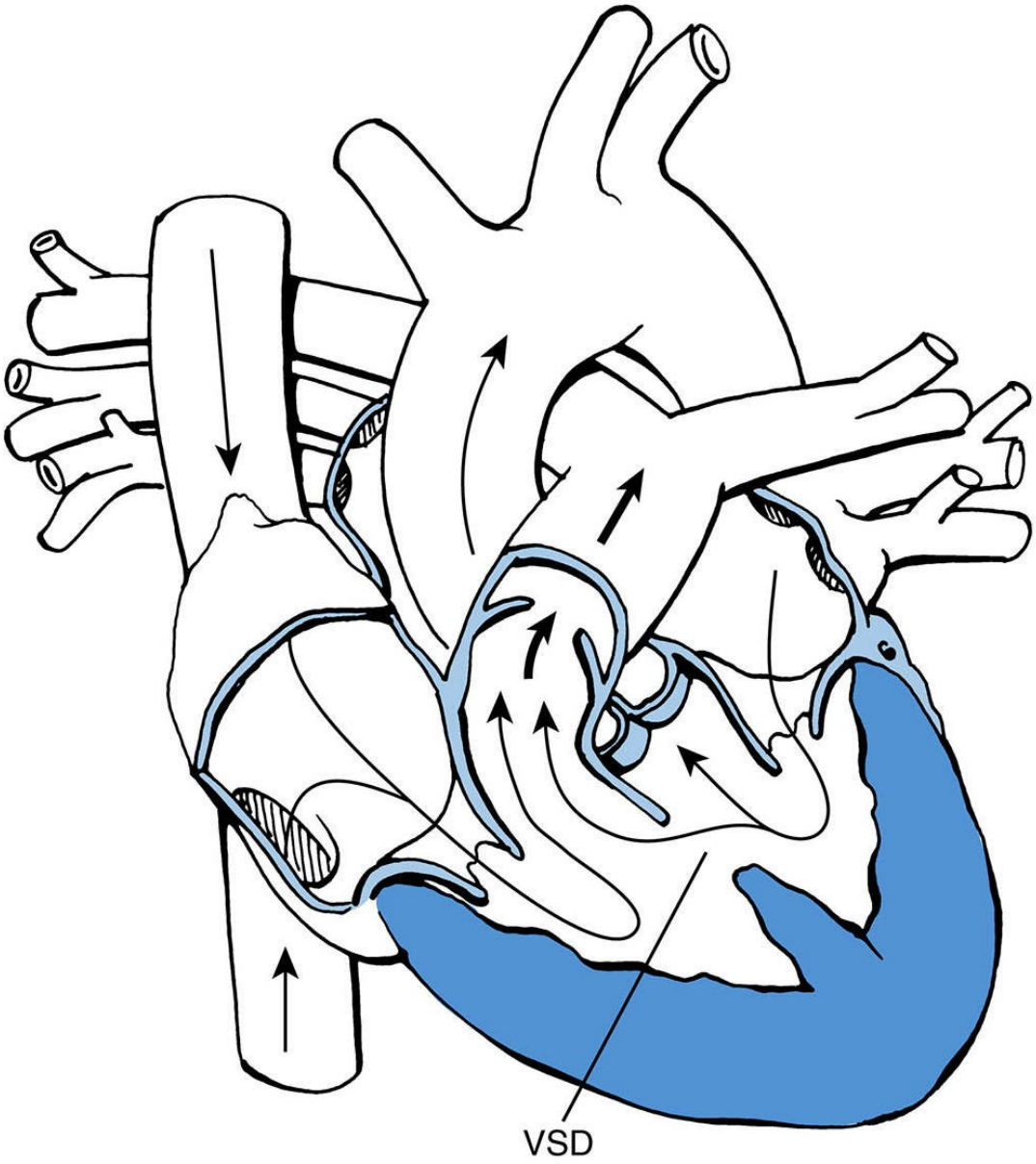

FIGURE 8.3 Trabecular (muscular) ventricular septal defect (VSD). Arrows designate the direction of blood flow. Thick arrows designate increased blood flow.

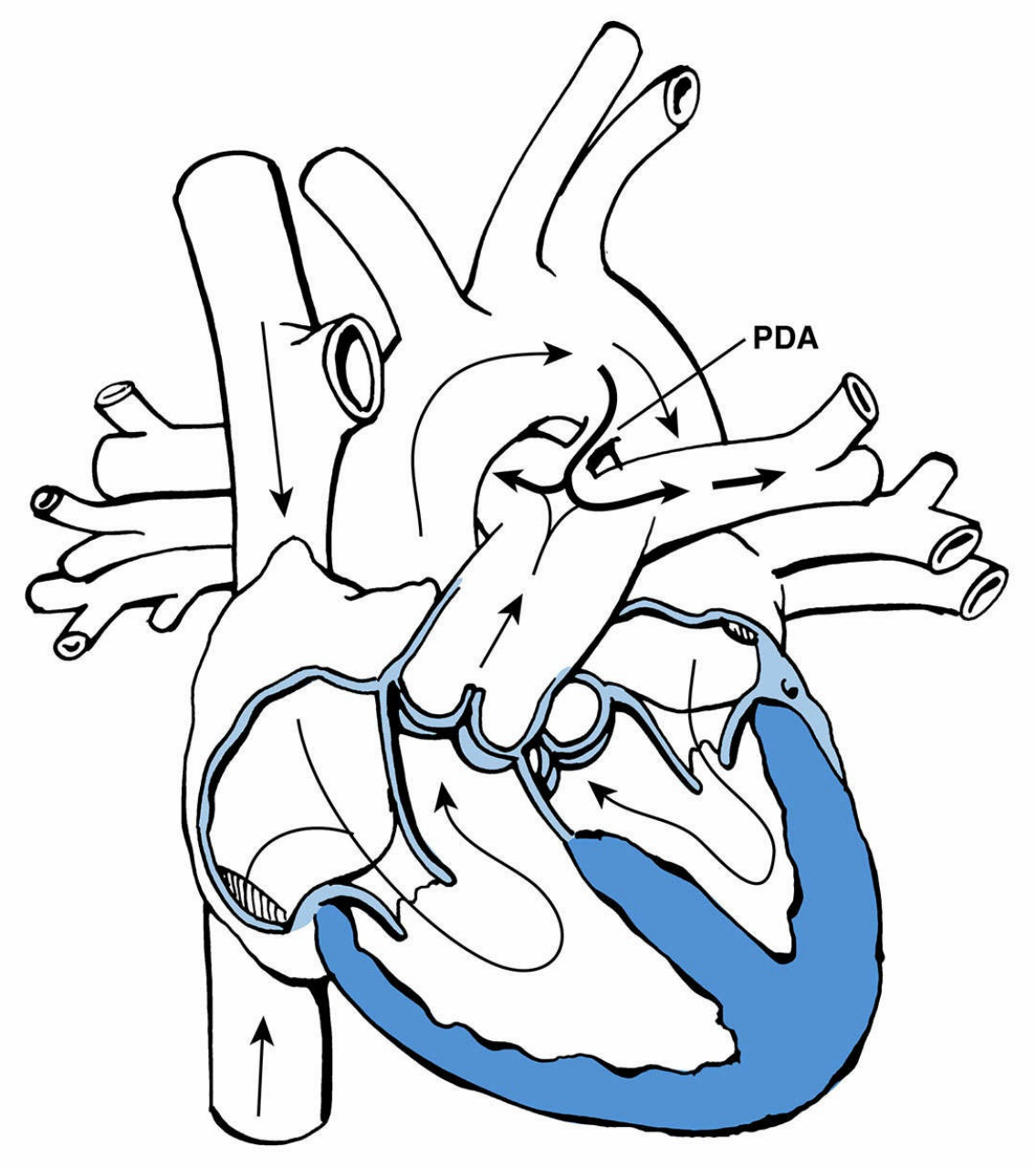

FIGURE 8.4 Patent ductus arteriosus (PDA). Arrows designate the direction of blood flow. Thick arrows designate increased blood flow.

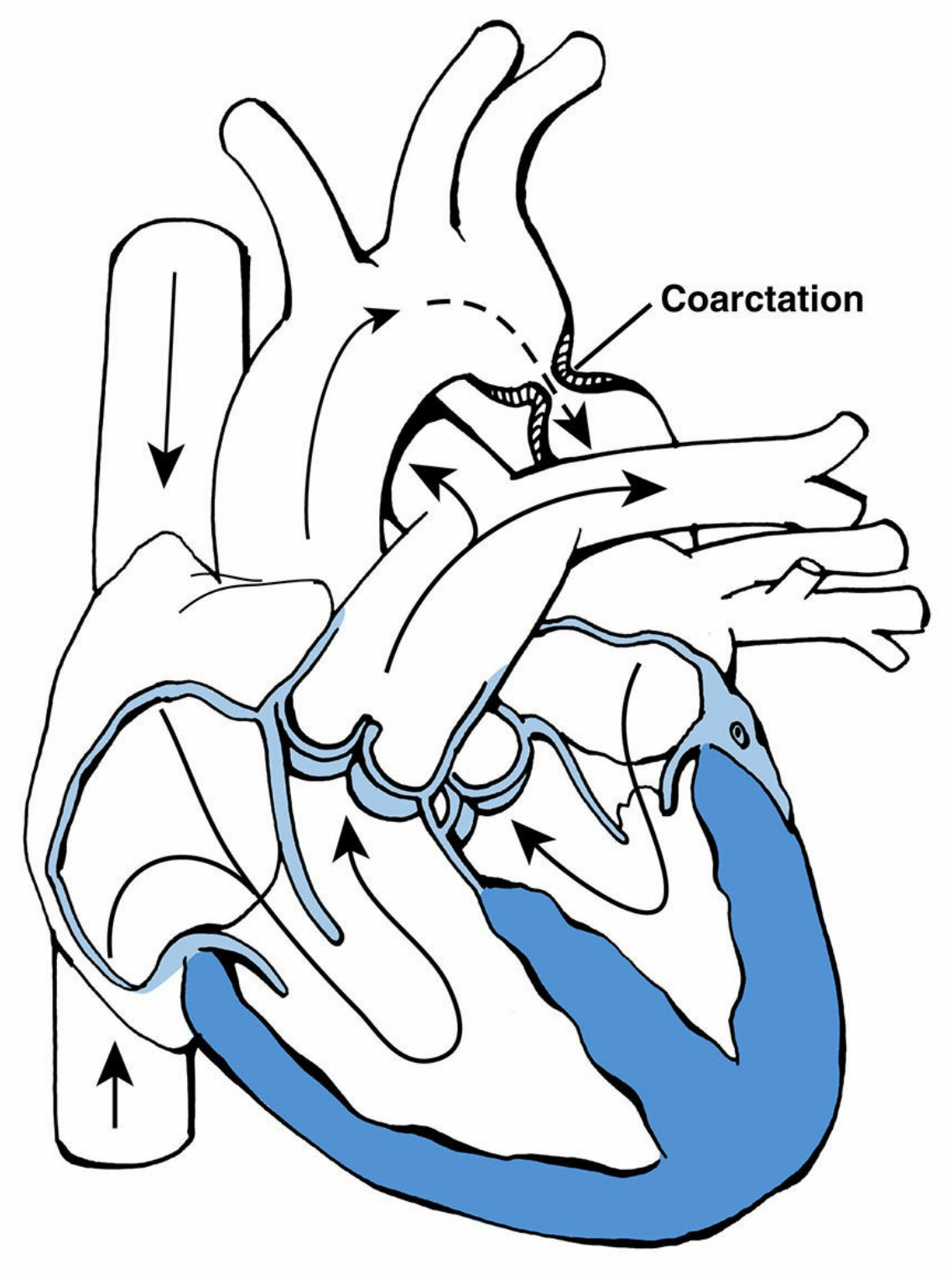

FIGURE 8.5 Coarctation of the aorta. Arrows designate the direction of blood flow.

IV. Cyanotic Congenital Heart Disease

A. **General concepts**
   1. **Cyanosis** may be peripheral, central, or both. **Peripheral cyanosis** is usually caused by vasomotor instability or vasoconstriction as a result of cold temperature. **Central cyanosis,** especially apparent in the tongue and inner mucous membranes, may be attributable to both cardiac and noncardiac causes:
      a. **Noncardiac causes of central cyanosis** include pulmonary disease, sepsis, hypoglycemia, polycythemia, and neuromuscular diseases that impair chest wall movement.
      b. The **most common cardiac causes of central cyanosis** may be remembered using the **mnemonic "5 T's":** *t*etralogy of Fallot, *t*ransposition of the great arteries, *t*ricuspid atresia, *t*runcus arteriosus, and *t*otal anomalous pulmonary venous return.
   2. **Evaluation**
      a. A thorough physical examination is essential.
      b. Other initial studies include pulse oximetry (in room air), complete blood count (CBC), arterial blood gas (ABG), ECG, and CXR. The degree of pulmonary blood flow seen on CXR may be useful in diagnosis (**Table 8-3**).
      c. The **100% oxygen challenge test** suggests cyanotic CHD when the PaO_2 fails to rise above 100–150 mm Hg despite the administration of 100% oxygen.
      d. **Echocardiogram** provides a definitive diagnosis.
   3. **Diagnosis.** The distinguishing features of the five types of cyanotic CHD are presented in **Table 8-4**.

B. **Tetralogy of Fallot** is the **most common cause of central cyanosis** presenting beyond the newborn period.
   1. **Definition.** Tetralogy of Fallot has four anatomic components:
      a. **VSD**
      b. **Overriding aorta** (aorta overlies a portion of the ventricular septum)
      c. **Pulmonary stenosis**
      d. **Right ventricular hypertrophy (RVH)**
   2. **Pathophysiology.** As a result of right ventricular outflow tract obstruction (RVOT; pulmonary stenosis), blood flows from right to left across the VSD and into the overriding aorta (**Figure 8-6**), resulting in cyanosis.
   3. **Clinical features.** Signs and symptoms depend on the severity of the RVOT obstruction.
      a. **Physical examination** findings include an **increased right ventricular impulse** because of RVH, a **systolic ejection murmur representing pulmonary stenosis** (see Table 8-2), and **cyanosis**.
      b. **Cyanosis** depends on the interplay between the resistance to flow out of the RVOT and the SVR. **It is important to remember that blood always flows from higher resistance to lower resistance.**
         1. **Actions** that **decrease SVR** (e.g., exercise, vasodilation, volume depletion) or **increase resistance through the RVOT** (e.g., crying, tachycardia) **increase right-to-left shunting** from the right ventricle through the VSD and to the aorta, resulting in cyanosis.
         2. **Actions** that **increase SVR** or **reduce resistance through the RVOT** (e.g., volume infusion, systemic hypertension, Valsalva maneuver, bradycardia) **reduce the right-to-left shunt** through the VSD and therefore increase systemic arterial saturation.
         3. Neonates with **severe pulmonary stenosis or atresia** present with **cyanosis**

immediately after birth once the PDA closes. These patients are dependent on the PDA for blood flow to the lungs.

c. **Tetralogy of Fallot (hypercyanotic or "tet") spells** are characterized by **sudden cyanosis** and **decreased murmur intensity**.
   1. The **trigger** may be any condition such as dehydration or crying that decreases arterial oxygen saturation.
   2. With desaturation, the child typically becomes irritable and cries, which increases resistance through the RVOT, worsening the cyanosis by increasing the right-to-left shunt, resulting in a cycle of increasing cyanosis.
   3. **Alterations in consciousness and hyperpnea** may occur as a result of severe hypoxia and acidosis.
   4. **To compensate,** a child with tetralogy of Fallot learns to **squat**. This position (knee-chest position in an infant) increases venous return to the heart and increases SVR, thereby decreasing the right-to-left shunt.

4. **Management** (Table 8-5 describes management of "tet" spell)
   a. **Definitive management is complete surgical repair** at 2–8 months of age.
   b. Some infants with unfavorable anatomy (small pulmonary arteries) or with recurrent tetralogy of Fallot spells may initially undergo a palliative procedure to improve systemic saturation and encourage pulmonary growth. The procedure involves either a modified **Blalock–Taussig shunt** (Gore-Tex graft interposed between the subclavian and ipsilateral pulmonary artery) or balloon pulmonary valvuloplasty. In the neonate who requires intervention, transcatheter stenting of the PDA is also an option.

C. **TGA**
1. **Definition.** TGA occurs when the aorta arises from the right ventricle and the main pulmonary artery from the left ventricle.
2. **Pathophysiology (Figure 8-7)**
   a. Pulmonary and systemic circulations are **in parallel,** rather than in series.
   b. **Adequate saturation** can only be achieved by **shunting blood from one circulation to the other** through a PFO, ASD, VSD, or PDA.
3. **Clinical features**
   a. **Cyanosis is present at, or shortly after, birth.** Cyanosis is more intense if the PFO is small. Cyanosis is less intense if the PFO is large or if there are additional sites of mixing, such as an ASD or VSD.
   b. **Physical examination** findings include an infant who appears healthy but who has **central cyanosis,** a quiet precordium, and on auscultation, a **single S_2** (because the aortic valve is anterior and the pulmonary valve is posterior in TGA, the closure of the pulmonary valve is difficult to hear) and **no murmur**.
4. **Management**
   a. Neonates may require **initial management** with **PGE** to improve oxygen saturation by keeping the ductus patent. **Emergent balloon atrial septostomy** (Rashkind procedure) is an often life-saving procedure that increases the size of an ASD or PFO.
   b. **Definitive repair** is the **arterial switch operation,** in which the great arteries are incised above their respective valves and implanted in the opposite root. The coronary arteries are attached to the original aorta, so the coronaries must also be incised and reimplanted.

D. **Tricuspid atresia**
1. **Definition.** Tricuspid atresia is defined anatomically as a plate of tissue located in the floor of the right atrium in the location of the tricuspid valve. An **ASD or PFO is always**

present to allow for right-to-left shunting.

2. **Pathophysiology.** Whether a VSD is also present plays a significant role in determining the clinical presentation.
    a. If no VSD is present and the **ventricular septum is intact, pulmonary atresia is also present**. For blood to flow to the lungs in this situation, a PDA must be present. As the PDA constricts after birth, visible cyanosis develops.
    b. If a **VSD is present,** blood flow from the left ventricle through the VSD and into the pulmonary artery (left-to-right shunt) may be adequate, facilitating acceptable systemic oxygen saturations (**Figure 8-8**).
3. **Clinical features. Signs also depend on anatomy.**
    a. Patients with an **intact ventricular septum and pulmonary atresia** have **no murmur** and a **single S_2**.
    b. Patients with a **VSD** have a VSD murmur (see Table 8-2).
    c. **ECG** shows right atrial enlargement, **left axis deviation (LAD),** and **left ventricular hypertrophy (LVH)**. **Tricuspid atresia is the only cause of cyanosis in the newborn period that results in LAD and LVH.**
4. **Management.** Treatment includes staged surgery with eventual **Fontan** procedure at 3–6 years of age.
    a. A bidirectional **Glenn shunt** (SVC is anastomosed to the right pulmonary artery) is usually performed at 4–6 months of age.
    b. In the **Fontan procedure,** flow from the inferior vena cava is directed into the pulmonary arteries, usually by means of an extracardiac conduit.
    c. The **net result of these procedures is systemic venous return directed to the pulmonary artery**.

E. **Truncus arteriosus**

1. **Definition.** Truncus arteriosus occurs when the aorta and pulmonary artery originate from a common artery, the **truncus**. The pulmonary arteries usually originate from the proximal truncus, and the truncal valve may be regurgitant or stenotic. A VSD is almost always present.
2. **Pathophysiology.** Because the aorta and pulmonary arteries are connected and the pulmonary arteries are well formed, excessive blood flows to the lungs and CHF commonly develops. Mixing of desaturated and saturated blood occurs within the truncus, and patients are commonly only *mildly desaturated and mildly cyanotic* (**Figure 8-9**).
3. **Clinical features**
    a. **Signs and symptoms of CHF are common.**
    b. **Physical examination findings**
        1. **Systolic ejection murmur** at the base from increased flow across the truncal valve and a **single S_2** caused by the presence of only one atrioventricular (AV) valve
        2. **Diastolic murmur** of flow across the mitral valve at the apex as a result of excessive pulmonary blood flow that returns to the left atrium
        3. **High-pitched diastolic murmur** at the base indicates regurgitation of the truncal valve.
        4. **Management.** Treatment includes medications for CHF and surgical repair early in infancy to close the VSD and to place a valved cadaveric homograft between the right ventricle and pulmonary artery.

F. **TAPVR**

1. **Definition.** TAPVR occurs when the pulmonary veins drain into the systemic venous side rather than into the left atrium. Sites of pulmonary venous drainage include

supracardiac (into the right SVC or innominate vein), cardiac (into the right atrium or coronary sinus), and infracardiac (into the portal system and eventually into the inferior vena cava).

2. **Pathophysiology. Systemic and pulmonary venous blood enters the right atrium and mixes together.** As a result, this mixture of systemic and pulmonary venous blood is present in all four cardiac chambers (blood also passes across a PFO or ASD into the left side of the heart), pulmonary arteries, and aorta, resulting in desaturated systemic blood and visible cyanosis on examination.
3. **Clinical features**
    a. **Cyanosis** is present, and if severe, may indicate obstruction of pulmonary venous return.
    b. **Pulmonary flow murmur** at the mid-left sternal border is caused by increased pulmonary blood flow.
4. **Management.** Treatment is surgical repair shortly after diagnosis. The pulmonary veins are anastomosed to the back of the left atrium, and the PFO or ASD is closed.

Table 8-3
Cyanotic Congenital Heart Disease Lesions and Pulmonary Blood Flow on Chest Radiograph

Increased Pulmonary Flow	Decreased Pulmonary Flow
Transposition of the great arteries	Tetralogy of Fallot
Total anomalous pulmonary venous return	Pulmonary atresia
Truncus arteriosus	Tricuspid atresia
Single ventricle	

Table 8-4
Key Differentiating Features of Cyanotic Congenital Heart Disease

Heart Lesion	Physical Examination Findings	ECG	Chest Radiograph
Tetralogy of Fallot	Systolic ejection murmur of pulmonary stenosis (Table 8-2)	RVH	Upturned cardiac apex (**"boot shaped"**)
			Decreased PVM
			Right aortic arch (commonly)
Transposition of the great arteries	No murmurSingle S_2	Normal or RVH	Small heart with narrow mediastinum ("**egg-on-a-string**" appearance)
			Increased PVM
Tricuspid atresia	No murmur and single S_2 if no VSD	LAD, RAE, and LVH	Small heart
	If VSD is present, systolic murmur of VSD (Table 8-2)		Decreased PVM
Truncus arteriosus	Single S_2	CVH	Enlarged heart
	Systolic ejection murmur along the left sternal border		Increased PVMRight aortic arch (commonly)
	Diastolic murmur at the apex		
Total anomalous pulmonary venous return	Pulmonary ejection murmur along the left sternal border	RVH and RAE	Enlarged heart in older, unrepaired children with supracardiac drainage ("**snowman appearance**")
			Increased PVM
			If obstruction is present, small heart and pulmonary edema

RVH = right ventricular hypertrophy; *LAD* = left axis deviation; *RAE* = right atrial enlargement; *CVH* = combined ventricular hypertrophy; *PVM* = pulmonary vascular markings; *LVH* = left ventricular hypertrophy; *VSD* = ventricular septal defect; S_2 = second heart sound.

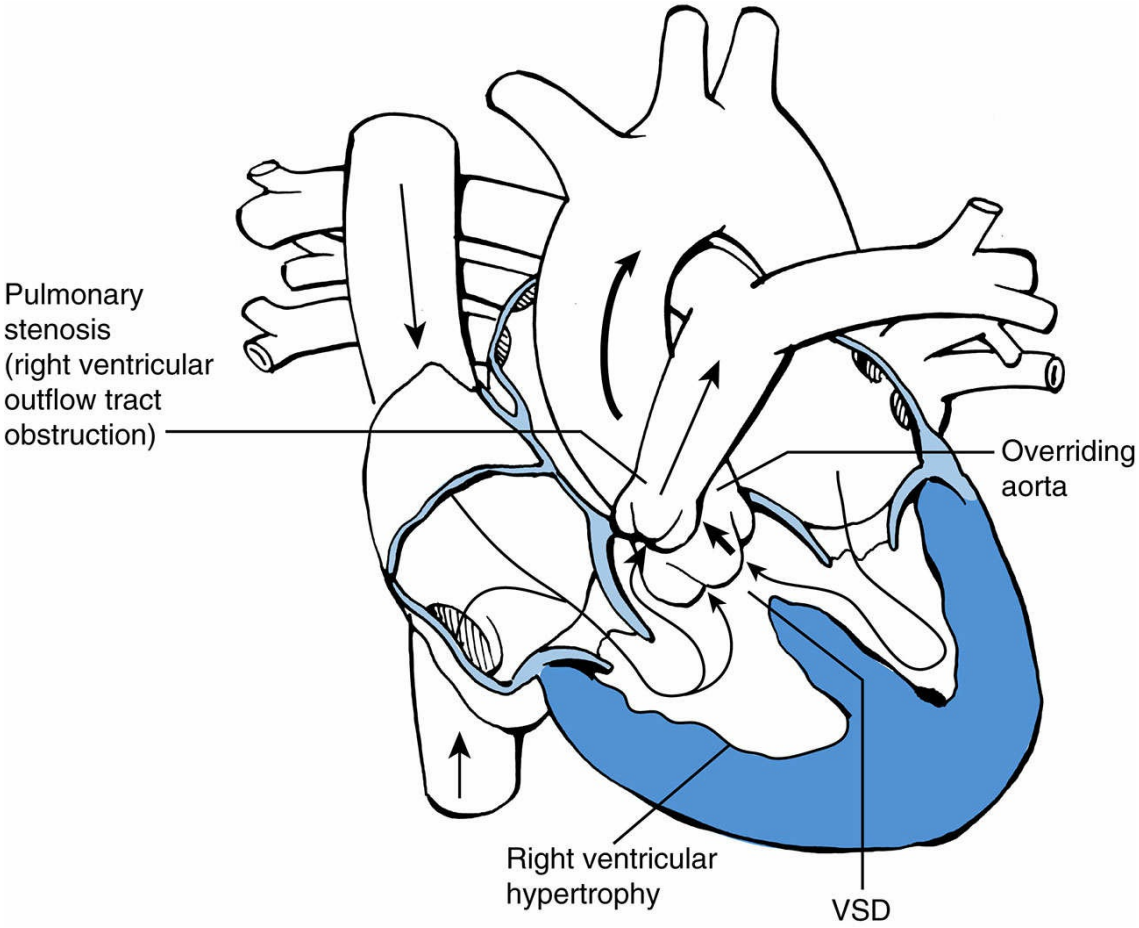

FIGURE 8.6 Tetralogy of Fallot. Arrows designate direction of blood flow. Thick arrows designate increased blood flow. *VSD* = ventricular septal defect.

Table 8-5
Acute Management of a Tetralogy of Fallot ("Tet" or Hypercyanotic) Spell

Placement in knee-chest position (mimics squatting position)
Intravenous fluid bolus
Oxygen
Sedation (morphine) to decrease agitation, which will then slow down the heart rate
β-Adrenergic blocker (e.g., propranolol) to slow down the heart rate, reduce contractility in right ventricular outflow tract, and augment pulmonary blood flow
Intravenous sodium bicarbonate to correct any acidosis from prolonged hypoxia
Correction of significant anemia with transfusion
Rarely, general anesthesia and surgery

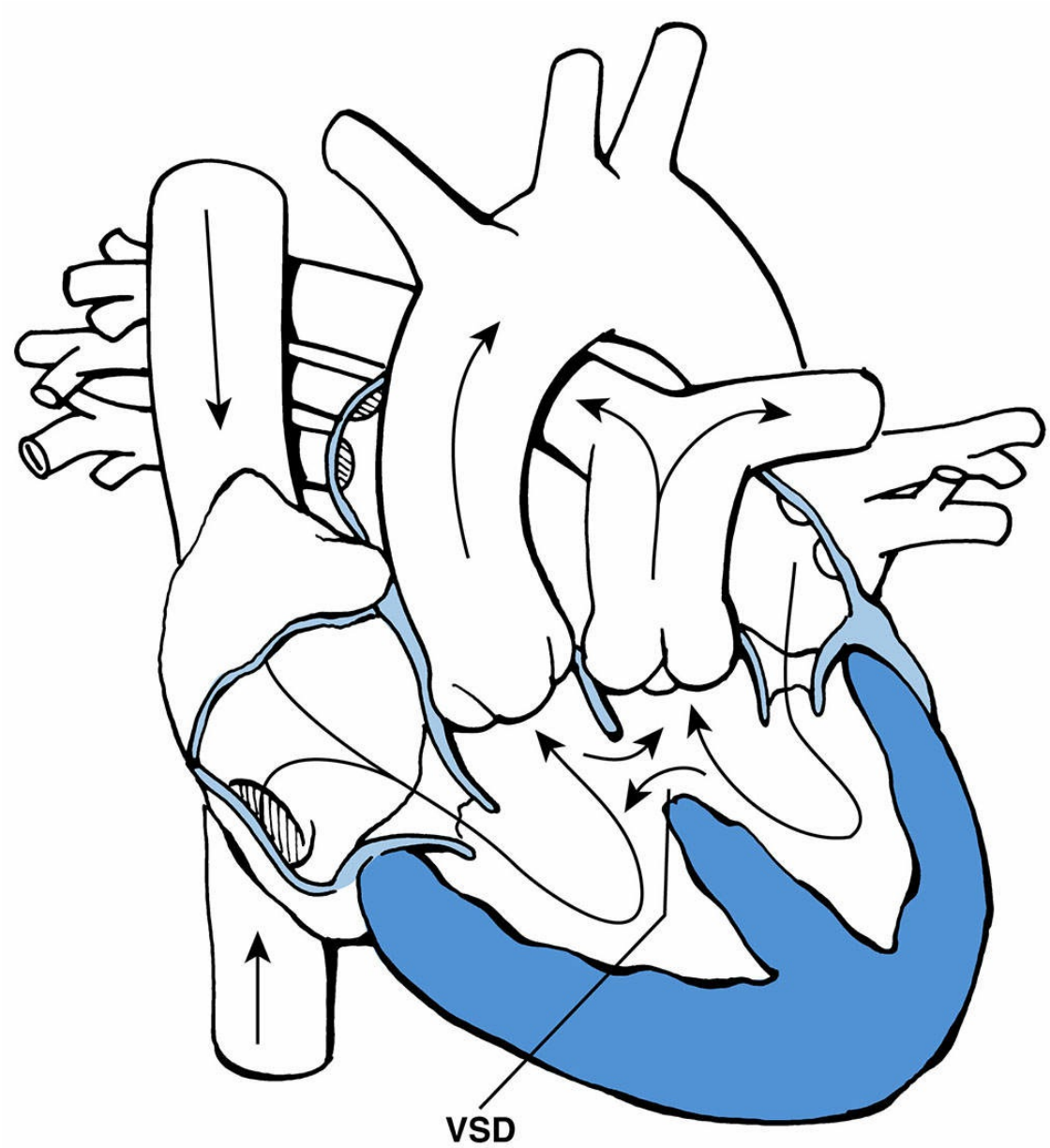

FIGURE 8.7 Transposition of the great arteries. A ventricular septal defect (VSD) is present. Arrows designate the direction of blood flow.

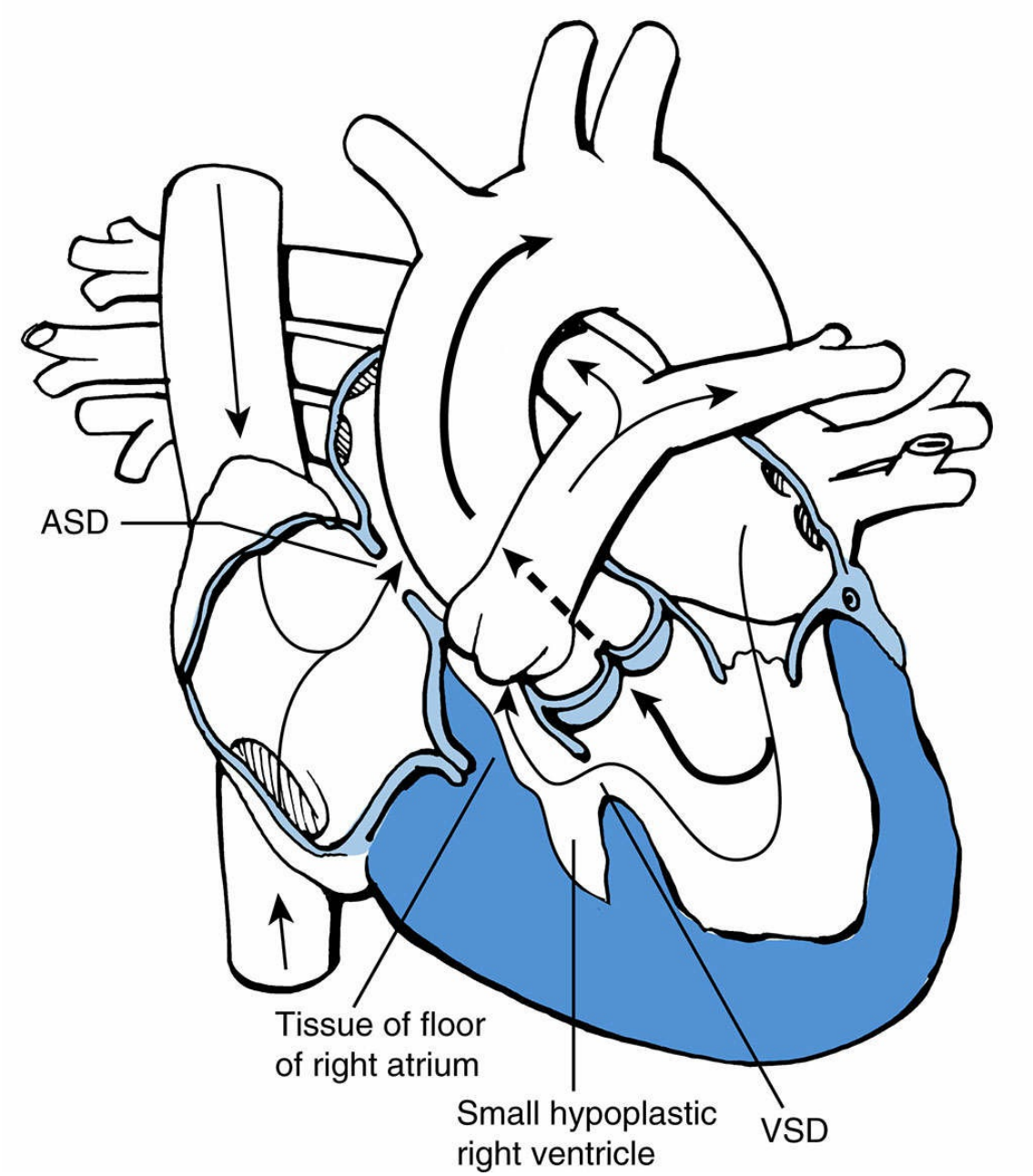

FIGURE 8.8 Tricuspid atresia with atrial septal defect (ASD) and ventricular septal defect (VSD). Arrows designate direction of blood flow. Thick arrows designate increased blood flow.

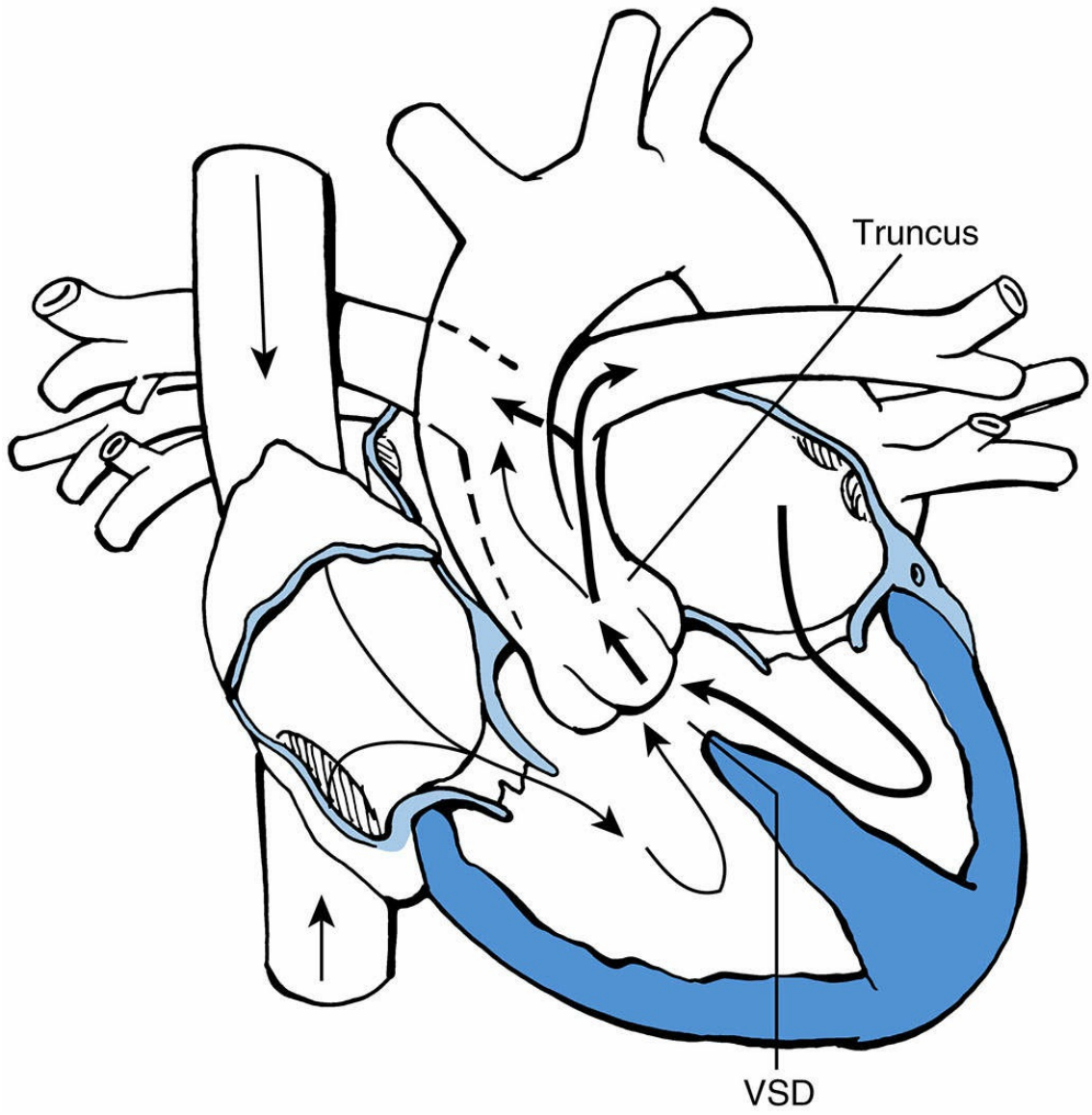

FIGURE 8.9 Truncus arteriosus with ventricular septal defect (VSD). Arrows designate the direction of blood flow. Thick arrows designate increased blood flow. The dashed line represents the other border of the pulmonary artery at the back of the truncus.

V. Acquired Heart Disease

A. **Kawasaki disease** is the **most common cause of acquired heart disease in children in the United States** and is discussed in Chapter 16, section II.

B. **Acute rheumatic fever** is the **most common cause of acquired heart disease worldwide** and is discussed in Chapter 16, section VI.

C. **Infective endocarditis**

1. **Definition.** Infective endocarditis is a microbial infection of the endocardium, or internal surface, of the heart.
2. **Epidemiology**
   a. **Eighty percent of cases** occur in children who have **structural abnormalities of the heart**. Endocarditis may also occur in anatomically normal hearts, especially in the hearts of neonates and infants.
   b. **Fifty percent of cases** occur soon **after cardiac surgery**.
3. **Etiology**
   a. **Gram-positive cocci,** including **α-hemolytic streptococcus** *(Streptococcus viridans)* and ***Staphylococcus*** species, are the most common bacterial agents.
   b. **Gram-negative** organisms are **rare causes of endocarditis**.
   c. **Fungal** endocarditis is extremely rare but may occur in a chronically ill child.
4. **Pathophysiology**
   a. **Bacteria are introduced into the blood** spontaneously or during an invasive procedure. Bacteria then infect injured cardiac endothelium.
   b. **Fibrin and platelets adhere** to the site of injury, creating a growth or **vegetation**. The vegetation may lead to incompetency of a valve.
   c. **Distal manifestations** of disease may occur, including embolic phenomena and immunologic sequelae (e.g., nephropathy).
5. **Clinical features (Table 8-6)**
6. **Diagnosis.** History and physical examination, in addition to several other studies, are the basis of diagnosis.
   a. **Blood culture** is the **single most important laboratory test**. Three sets of aerobic and anaerobic blood cultures should be drawn to maximize the likelihood of identifying the infecting organism. Because bacteremia is continuous in endocarditis, blood cultures may be drawn even if the patient is afebrile.
   b. The **erythrocyte sedimentation rate (ESR)** is usually **elevated,** unless polycythemia is present. (Patients with cyanotic CHD may have reactive erythrocytosis.)
   c. **Other acute-phase reactants** (e.g., **rheumatoid factor**) are found in **50% of patients**.
   d. Although **transthoracic echocardiography** may detect vegetations, **transesophageal echocardiography is more sensitive** than transthoracic echocardiography at identifying vegetations. However, a normal echocardiogram does not exclude endocarditis.
7. **Management**
   a. **Intravenous antimicrobial therapy** is directed against the identified organism. Treatment for 4–6 weeks is required.
   b. Because endocarditis is rarely a medical emergency, therapy may be safely withheld until an adequate number of blood cultures are obtained and the diagnosis is confirmed.
8. **Antibiotic prophylaxis** for endocarditis is recommended before invasive procedures in certain patients. Such procedures include dental work likely to produce bleeding, surgery (including tonsillectomy), and invasive gastrointestinal or urologic procedures.

This applies to a patient with any of the following circumstances:

a. A prosthetic cardiac valve or prosthetic material used for a valve repair
b. A personal history of infective endocarditis
c. CHD
    1. Unrepaired cyanotic CHD
    2. Completely repaired CHD with prosthetic material or device by surgery or catheter intervention within 6 months after the procedure
    3. Repaired CHD with residual defects at or adjacent to a site of a prosthetic patch or device
d. A patient with a history of cardiac transplantation who develops a cardiac valvulopathy (e.g., valvular regurgitation or stenosis)

D. **Pericarditis**

1. **Definition.** Pericarditis is inflammation of the pericardial space.
2. **Etiology. Causes** most commonly include **infection, collagen vascular disease** (e.g., systemic lupus erythematosus [SLE]), **uremia,** and **inflammatory response after cardiac surgery (postpericardiotomy syndrome)**.
    a. **Viral infection** is the **most common** cause of pericarditis in children. Viruses include coxsackievirus, echovirus, adenovirus, influenza, parainfluenza, and Epstein–Barr virus (EBV).
    b. **Purulent pericarditis** is usually caused by **bacterial infection,** either primary infection or disseminated from pneumonia or meningitis.
        1. ***Staphylococcus aureus*** and ***Streptococcus pneumoniae*** are the most common agents.
        2. Patients with purulent pericarditis have a **high incidence of constrictive pericarditis** owing to the intense inflammatory response.
    c. **Postpericardiotomy syndrome** may occur in as many as one-third of patients whose pericardium has been opened during surgery. Patients typically present 1–6 weeks after cardiac surgery with fever, pleuritis, and pericarditis with or without a pericardial effusion.
3. **Pathophysiology.** Inflammation of parietal and visceral pericardial layers leads to exudation or transudation of fluid and impairment of venous return and cardiac filling.
4. **Clinical features**
    a. **Symptoms** include fever, dyspnea, malaise, and **chest pain most intense while supine and relieved when sitting upright**.
    b. **Physical examination** findings include a **pericardial friction rub, distant heart sounds** if the effusion is large, **pulsus paradoxus** (>10 mm Hg reduction in systolic blood pressure on deep inspiration), and hepatomegaly. **Cardiac tamponade,** or critically impaired LV output due to an acute accumulation of pericardial fluid, may occur and is life-threatening.
5. **Diagnosis**
    a. Pericarditis should be considered in any child with dyspnea and fever, and in any patient who recently underwent cardiac surgery and has hemodynamic instability or nonspecific complaints of dyspnea or malaise.
    b. **Pericardiocentesis,** in which a needle is inserted into the pericardial sac and fluid is withdrawn, is both diagnostic and therapeutic. Fluid should be sent for cell and serologic analysis and for culture.
    c. **ESR,** although not specific for pericarditis, is **elevated**.
    d. **Imaging studies**
        1. **ECG** may show diffuse ST-segment elevations (Figure 8-10) or low-voltage QRS complexes in patients with large pericardial effusions.

2. **CXR** shows an enlarged heart shadow in patients with large effusions.
3. **Echocardiogram** demonstrates the size of the pericardial effusion.

6. **Management**
   a. **Appropriate antibiotics** should be given if bacterial pericarditis is suspected.
   b. **Anti-inflammatory agents,** such as aspirin or steroids, are indicated for viral pericarditis or postpericardiotomy syndrome.
   c. **Drainage** of pericardial effusion by placement of a pericardial catheter or surgical window may be indicated.

E. **Myocarditis**

1. **Definition.** Myocarditis is inflammation of the myocardium, characterized by cellular infiltrate and myocardial cell death.
2. **Epidemiology.** Myocarditis is one of several **common causes of sudden death** in young athletes. Overall incidence is unknown, but evidence of myocarditis is apparent in 20% of children who die suddenly.
3. **Etiology**
   a. **Viruses,** such as enteroviruses, especially coxsackievirus
   b. **Bacteria,** such as *Corynebacterium diphtheriae, Streptococcus pyogenes, S. aureus,* and *Mycobacterium tuberculosis*
   c. **Fungi,** such as *Candida* and *Cryptococcus*
   d. **Protozoa,** such as *Trypanosoma cruzi* (Chagas disease)
   e. **Autoimmune diseases,** such as SLE, rheumatic fever, and sarcoidosis
   f. **Kawasaki disease**
4. **Pathophysiology.** Myocarditis may involve infectious infiltration that damages myocardial cells, or activated lymphocytes that are misdirected to attack the myocardium.
5. **Clinical features**
   a. **Myocarditis frequently follows a viral or flul-ike illness.**
   b. **Symptoms** include dyspnea and malaise.
   c. **Physical examination** shows **resting tachycardia, muffled heart sounds,** gallop heart rhythm, hepatomegaly, tachypnea, and pulmonary rales.
6. **Diagnosis**
   a. **Laboratory studies. Findings** include **elevated ESR, creatine kinase (CK)–MB fraction, troponin,** and **C-reactive protein (CRP)** in most, but not all, cases. The etiologic organism may be identified by viral serology or polymerase chain reaction (PCR) of **endomyocardial biopsy** specimens.
   b. **Accessory tests**
      1. **ECG** may show T-wave and ST-segment changes. Atrial or ventricular dysrhythmias may be present.
      2. **Echocardiogram** shows an anatomically normal heart with **global ventricular dysfunction**. Pericardial effusion and valvular regurgitation may be present.
7. **Management.** Treatment is largely supportive, with use of inotropic agents, diuretics, and afterload-reducing drugs as needed. Intravenous immune globulin may be helpful in some cases. **Cardiac transplantation** is an option for patients with CHF refractory to medical management.
8. **Prognosis.** Outlook is variable. Mortality is 10–20% and is especially high in young infants and in those with ventricular dysrhythmias.

F. **Cardiomyopathy**

1. **Definition.** Cardiomyopathy is defined as an abnormality of cardiac muscle manifested by systolic or diastolic dysfunction. There are three types of cardiomyopathy, including dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathy.

2. **Dilated cardiomyopathy**
    a. **Definition.** This primary myocardial disorder (i.e., not attributable to valvular, coronary artery, pericardial, or CHD) is characterized by ventricular dilation and reduced cardiac function.
    b. **Etiology.** Dilated cardiomyopathy is frequently **idiopathic,** but many causes have been identified.
        1. **Viral myocarditis**
        2. **Mitochondrial abnormalities**
        3. **Carnitine deficiency**
        4. **Nutritional deficiency,** such as selenium and thiamine deficiency
        5. **Hypocalcemia**
        6. **Chronic tachydysrhythmias**
        7. **Anomalous origin of left coronary artery from the pulmonary artery** (ALCAPA), which results in myocardial ischemia and infarction
        8. **Medications** (e.g., doxorubicin)
    c. **Clinical features.** Signs and symptoms of CHF may be present.
    d. **Diagnosis. Evaluation** should include **viral serologies** and **serum carnitine level**. In addition:
        1. **ECG** shows sinus tachycardia, low cardiac voltage, and ST-segment and T-wave changes. With ALCAPA, evidence of infarction is typically noted, with Q waves in leads I and aVL.
        2. **Echocardiogram** shows a dilated left ventricle with poor ventricular function.
    e. **Management**
        1. **Medical management of CHF**
        2. **Treatment of underlying metabolic or nutritional problem**
        3. **Surgical repair of ALCAPA** (implantation of left coronary artery into the aortic sinus)
        4. **Cardiac transplantation** if CHF is unresponsive to medical management (true for all cardiomyopathies, including those listed below).
3. **Hypertrophic cardiomyopathy**
    a. **Definition.** Hypertrophic cardiomyopathy is LVH in the absence of any systemic or cardiac disease known to cause the hypertrophy. The **most typical anatomic finding is asymmetric septal hypertrophy**.
    b. **Etiology.** Inheritance is **autosomal dominant** in 60% of cases. Infants of mothers with diabetes mellitus may have transient septal hypertrophy.
    c. **Pathophysiology**
        1. **Poor LV filling due to reduced LV compliance**
        2. **Dynamic left ventricular outflow tract (LVOT) obstruction** is present and caused by the anterior mitral leaflet being swept into the subaortic region and coming into contact with the ventricular septum during systole.
        3. Mismatch between myocardial oxygen demand and supply (owing to hypertrophy) may result in myocardial ischemia.
    d. **Clinical features.** Hypertrophic cardiomyopathy is *the most common cause of sudden death in athletes.*
        1. **Symptoms may be absent until syncope or sudden death** occurs, or may include **chest pain and exercise intolerance**.
        2. **Physical examination** shows a classic **harsh, systolic ejection murmur at the apex** that is accentuated with physiologic maneuvers that reduce LV volume, such as **Valsalva or standing** (by reducing LV volume, these maneuvers worsen the outflow obstruction, increasing the intensity of the murmur).

e. **Diagnosis**
    1. **ECG** shows LVH, ST-segment and T-wave changes, LAD, and abnormally deep and wide Q waves in the inferior and lateral leads.
    2. **Echocardiogram** shows the hypertrophy.
f. **Management.** Treatment is generally reserved for patients with symptoms.
    1. **β-Adrenergic blockers or calcium-channel blockers** reduce the LVOT obstruction and improve diastolic compliance.
    2. **Surgical myomectomy** has been recommended for patients with severe obstruction refractory to medical management.
    3. **Antiarrhythmic medications** may be needed, as ventricular dysrhythmias are common.
    4. **Automatic implantable cardioverter defibrillator, or AICD,** is implanted in patients who are felt to be at high risk for ventricular dysrhythmias and sudden death.
    5. *Participation in competitive athletic sports should be prohibited.*
    6. β_2-agonists, such as albuterol, are contraindicated in hypertrophic cardiomyopathy.

4. **Restrictive cardiomyopathy**
    a. **Definition.** Restrictive cardiomyopathy is defined as excessively rigid ventricular walls that impair normal diastolic filling.
    b. **Etiology**
        1. **Amyloidosis**
        2. **Inherited infiltrative disorders** (e.g., Fabry disease, Gaucher disease, hemosiderosis, hemochromatosis)
    c. **Clinical features**
        1. **Symptoms** include **exercise intolerance** (because of limitation of cardiac output), **weakness,** and **dyspnea**.
        2. **Physical examination** shows edema, hepatomegaly, and ascites. These findings are caused by **elevated central venous pressure (CVP)**.
    d. **Management.** Treatment is related to reducing CVP with diuretics and improving diastolic compliance with β-adrenergic blockers and calcium-channel blockers.

Table 8-6
Clinical Features of Bacterial Endocarditis

Symptoms
Fever (most common symptom)
Nonspecific complaints, such as malaise, arthralgia, headache, weight loss, night sweats, and anorexia
Signs
New or changing murmur
Splenomegaly
Microscopic or gross hematuria (as a result of embolism or endocarditis-associated glomerulonephritis)
Splinter hemorrhages (linear hemorrhages beneath the nails)
Retinal hemorrhages
Osler nodes (small, raised pink, red, or blue swollen tender lesions on the palms, soles, or pads of the toes or fingers)
Janeway lesions (small, erythematous hemorrhagic lesions on the palms or soles)
Roth spots (round or oval white spots seen in the retina)

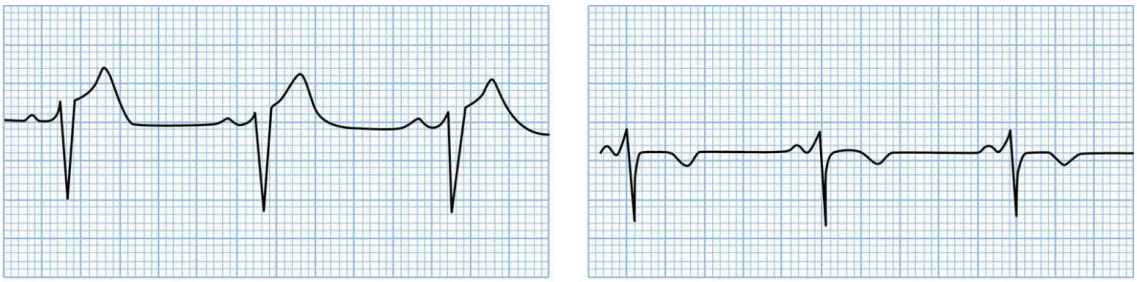

FIGURE 8.10 ST-segment elevation in a patient with acute pericarditis. **A.** Lead V3 shows the ST-segment elevation of acute pericarditis. **B.** Several days later, the same lead shows that the ST segments have returned to baseline and the T waves have inverted. There are no Q waves.

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VI. Dysrhythmias

The most common dysrhythmias of childhood include supraventricular tachycardia (SVT), heart block, and long QT syndrome.

A. **SVT**
   1. **Definition.** SVT is an abnormally accelerated heart rhythm that originates proximal to the bifurcation of the bundle of His. **SVT is the most common dysrhythmia in childhood**. It is necessary to distinguish SVT from sinus tachycardia, as detailed in **Table 8-7**.
   2. **Pathophysiology.** Two types of SVT occur.
      a. **Atrioventricular reentrant tachycardia (AVRT).** Retrograde conduction through an accessory pathway leads to SVT.
      b. **Atrioventricular node reentrant tachycardia (AVNRT).** The conduction abnormality occurs in different pathways within the AV node itself.
      c. When anterograde conduction occurs through a bypass tract between the atria and ventricles, **Wolff–Parkinson–White (WPW) syndrome** is present. WPW is associated with **sudden cardiac death**.
   3. **Clinical features.** Symptoms include **palpitations, chest pain,** dyspnea, and sometimes **altered level of consciousness**. Prolonged SVT may lead to signs and symptoms of **CHF,** especially in the neonate.
   4. **Diagnosis.** WPW may be identified on ECG by the presence of a **delta wave** (i.e., slurred upslope of the QRS complex with a short PR interval; *Figure 8-11*).
   5. **Management**
      a. **Vagal maneuvers**, such as Valsalva, placement of an **ice pack to the face,** unilateral carotid massage, placing the child upside down, and orbital pressure in an older child may all convert SVT into a sinus rhythm.
      b. **Intravenous adenosine** is the primary medication used for acute conversion to a sinus rhythm. Other medications used acutely include propranolol, digoxin, procainamide, and amiodarone.
      c. **Synchronized cardioversion** may be used in patients who are hemodynamically unstable.
      d. **Chronic medical management** typically includes ß-adrenergic blockers.
      e. Patients with WPW should undergo an **exercise stress test** for sudden cardiac death risk stratification. If the delta wave disappears during exercise, the pathway is considered low risk. If the delta wave persists during exercise, patients should be referred to a cardiac electrophysiologist for possible ablation.
      f. **Radiofrequency catheter ablation** may be used to remove the accessory pathway in chronic SVT or in high-risk WPW.

B. **Heart block or AV block**
   1. **Definition and classification**
      a. **Definition. Heart block** is delayed or interrupted conduction of sinus or atrial impulses to the ventricles.
      b. **Classification.** Heart block is classified on the basis of ECG findings (e.g., first, second, or third degree) and by the ratio of atrial to ventricular impulses (e.g., 1:1, 3:1, 3:2, and so on).
         1. **First-degree** AV block is prolongation of the PR interval.
         2. **Second-degree** AV block
            a. **Type I,** also known as **Wenckebach,** is progressive prolongation of the PR interval leading to failed AV conduction.

b. **Type II** is abrupt failure of AV conduction without progressive prolongation of the PR interval.

3. **Third-degree** AV block is a **complete block,** with no conduction of atrial impulses to the ventricles.

2. **Etiology**
   a. **Congenital third-degree AV block** is associated with **children born to mothers with SLE**.
   b. **Postsurgical AV block** may occur as a result of cardiac surgery, especially after closure of a VSD that lies close to the conduction system.
   c. **Bacterial endocarditis** may be associated with AV block.
3. **Clinical features**
   a. First-degree AV block is typically asymptomatic.
   b. Second- and third-degree AV block can have clinical features ranging from being asymptomatic to developing fatigue, dizziness or syncope, and rarely, sudden death.
4. **Management**
   a. No treatment is indicated for first-degree AV block.
   b. No treatment is indicated for type I second-degree AV block.
   c. Cardiac pacemakers are indicated in type II second-degree AV block and symptomatic third-degree AV block.

C. **Long QT syndrome**

1. **Definition.** Long QT syndrome is prolongation of the QT interval. Prolongation increases the risk of lethal ventricular arrhythmias known as **torsades de pointes**.
2. **Etiology**
   a. In **50%** of cases, inheritance is either **autosomal recessive (i.e., Jervell–Lange-Nielsen syndrome, associated with congenital deafness)** or **autosomal dominant (i.e., Romano–Ward syndrome, not associated with deafness)**.
   b. Some cases may result from the use of **drugs,** which may directly, or in combination, prolong the QT interval (e.g., antifungals, phenothiazines, tricyclic antidepressants, erythromycin, terfenadine).
   c. The remainder of cases are likely due to deletions in genes that are normally responsible for repolarization.
3. **Clinical features.** Presenting signs and symptoms include **syncope (most common),** seizure, palpitations, or **sudden cardiac arrest**. Exercise and emotion are often inciting factors.
4. **Diagnosis.** The corrected QT interval (**QTc)** is calculated by taking the measurement of the QT interval divided by the square root of the previous RR interval. Diagnosis of long QT is made on the basis of **ECG** showing a QTc greater than 0.44 seconds (up to 0.49 seconds may be normal in the first 6 months of life).
5. **Management.** Treatment of symptomatic patients includes a β-adrenergic blocker to reduce symptoms, although the QT interval usually remains prolonged. Treatment of asymptomatic individuals is controversial. Other therapeutic modalities include cardiac pacing, left stellate ganglionectomy, and an AICD.

Table 8-7
Features Differentiating Sinus Tachycardia from Supraventricular Tachycardia

Feature	Sinus Tachycardia	Supraventricular Tachycardia
Rate (beats/minute)	<230 in newborns	Frequently >250
<210 in children		
Heart rate variation	Present	Absent

P waves on ECG	Normal (axis is 0°–90°)	Absent or abnormal axis
Predisposing factors	Fever, infection, anemia, and hyperthyroidism	None
Response to intervention (e.g., adenosine, antipyretics, fluids)	Gradual	Rapid

ECG = electrocardiogram.

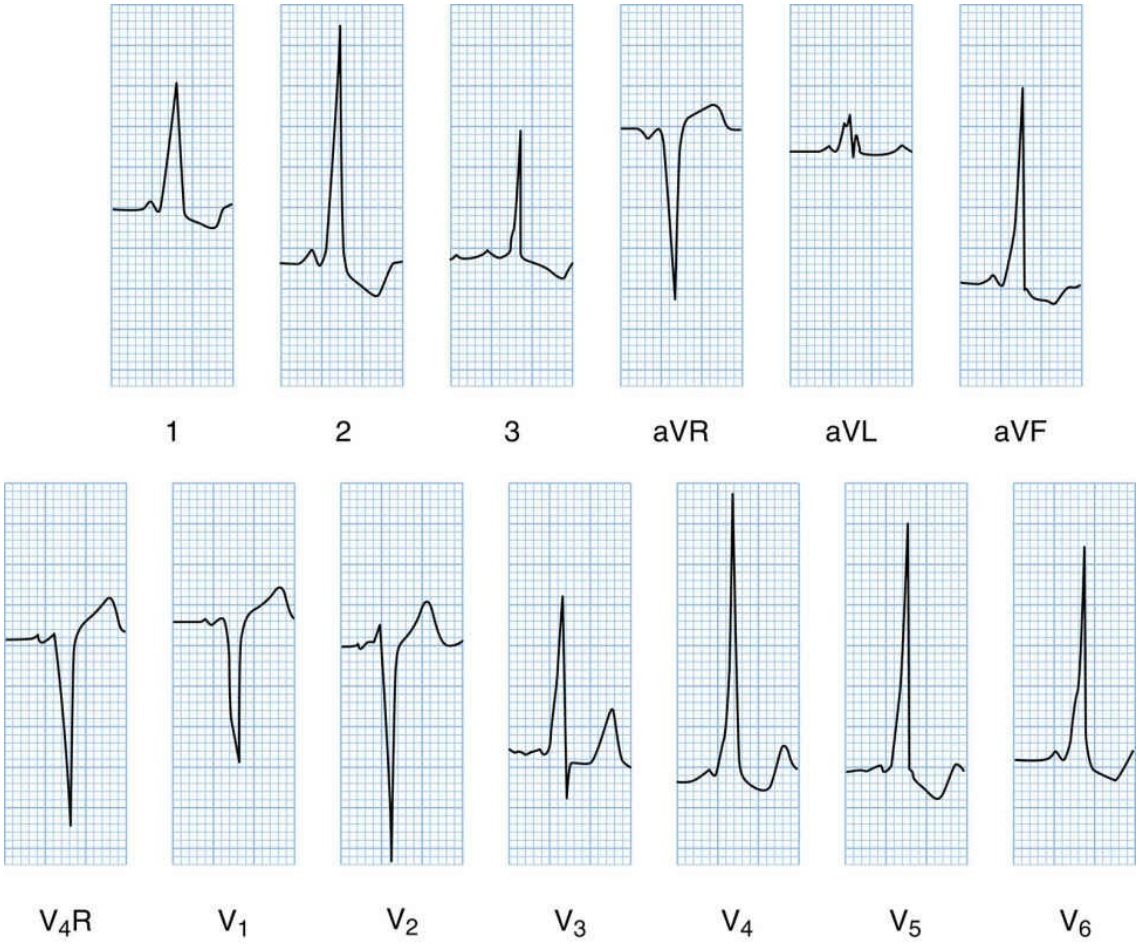

FIGURE 8.11 Electrocardiogram in a patient with Wolff–Parkinson–White syndrome. Note the wide QRS complex, the presence of a delta wave (slurred upstroke of R), and the short PR interval.

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VII. Chest Pain

Chest pain is a common presenting complaint in children and adolescents. However, this symptom is rarely of cardiac origin. **Figure 8-12** schematically presents the differential diagnosis of chest pain.

A. **Cardiac chest pain**
   1. **Pericarditis** is the most common cause [see section V.D].
   2. Chest pain or chest pressure that occurs with exercise or is associated with syncope, shortness of breath, or abnormal heart rhythm should be investigated further by a cardiologist. Appropriate testing (e.g., continuous ECG monitoring, echocardiography, exercise stress test) is necessary.

B. **Noncardiac chest pain.** Common causes include asthma, esophagitis, and costochondritis (tenderness in one or more costochondral joints).

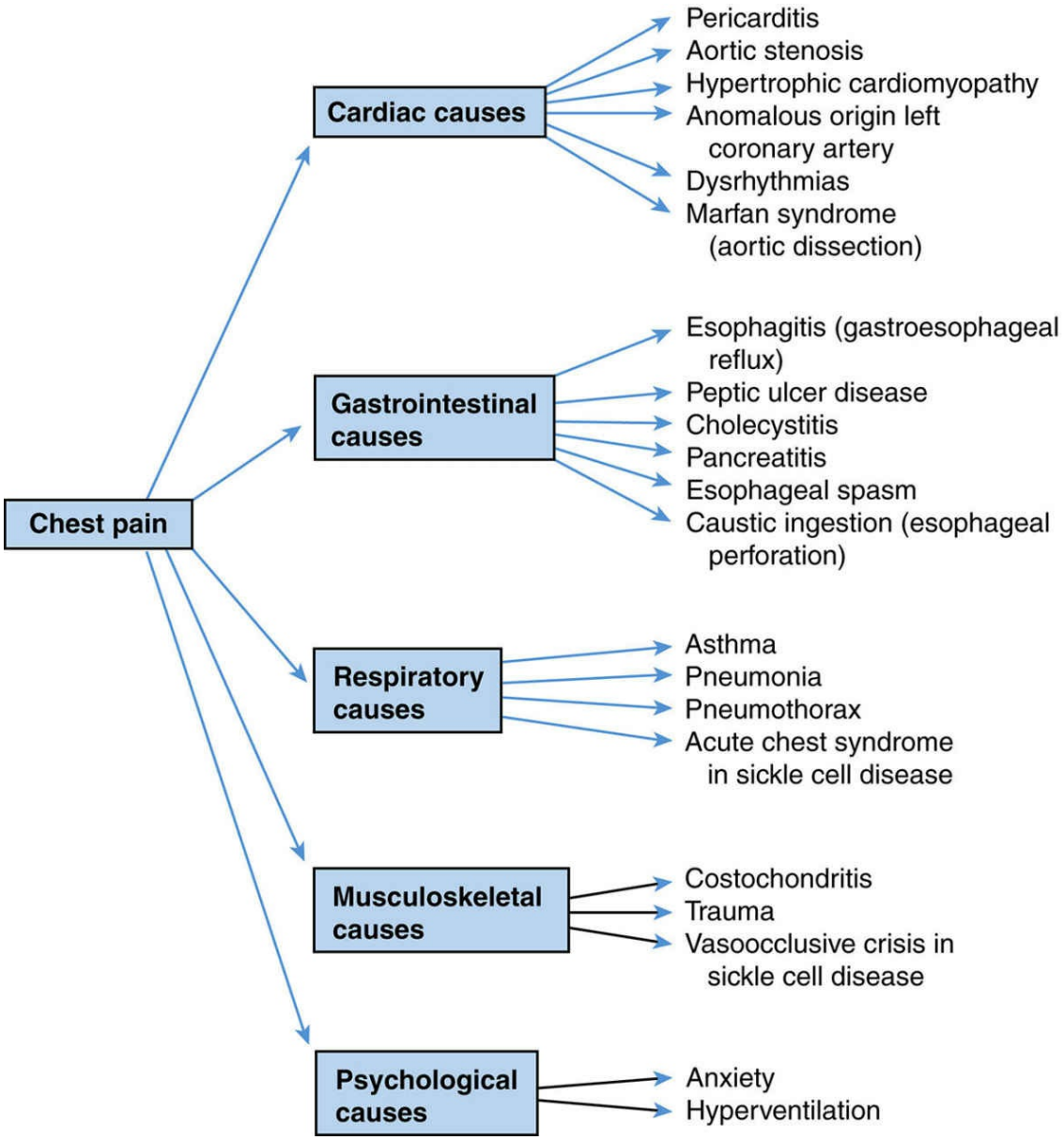

FIGURE 8.12 Differential diagnosis of chest pain in children and adolescents.

Review Test

1. You are called to the newborn nursery to evaluate a 2-hour-old newborn who has suddenly become cyanotic. The oxygen saturation on room air is 69%, and the patient is tachycardic and tachypneic. Oxygen is administered without improvement in the patient's oxygen saturation. On examination, you hear a loud S_2 and no murmur. A chest radiograph shows increased pulmonary vascular markings, a narrow mediastinum, and a small heart. Which of the following would be the next step in management?
   A. Start digoxin.
   B. Refer the patient to surgery for placement of a Blalock–Taussig shunt.
   C. Refer the patient to surgery for repair of a ventricular septal defect.
   D. Proceed with pulmonary balloon valvuloplasty.
   E. Begin infusion of prostaglandin E (PGE).
2. A 20-month-old boy with tetralogy of Fallot is admitted for evaluation of cyanosis that is increasing in frequency. As you conclude your history and physical examination, you witness an episode of cyanosis when the patient's brother makes him cry. As the crying increases, the patient becomes more and more cyanotic. On examination, his cardiac murmur is now much softer than before he began crying. What is the next most appropriate step in management?
   A. Intubate and begin mechanical ventilation.
   B. Administer intravenous dopamine.
   C. Place the patient in a knee-chest position.
   D. Administer subcutaneous epinephrine.
   E. Call for a cardiology consult.
3. A 10-year-old girl is seen for a routine health maintenance evaluation. Five years ago, she underwent surgical repair of coarctation of the aorta. On examination, the blood pressure in her right arm is 173/81 mm Hg, and her oxygen saturation is 97% in room air. Auscultation reveals a systolic ejection murmur audible throughout the precordium. The patient is otherwise asymptomatic. Which of the following would be the most appropriate next step in management?
   A. Check the blood pressure in all extremities.
   B. Refer the patient to a cardiac surgeon promptly.
   C. Obtain an echocardiogram to rule out a bicuspid aortic valve.
   D. Recheck the oxygen saturation in 100% oxygen.
   E. Have the patient return in 6 months for reevaluation.
4. A 7-year-old boy presents with a 3-day history of fever (temperature to 39.7°C [103.5°F]), shortness of breath, and weakness. He also complains of chest pain, which is most intense when he lies down and improves when he sits upright. His past medical history is significant for closure of a ventricular septal defect 2 weeks ago. Which of the following findings is consistent with the most likely diagnosis?
   A. Splinter hemorrhages
   B. Pulsus paradoxus
   C. Heart rate of 260 beats/minute with absent P waves
   D. Prolongation of his QT interval
   E. Tenderness at two of his costochondral joints
5. A 1-month-old female infant is seen in your office for a routine health maintenance evaluation. On examination, you hear a grade 4 holosystolic murmur at the left sternal border. Femoral pulses and oxygen saturation in room air are normal. The infant is otherwise well and growing normally. Which of the following statements regarding this patient's condition is correct?

A. Without intervention, congestive heart failure will develop.
B. Eisenmenger syndrome will eventually occur.
C. Surgical closure of the patent ductus arteriosus is indicated.
D. The murmur may disappear without intervention.
E. Balloon valvuloplasty is indicated.

6. You are called to the nursery to evaluate a male newborn with cyanosis. On auscultation, you hear a single S_2 but no murmur. Pulse oximetry shows an oxygen saturation of 72% in room air. An electrocardiogram reveals left axis deviation and left ventricular hypertrophy. What is his likely diagnosis?
   A. Tetralogy of Fallot
   B. Transposition of the great arteries
   C. Truncus arteriosus
   D. Total anomalous pulmonary venous return
   E. Tricuspid atresia with intact ventricular septum
7. A 4-year-old boy is in the office for a routine health maintenance evaluation. His examination is normal except for multiple deep dental cavities. You plan on referring him for dental evaluation and possible dental extraction. His mother reminds you that he has a "heart condition." Which of the following cardiac conditions requires antibiotic prophylaxis against endocarditis?
   A. Patch repair of ventricular septal defect repaired 4 months ago
   B. History of uncomplicated Kawasaki disease
   C. Wolff–Parkinson–White syndrome
   D. Patent ductus arteriosus
   E. Ostium secundum atrial septal defect
8. You see a 7-week-old male infant with cough and poor feeding. Examination reveals a respiratory rate of 72 breaths/minute and a heart rate of 170 beats/minute. His weight is 7 pounds 6 oz, just 2 oz more than his birth weight. You hear diffuse rales throughout the lung fields and a systolic murmur on auscultation. The liver is 4 cm below the right costal margin. Which of the following conditions is the most likely cause of his signs and symptoms?
   A. Large ventricular septal defect
   B. Ostium secundum atrial septal defect
   C. Small patent ductus arteriosus
   D. Critical or severe aortic stenosis
   E. Mild to moderate pulmonary stenosis
9. A thin 5-year-old boy presents for a routine health maintenance evaluation. He feels well and is growing normally. On examination, you hear a continuous murmur below the right midclavicle. The murmur is loudest while the patient is sitting and disappears while he is supine. The femoral pulses are normal. Which of the following conditions is the most likely diagnosis?
   A. Aortic stenosis with regurgitation
   B. Venous hum
   C. Patent ductus arteriosus
   D. Still's murmur
   E. Pulmonic systolic murmur
10. A 15-year-old boy complaints of chest pain that occurs during basketball practice. He is otherwise healthy and has no history of cardiac problems. Examination is normal except for a harsh systolic ejection murmur at the apex that worsens with standing and the Valsalva maneuver. An electrocardiogram demonstrates left ventricular hypertrophy and left axis deviation. Which of the following is the most appropriate initial management at this time regarding the likely diagnosis?

A. Start propranolol to reduce left ventricular outflow tract obstruction.
B. Admit for urgent aortic balloon valvuloplasty.
C. Reassure the patient that the murmur is innocent and allow complete athletic participation.
D. Admit for surgical myomectomy for septal hypertrophy.
E. Begin albuterol, as the patient's chest pain is likely caused by asthma.

The response options for statements 11–13 are the same. You will be required to select one answer for each statement in the set.

A. Sinus tachycardia
B. Supraventricular tachycardia
C. Third-degree atrioventricular (AV) heart block
D. Wolff–Parkinson–White syndrome
E. Second-degree AV heart block, Wenckebach type
F. Prolonged QT syndrome
G. First-degree AV heart block

For each patient, select the most likely associated heart rhythm abnormality.

1. A female newborn is born to a mother with systemic lupus erythematosus.
2. A 10-year-old girl has congenital deafness.
3. A 5-year-old boy has an electrocardiogram that demonstrates a slurred upslope of the QRS complex.

The response options for statements 14–17 are the same. You will be required to select one answer for each statement in the set.

A. Tetralogy of Fallot
B. Truncus arteriosus
C. Transposition of the great arteries
D. Total anomalous pulmonary venous return with supracardiac drainage
E. Tricuspid atresia with ventricular septal defect

For each clinical description, select the cyanotic congenital heart disease lesion.

1. A male newborn has cyanosis and no heart murmur on auscultation.
2. When a 4-year-old boy with cyanosis squats, his cyanosis improves.
3. A male newborn with cyanosis has an electrocardiogram that demonstrates left ventricular hypertrophy.
4. An 8-year-old boy has a chest radiograph that shows cardiomegaly with a "snowman" appearance.

Answers and Explanations

1. **The answer is E** [IV.C.4]. This patient's clinical presentation and physical examination are most consistent with transposition of the great arteries (TGA). Because the pulmonary and systemic circulations are in parallel, rather than in series, blood must be shunted from one circulation to the other for survival, either by a patent ductus arteriosus or by a patent foramen ovale. Intravenous prostaglandin E (PGE) helps keep the ductus patent, which improves oxygen saturation. In some cases, a balloon atrial septostomy will be indicated. This patient's presentation is not consistent with a ventricular septal defect. Neither digoxin, pulmonary balloon valvuloplasty, nor a Blalock–Taussig shunt is indicated in the management of a patient with TGA.
2. **The answer is C** [IV.B.3.c and Table 8-5]. Tetralogy of Fallot (hypercyanotic or "tet") spells are defined as paroxysmal episodes of hyperpnea, irritability, and prolonged crying that result in increasing cyanosis and decreasing intensity of the heart murmur. This condition is often triggered by crying. Initial management is to increase systemic vascular resistance by placing the patient in a knee-chest position. Other therapeutic modalities include the administration of morphine sulfate, sodium bicarbonate, and intravenous fluids and the use of oxygen. Mechanical ventilation in combination with general anesthesia may be effective but would only be used when other management options fail to reverse the cyanosis. Dopamine and epinephrine are contraindicated because they may worsen the spell. A cardiology consultation may be useful, but the acuity of the patient's clinical presentation requires immediate intervention.
3. **The answer is A** [III.F.3.b]. Restenosis is a known complication from repair of coarctation of the aorta, and these clinical features are consistent with restenosis. Patients with coarctation of the aorta classically present with hypertension in the right arm, and commonly in the left arm, and reduced blood pressures in the lower extremities. Therefore, the most appropriate initial step in this patient would be to obtain blood pressures in all four extremities. Balloon angioplasty with or without endovascular stenting is the treatment of choice for restenosis, rather than surgical repair, after the patient undergoes a complete evaluation. Confirmation of a bicuspid aortic valve is important because it may accompany coarctation in up to half of patients; however, it is not the most appropriate initial step in this patient's management. The oxygen saturation is normal in room air and therefore does not require reassessment in 100% oxygen. Given the significantly elevated blood pressure, it is not appropriate to wait 6 months for reevaluation.
4. **The answer is B** [V.D.2.c, V.D.4]. This patient's clinical presentation is most consistent with pericarditis. The likely cause of his pericarditis is postpericardiotomy syndrome, given the recent closure of his ventricular septal defect before the onset of his symptoms. Postpericardiotomy syndrome is believed to be an autoimmune response to a concomitant viral infection and is associated with opening of the pericardium during cardiac surgery. Pulsus paradoxus, or a greater-than-10 mm Hg drop in systolic blood pressure on deep inspiration, is found in patients with pericarditis. Splinter hemorrhages are noted in patients with endocarditis, which is also associated with fever. Supraventricular tachycardia, which would present as a rapid heart rate with absent P waves on electrocardiogram, may cause chest pain, but the pain would not change with position and fever would be absent. Prolonged QT syndrome is most often associated with syncope and sudden cardiac arrest. Costochondritis is a common cause of chest pain, but fever is not associated with this diagnosis.
5. **The answer is D** [III.D.3]. This patient's murmur is consistent with a small ventricular septal defect (VSD). With a small VSD, a patient is likely to remain asymptomatic with normal

growth and development. Typically, the smaller the VSD, the louder the murmur. Small muscular or membranous VSDs may close on their own without intervention. Small VSDs do not generally result in congestive heart failure or in Eisenmenger syndrome. A patent ductus arteriosus would more commonly present with a machinery-like continuous murmur at the upper left sternal border. Balloon valvuloplasty is not indicated for a VSD.

6. **The answer is E** [IV.D.3 and Table 8-4]. Tricuspid atresia is the only cause of cyanosis in the newborn period that manifests with left axis deviation and left ventricular hypertrophy on electrocardiogram (ECG). Patients with tricuspid atresia without a ventricular septal defect have a single S_2 as a result of the usual coexistence of pulmonary atresia and do not have a murmur. Patients with tetralogy of Fallot present with a systolic murmur of pulmonary stenosis and right ventricular hypertrophy (RVH) on ECG. Patients with transposition of the great arteries also have no murmur and a single S_2 but will have RVH on ECG. Similarly, RVH is present in total anomalous pulmonary venous return, along with a systolic murmur. Truncus arteriosus manifests as combined ventricular hypertrophy with both a systolic and diastolic murmur.
7. **The answer is A** [V.C.8]. Before any invasive procedures that may result in bacteremia, prophylaxis against bacterial endocarditis is required for any patient who had structural heart disease repaired within the past 6 months. Patients with uncomplicated Kawasaki disease and cardiac dysrhythmias, including Wolff–Parkinson–White syndrome, or with acyanotic structural heart defects, such as patent ductus arteriosus, do not require antibiotic prophylaxis.
8. **The answer is A** [I.C.1.a]. This patient's signs and symptoms are consistent with congestive heart failure (CHF). Forms of congenital heart disease that increase pulmonary blood flow, obstruct outflow, or overload portions of the heart through valvular regurgitation are among the many causes of CHF. Of the choices listed, only a large ventricular septal defect, which has a large left-to-right shunt with increased pulmonary blood blow, would cause CHF in a child of this age. Atrial septal defects, small patent ductus arteriosus defects, and mild to moderate pulmonary stenosis do not typically cause CHF. Critical or severe aortic stenosis may cause CHF, but this usually occurs within 24 hours of birth.
9. **The answer is B** [Table 8-1]. This murmur is most consistent with a venous hum, an innocent heart murmur. Aortic stenosis with regurgitation presents with systolic ejection and decrescendo diastolic murmurs. The murmur of a patent ductus arteriosus (PDA) is generally continuous and machinery-like and does not vary with position. Patients with PDAs generally also have brisk pulses. Both a Still's murmur and a pulmonic systolic murmur are innocent systolic murmurs. A Still's murmur is usually a grade 1–3 systolic murmur best heard at the mid-left sternal border. A pulmonic systolic murmur is a grade 1–2 high-pitched systolic murmur best heard at the upper left sternal border. Both the Still's murmur and the pulmonic systolic murmur are loudest supine.
10. **The answer is A** [V.F.3]. This patient's presentation, including the heart murmur and electrocardiogram findings, is consistent with hypertrophic cardiomyopathy. Initial management typically includes medications, such as β-adrenergic blockers or calcium-channel blockers, to reduce the left ventricular outflow tract obstruction and improve ventricular compliance. Aortic balloon valvuloplasty is a treatment for aortic stenosis. In aortic stenosis, the murmur would not be expected to increase with the Valsalva maneuver or with standing. Patients with hypertrophic cardiomyopathy are at risk for sudden death and should be restricted from athletic participation. Myomectomy is recommended for severe obstruction refractory to medical management. Albuterol is a β_2-agonist and is contraindicated in hypertrophic cardiomyopathy.
11. **The answers are C, F, and D, respectively** [VI.A–VI.C]. Congenital third-degree atrioventricular block is a complete heart block, with no conduction of atrial impulses to the ventricles. It is associated with infants born to mothers with systemic lupus erythematosus.

Long QT interval is a lengthening of the QT interval, which increases the risk of lethal ventricular arrhythmias. There are two inherited forms of the disorder, one associated with congenital deafness (autosomal recessive Jervell–Lange-Nielsen syndrome) and one not associated with congenital deafness (autosomal dominant Romano–Ward syndrome). Wolff–Parkinson–White syndrome is a form of supraventricular tachycardia that is identified by the presence of a delta wave (slurred upslope of the QRS complex) on electrocardiogram.

12. **The answers are C, A, E, and D, respectively** [IV.B–IV.D, IV.F, and Table 8-4]. Transposition of the great arteries presents with no murmur and a single S_2 on auscultation. Squatting, or knee-chest positioning, increases systemic vascular resistance, which decreases the right-to-left shunt through a ventricular septal defect in tetralogy of Fallot. It is usually the first maneuver attempted to resolve a "tet" or hypercyanotic spell. Tricuspid atresia is the only cyanotic congenital heart disease lesion that manifests left ventricular hypertrophy on electrocardiogram in the newborn period. The classic chest radiograph in older children with unrepaired total anomalous pulmonary venous return and with supracardiac drainage is cardiomegaly with a "snowman" appearance.

CHAPTER 9

Pulmonology

Lauren J. Witcoff

I. Anatomy and Physiology of the Respiratory System

A. **Development**
   1. By 16 weeks' gestation, the **bronchial tree** has developed. By 26–28 weeks' gestation, sufficient air sacs and pulmonary vasculature have developed so that the fetus is able to survive.
   2. **Alveolarization begins around 36 weeks' gestational age** with most alveoli forming during the first few years of life, followed by a slower rate later in childhood and continuing through adolescence.

B. **Anatomy**
   1. The **right lung contains three lobes,** and the **left lung contains two lobes,** plus the lingula.
   2. **Infants are at higher risk for respiratory insufficiency** than older children and adults because infants have anatomically smaller air passages, less compliant (stiffer) lungs with a more compliant chest wall, and less efficient pulmonary mechanics.
   3. The **cricoid cartilage ring is the narrowest part of pediatric airway**, predisposing to upper airway obstruction with any inflammation or narrowing. *A small incremental decrease in lumen diameter in infants and small children can be critical, resulting in a large increase in airway resistance and increased work of breathing.*
   4. **Congenital malformations** of the respiratory tract may be associated with other congenital anomalies, especially of the cardiovascular system.

C. **Physiology**
   1. **Pulmonary vascular resistance** decreases after birth when the fetal pulmonary and systemic circulations separate and the lungs ventilate for the first time.
   2. The **primary function** of the lungs is gas exchange.
   3. **Lung disorders** may be classified as **obstructive or restrictive**.
      a. **Obstructive defects** are secondary to decreased airflow through narrowed airways. Examples include asthma, bronchiolitis, and foreign body aspiration.
      b. **Restrictive defects** are secondary to processes that decrease lung volume (the amount of air filling the alveoli). Examples include pulmonary edema, scoliosis, pulmonary fibrosis, and respiratory muscle weakness.
   4. During normal respiration, the extrathoracic upper airway narrows during inspiration and the intrathoracic lower airways narrow during expiration.

II. Clinical Assessment of Pulmonary Disease

A. **History** is most important in determining the diagnosis of pulmonary disorders.
   1. The **antenatal, prenatal, and neonatal histories** are very important because complications of pregnancy, fetal or postnatal tobacco exposure, prematurity, and airway instrumentation can predispose to pulmonary problems.
   2. **Past medical history** should include previous respiratory problems, including frequent respiratory tract infections, cough, wheeze, stridor, snoring, and exercise intolerance.
   3. **Review of systems** should include documentation of atopy (asthma), failure to thrive or steatorrhea (cystic fibrosis), choking (aspiration), and recurrent infections (immunodeficiencies).
   4. **Family history** should include assessment for genetic diseases (e.g., cystic fibrosis, asthma).
   5. **Environmental history** is extremely important because fumes, strong odors, tobacco smoke, allergens, animals, and day care attendance may cause or exacerbate pulmonary disease.

B. **Physical examination** should emphasize the chest and respiratory system.
   1. In the general assessment, **assess for evidence of increased work of breathing,** such as tachypnea, nasal flaring, expiratory grunting, and chest wall retractions.
   2. Evaluate the **ears, nose, and throat** for signs of obstruction, atopy, or infection.
   3. **Perform a chest examination.**
      a. **Inspiratory stridor suggests extrathoracic obstruction,** such as in croup and **laryngomalacia** (softening and weakness of laryngeal cartilage during the first year of life, in which the cartilage collapses into the airway, especially when in the supine position).
      b. **Expiratory wheezing suggests intrathoracic obstruction,** such as in asthma and bronchiolitis.
      c. **Crackles or rales suggest parenchymal disease,** such as in pneumonia and pulmonary edema.
      d. **Prolonged expiratory phase and/or a hyperinflated thorax** suggest **obstructive disease**.
      e. **Rapid, shallow breathing and/or a small thorax** suggest **restrictive disease**.
   4. **Assess for related findings in other organs**, such as heart murmurs, a prominent second heart sound (suggests elevated pulmonary artery pressure), eczema, and digital clubbing.

C. **Accessory tests help to evaluate pulmonary function.**
   1. **Imaging studies** may include chest radiograph (CXR), computed tomography (CT) scan, magnetic resonance imaging (MRI), and nuclear studies (e.g., ventilation–perfusion scans). Ultrasound is helpful to localize pleural effusions.
   2. **Arterial blood gas** (ABG) is the gold standard to measure oxygenation (PO_2) and ventilation (PCO2).
   3. **Pulse oximetry** noninvasively measures oxygen saturation (SpO_2).
   4. **Pulmonary function testing** (PFT) helps determine the type and severity of pulmonary dysfunction. The most common PFTs measure airflow as a function of time (**spirometry**) and lung volumes (plethysmography).

D. **Laryngoscopy and bronchoscopy** are performed in some conditions to visualize the upper and lower airways and/or to obtain bronchoalveolar lavage specimens for laboratory analysis. Common indications include **persistent or recurrent cough, stridor, wheezing, and pulmonary infiltrates**.

III. Infectious Disorders of the Respiratory Tract

A. **Epiglottitis (supraglottitis)**
   1. **Definition.** Epiglottitis is **bacterial cellulitis of the supraglottic structures**: epiglottis, arytenoids, and aryepiglottic folds.
   2. **Epidemiology.** The disorder is **most common** in children **2–7 years of age,** with equal incidence in males and females.
   3. **Etiology**
      a. **Infection** with ***Haemophilus influenzae*** **type b (HIB)** was the most common cause before HIB immunization. Epiglottitis is **now rare** because of the success of the HIB immunization program.
      b. **Group A β-hemolytic streptococcus,** *Streptococcus pneumoniae,* and *Staphylococcus* species may also cause epiglottitis.
   4. **Clinical features**
      a. **Abrupt onset** of **rapidly progressive** upper airway obstruction without a prodrome. The following signs and symptoms may occur:
         1. **High fever and toxic appearance**
         2. **Muffled speech** and quiet stridor
         3. **Dysphagia with drooling**
         4. **Sitting forward in tripod position** with neck hyperextension
      b. **Complete airway obstruction** with respiratory arrest **may occur suddenly**.
      c. **Laboratory studies** demonstrate leukocytosis with left shift. **Ninety percent of patients have a positive blood culture,** if the epiglottitis is secondary to HIB.
      d. **Epiglottis** appears like a **"thumbprint" on a lateral radiograph of the neck**.
   5. **Differential diagnosis.** Croup, bacterial tracheitis, and retropharyngeal abscess are diagnoses to also consider. *Table 9-1* compares the clinical features that differentiate supraglottic disorders (e.g., epiglottitis) from subglottic disorders (e.g., viral croup).
   6. **Diagnosis.** Epiglottitis should be suspected on the basis of clinical features. Visualization of a **cherry red** swollen epiglottis is made when the airway is established.
   7. **Management**
      a. **Epiglottitis is a medical emergency.**
      b. **Controlled nasotracheal intubation** should be performed by **experienced personnel in a controlled environment** (e.g., operating room)**.**
      c. **Before intubation, minimize stimulation** while offering humidified oxygen. **Avoid causing distress** or examining the throat with a tongue depressor, as this may cause sudden respiratory arrest.
      d. **Intravenous antibiotic therapy** typically includes a second- or third-generation intravenous cephalosporin to cover HIB and *Streptococcus*. If epiglottitis is secondary to HIB, **rifampin prophylaxis** is indicated for unimmunized household contacts younger than 4 years of age.

B. **Laryngotracheobronchitis (croup)**
   1. **Definition.** Croup syndromes include viral croup and spasmodic croup and are secondary to mucosal **inflammation and edema** of the **subglottic** larynx, trachea, and bronchi.
   2. Epidemiology
      a. **Viral croup** is the **most common cause of stridor.** It typically occurs in children 6 months of age to 4 years of age in the late fall and winter. The male to female ratio is 2:1.
      b. **Spasmodic croup** occurs year round in preschool age children.

3. **Etiology**
    a. **Viral croup is most commonly secondary to parainfluenza viruses.** It may be recurrent owing to lack of complete immunity after initial infection, and because it can be caused by a variety of viruses in addition to parainfluenza.
    b. The cause of **spasmodic croup** is unknown but possibly secondary to a **hypersensitivity reaction**.
4. **Clinical features**
    a. **Viral croup**
        1. **Begins with** an upper respiratory infection prodrome for 2–3 days, followed by stridor and cough.
        2. **Symptoms include inspiratory stridor,** fever, **barky cough,** and hoarse voice, which typically last 3–7 days. Respiratory distress may occur.
        3. **Stridor** and cough **worsen at night and with agitation**.
        4. **Wheezing** may occur if the lower respiratory tract is involved.
        5. **Anterior–posterior radiograph of the neck** demonstrates the **"steeple sign"** of subglottic narrowing.
    b. **Spasmodic croup**
        1. Characteristic acute onset of stridor without fever or other symptoms usually occurs at night.
        2. Spasmodic croup typically recurs and resolves without treatment.
5. **Diagnosis.** Croup should be suspected on the basis of clinical features.
6. **Management**
    a. **Supportive care** may involve hydration, antipyretics, and possibly oxygen, in addition to avoiding agitation. Improvement has been anecdotally noted when patients are exposed to humidified air, although use of cool mist or steam has not been proven efficacious.
    b. A single dose of **systemic corticosteroids,** such as oral or intramuscular dexamethasone, has been shown to reduce croup severity and duration.
    c. **Children with respiratory distress** get transient improvement from **racemic epinephrine aerosols,** which vasoconstrict subglottic tissues.
    d. **Hospitalization** is indicated for children in respiratory distress.

C. **Bacterial tracheitis** is an uncommon, but re-emerging, cause of stridor.
1. **Definition.** Bacterial tracheitis is **acute infectious inflammation of the trachea.**
2. **Etiology.** Causes include *Staphylococcus aureus* (60%), *Streptococcus*, *Haemophilus influenzae,* and *Moraxella catarrhalis.*
3. **Clinical features**
    a. Abrupt deterioration
    b. *Toxicity, high fever,* stridor, brassy cough, choking, and acute respiratory distress secondary to mucus and pus in the trachea
4. **Management.** Bronchoscopy can be both diagnostic and therapeutic to remove secretions and sloughed tissue from the trachea. Appropriate antistaphylococcal antibiotics and airway support are indicated.

D. **Pertussis.** This highly contagious respiratory infection is also known as **"whooping cough."**
1. **Etiology.** ***Bordetella pertussis*** is the major pathogen responsible for infection. *Bordetella parapertussis* causes illness that appears clinically very similar to pertussis.
2. **Epidemiology and pathophysiology**
    a. **Adolescents and adults** whose immunity has waned are the **major source** for pertussis infection of unimmunized or underimmunized children.
    b. Sneezed or coughed droplets are inhaled into airways of close contacts. A toxin is subsequently produced, which damages respiratory cells and enters the

bloodstream.

c. **Infants younger than 6 months of age** are most at risk for **severe disease**.
d. Routine immunization beginning at 2 months of age has been effective in reducing the overall incidence of pertussis infection (see Chapter 1, section III.C.2).

3. **Clinical features**
   a. The incubation period is typically 7–10 days.
   b. Pertussis is characterized by **three stages**.
      1. **Catarrhal stage** (**1–2 weeks**) is characterized by upper respiratory symptoms such as rhinorrhea, nasal congestion, conjunctival redness, and low-grade fever.
      2. **Paroxysmal stage (1–6 weeks)** is characterized by *paroxysms of coughing* that are the hallmark of pertussis. A **whoop** is an inspiratory gasp that may be heard at the very end of a coughing fit (although rarely observed in young infants). The coughing fits are exhausting, and posttussive vomiting is common. Young infants may have **cyanosis, apnea, and choking** during the paroxysms of cough. Between the coughing fits, children appear well and are afebrile.
      3. **Convalescent phase** (**weeks to months**) is a recovery stage in which paroxysmal cough continues but becomes less frequent and severe over time.
4. **Diagnosis**
   a. **Diagnosis is suspected based on clinical features.**
   b. White blood cell (WBC) count is elevated with a significant **lymphocytosis.**
   c. Diagnosis is confirmed by *identification of B. pertussis by nasopharyngeal culture or polymerase chain reaction (PCR).*
5. **Management**
   a. **Hospitalization** of young infants often occurs during the paroxysmal phase because of choking, apnea, or cyanosis. Supportive care and oxygen (if needed) are important therapies.
   b. **Macrolide antibiotics** are given to all patients and close contacts to **prevent the spread of infection**. Antibiotics do not alter the patient's clinical course, unless they are administered during the catarrhal phase or very early in the paroxysmal phase.
   c. **Respiratory isolation** is needed until antibiotics have been given for at least 5 days.

E. **Bronchiolitis**

1. **Definition.** Bronchiolitis is **inflammatory bronchiolar obstruction with cellular debris and mucus plugging, most commonly secondary** to a **viral lower respiratory tract infection**.
2. **Epidemiology**
   a. Bronchiolitis is the **most common lower respiratory tract infection in the first 2 years of life** and the most common cause of hospitalization during the first year.
   b. This disorder **predominantly affects children younger than 2 years of age**.
   c. The male to female ratio is 2:1.
   d. **Epidemics occur from November to April.**
   e. **Risk of infection is increased** with day care attendance, multiple siblings**,** exposure to tobacco smoke, and lack of breastfeeding.
   f. **More significant disease** occurs in patients with **chronic lung disease, congenital heart disease, history of prematurity**, immunodeficiency diseases, and genetic abnormalities, as well as in infants younger than 3 months of age.
3. **Etiology**
   a. **Respiratory syncytial virus (RSV)** is the most common cause.
   b. **Less common** causes include human metapneumovirus, parainfluenza, adenovirus,

rhinovirus, influenza, and coronavirus.

4. **Clinical features**
    a. **Onset is gradual,** with upper respiratory symptoms, such as rhinorrhea, nasal congestion, fever, and cough.
    b. **Progression** of respiratory symptoms includes tachypnea, fine rales, wheezing, and increased work of breathing.
    c. **Hypoxemia** may occur.
    d. **Apnea may occur,** especially in young infants and in children with a history of apnea of prematurity.
    e. **CXR** may reveal **hyperinflation** with air trapping, **patchy infiltrates,** and **atelectasis**.
    f. **Improvement is usually noted within 2 weeks. More than 50% develop recurrent wheezing.**
    g. **Complications** may include **apnea,** respiratory insufficiency, respiratory failure, and death. Bacterial superinfection occurs rarely.
    h. **Immunity is incomplete**, although repeat infections tend to be less severe.
5. **Diagnosis** is made on the basis of clinical features. Virologic testing is available if needed.
6. **Management**
    a. Treatment is **primarily supportive** with nasal bulb suctioning (infants are obligatory nose breathers), hydration, and oxygen as needed for $SpO_2 < 90\%$.
    b. **Hand decontamination (preferably with alcohol-based rubs)** is an essential part of contact isolation to prevent spread of infection.
    c. **Exposure to environmental tobacco smoke should be avoided.**
    d. **Nebulized hypertonic saline may help hospitalized infants, but albuterol, epinephrine, and corticosteroids are no longer recommended.**
    e. **Hospitalization** is indicated for respiratory distress, hypoxemia, apnea, dehydration, or underlying cardiopulmonary disease.
    f. **RSV monoclonal antibody** (palivizumab) may be given prophylactically as five monthly intramuscular injections during RSV season to prevent severe disease in infants with a history of prematurity, chronic lung disease, or hemodynamically significant congenital heart disease.

F. **Pneumonia**

1. **Definition.** Pneumonia involves **infection and inflammation of the lung parenchyma associated with infiltrates on CXR**.
2. **Epidemiology.** Pneumonia is associated with poverty, multiple siblings, exposure to tobacco smoke, and prematurity, as well as urban residence.
3. **Etiology.** Causes may be classified based on the child's age (**Table 9-2**).
    a. **Viruses are the most common cause of pneumonia in all age groups.**
    b. ***S. pneumoniae*** is the single *most common bacterial pathogen* after first few weeks of life.
    c. Staphylococcal pneumonias are often complicated by empyema.
    d. **Recurrent or persistent pulmonary infiltrates** may have many causes and are further differentiated if occurring in a single lobe versus multiple lobes (**Table 9-3**).
4. **Clinical features, diagnosis, and management** vary depending on the etiologic agent.
    a. **Viral pneumonia**
        1. **Symptoms** often begin with upper respiratory complaints, such as nasal congestion and rhinorrhea. Fever, cough, and dyspnea typically follow.
        2. **Physical examination** may demonstrate tachypnea, wheezing, rales, or respiratory distress.

3. **Diagnosis** is suggested by **interstitial infiltrates** on CXR and a **WBC count <20,000 cells/mm^3** with a lymphocyte predominance.
4. **Management** is supportive.

b. **Bacterial pneumonia**
1. **Symptoms** have *more rapid onset and greater severity*. Fever, cough, and dyspnea typically occur without preceding upper respiratory symptoms.
2. **Physical examination** may demonstrate rales, tachypnea, decreased breath sounds, egophony (changes in voice transmission through consolidated lung), and evidence of respiratory distress.
3. **Diagnosis** is suggested by a **WBC count >20,000 cells/mm^3** with a neutrophil predominance, elevated C-reactive protein (CRP), and **lobar consolidation** on CXR.
4. **Management** includes appropriate antibiotics and supportive care.

c. ***Chlamydia trachomatis*** is a cause of **afebrile** pneumonia at **1–3 months** of age, secondary to a perinatal-acquired infection from the maternal genital tract.
1. **Symptoms** include a **staccato-type cough**, dyspnea, and absence of fever. A history of *conjunctivitis after birth may be identified in 50% of patients.*
2. **Physical examination** may demonstrate tachypnea and wheezing.
3. **Diagnosis** is suggested by **eosinophilia** and a CXR with **interstitial infiltrates**. **Definitive diagnosis** is by positive culture, antigen detection, or nucleic acid amplification test from conjunctiva or nasopharynx.
4. **Management** includes an oral **macrolide**.

d. ***Mycoplasma pneumoniae*** is one of the most common causes of pneumonia in older children and adolescents.
1. **Symptoms** include low-grade fever, chills, nonproductive cough, headache, pharyngitis, and malaise. The cough may last 3–4 weeks.
2. **Lung examination** may demonstrate widespread rales. Examination findings are often worse than expected by history.
3. **Diagnosis**
   a. **Positive cold agglutinins** are suggestive but are **not specific**.
   b. *Elevated* **EIA-IgM (enzyme-linked immunoassay for the detection of IgM) is useful; PCR obtained by a nasopharyngeal swab is more sensitive**.
   c. **CXR** findings are variable and may show unilateral or bilateral infiltrates.
4. **Management** includes an oral macrolide, tetracycline, or quinolone.

e. ***Mycobacterium tuberculosis*** should be considered in all patients with risk factors for tuberculosis (see Chapter 7, section XVII.C).

Table 9-1
Differentiating Features of Supraglottic and Subglottic Disorders*

Feature	Supraglottic Disorders	Subglottic Disorders
Stridor	Quiet	Loud
Cough	None	Barky
Voice	Muffled	Hoarse
Dysphagia/drooling	Present	Absent
Fever	High	Low to moderate (croup)
		High (tracheitis)
Toxicity	Present	Absent, unless tracheitis is present
Posture	Neck extended, tripod position	Normal

*Supraglottic disorders include epiglottitis and retropharyngeal abscess. Subglottic disorders include bacterial tracheitis and viral croup.

Table 9-2

Age and Its Relationship to Pneumonia Etiology

Age	Typical Causes
0–3 months	Congenital infections, such as syphilis, toxoplasmosis, CMV, rubella, herpes simplex virus, and tuberculosis
	Intrapartum-acquired infections, such as group B streptococcus (most common infection), Gram negative rods, and *Listeria monocytogenes*
	Postpartum infections, such as RSV and other respiratory viruses
	Afebrile pneumonitis caused by *Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis,* CMV, and PCP
3 months–5 years	Viruses, such as adenovirus, influenza A and B, parainfluenza, HMPV, and RSV (note that RSV pneumonia is generally uncommon beyond 2–3 years of age)
	Bacteria, most commonly *Streptococcus pneumoniae,* but may also include *Staphylococcus aureus* and HIB
Age 6 and older	*Mycoplasma pneumoniae* and *Chlamydia pneumoniae* increasingly common
	Viruses, such as adenovirus, influenza A and B, HMPV, and parainfluenza
	Bacteria, most commonly *S. pneumoniae*

CMV = cytomegalovirus; *RSV* = respiratory syncytial virus; *HMPV* = human metapneumovirus; *HIB* = *Haemophilus influenzae* type b; *PCP* = *Pneumocystis jiroveci* pneumonia.

Table 9-3

Causes of Recurrent or Persistent Pulmonary Infiltrates

Single Lobe	Multiple Lobes
Intraluminal obstruction	Aspiration
Foreign body	Impaired gag or swallow
Tumor	Esophageal obstruction or dysmotility, GERD
Mucus plug	Mucociliary clearance dysfunction
Extraluminal obstruction	Cystic fibrosis
Enlarged lymph node from infection or malignancy	Ciliary dyskinesia (e.g., immotile cilia syndrome)
	Bronchopulmonary dysplasia (chronic lung disease)
Structural abnormalities	Congenital heart disease
Bronchial stenosis	α_1-antitrypsin deficiency
Bronchiectasis	Sickle cell disease
Right middle lobe syndrome	Hypersensitivity pneumonitis
Congenital lung abnormalities, such as cysts or sequestration	Pulmonary hemosiderosis
	Asthma
	Immunodeficiency diseases

GERD = gastroesophageal reflux disease.

IV. Noninfectious Disorders of the Respiratory Tract

A. **Asthma (reactive airway disease)**
   1. **Definition**
      a. Asthma is a **chronic inflammatory** disorder of the airways that causes recurrent episodes of wheezing, cough, dyspnea, and chest tightness.
      b. **Symptoms** are typically associated with widespread, variable **airflow obstruction that is at least partially reversible,** either spontaneously or with therapy.
      c. **Inflammation** causes **airway hyperresponsiveness** to many stimuli.
   2. **Epidemiology.** Asthma is the **most common chronic pediatric disease**.
      a. Between 50 and 80% of children who have asthma develop symptoms before their fifth birthday.
      b. Most patients with recurrent episodes of viral-triggered wheezing during their first year of life do not become asthmatics. This risk is increased if the child has a **positive asthma predictive index**. A positive asthma predictive index is either
         1. **One of the following**: physician diagnosis of atopic dermatitis, parental history of asthma, or evidence of sensitization to aeroallergens **OR**
         2. **Two of the following**: wheezing apart from colds, sensitization to foods, ≥4% eosinophils on CBC differential
      c. **Higher prevalence and severity in** African American, Puerto Rican, and **low socioeconomic populations**.
   3. **Etiology**
      a. **Predisposing factors** involve interplay between host and environment, including multiple interacting genes, atopy, family history of asthma, and exposure to tobacco smoke. Viral respiratory infections, diet, and pollution can increase susceptibility in predisposed patients.
      b. **Triggers** of exacerbations include respiratory infections, exercise, cold air, emotions, allergens, gastroesophageal reflux, and exposure to pollutants.
      c. Asthma may accompany other acute or chronic lung diseases, such as cystic fibrosis.
   4. **Pathophysiology.** Increased production and infiltration of inflammatory cells and mediators result in **smooth muscle bronchoconstriction, airway mucosal edema, increased secretions with airway plugging, and possible airway wall remodeling**.
   5. **Clinical features**
      a. **Typical features during an exacerbation** include tachypnea, dyspnea, nasal flaring, retractions, and multiphonic wheezing with a prolonged expiratory phase.
      b. Some patients have **only chronic or recurrent cough (especially at night)**.
      c. **CXR** often reveals **hyperinflation, peribronchial thickening, and patchy atelectasis**.
      d. **PFTs** reveal **increased lung volumes and decreased expiratory flow rates**.
   6. **Diagnosis**
      a. **The basis of diagnosis** is clinical features and usually a therapeutic response to a bronchodilator trial.
      b. **Spirometry** (possibly with bronchoprovocation) can support diagnosis and should be attempted in a child 5 years of age or older. It can show airflow obstruction, which reverses following administration of bronchodilators.
      c. **"All that wheezes is not asthma."**
         1. Differential diagnosis of acute wheezing (*Figure 9-1*)
         2. Differential diagnosis of recurrent or chronic wheezing (*Figure 9-2*)

7. **Management.** Therapy is initiated based on **asthma severity,** and is subsequently adjusted to obtain the goal of **asthma control,** with reduction of ongoing impairment as well as prevention of future risk.
    a. **Assessment and monitoring** are performed at each visit to assess asthma control, medication administration technique, and patient adherence, as well as to address concerns.
    b. **Education** is provided for self-monitoring and to reinforce self-management with oral demonstrations and written instructions. A spacer device (valved holding chamber) is recommended for administration of metered-dose inhalers.
    c. Measures are recommended to **control environmental factors** (e.g., avoidance of allergens, pollutants, irritants) and **treat comorbid** conditions (e.g., allergic rhinitis, gastroesophageal reflux, obesity, stress).
    d. **Medications are prescribed and titrated using a stepwise approach.** National guidelines classify asthma treatment by severity for three different age groups: 0–4 years, 5–11 years, and 12 years and older. *Table 9-4* reviews the classification of asthma and initiating therapy. *Table 9-5* reviews the stepwise approach to managing asthma long term.
        1. Asthma is usually classified as **"intermittent"** if symptoms and/or short-acting beta- agonist (SABA) use are ≤2 days/week, nighttime awakenings are ≤2×/month, and corticosteroid-requiring exacerbations are 0–1×/year. Treatment is with an **short-acting beta-2 agonist (SABA), usually albuterol,** as needed for quick relief of symptoms.
        2. Patients with more frequent symptoms are classified as **mild, moderate, or severe "persistent"** asthma and require long-term controller medications, in addition to SABA for quick relief of symptoms.
            a. **Inhaled corticosteroids (ICS)** are the most effective long-term control therapy for all ages. Start with low dose for mild persistent asthma.
            b. **Leukotriene modifiers (leukotriene receptor antagonist [LTRA])**, such as montelukast, are alternative although less effective controllers.
            c. With increased symptoms/severity (**moderate–severe persistent asthma**), consider increasing the ICS dose and/or adding an inhaled **long-acting beta-agonist (LABA)**, theophylline, or LTRA.
        3. Long-term control therapy with low-dose ICS or montelukast should also be considered for children who are 0–4 years of age and who have had ≥4 episodes of wheezing in the past year that lasted >1 day and affected sleep AND who have a positive Asthma Predictive Index.
        4. To prevent **exercise-induced bronchospasm**, pretreatment with SABA or LTRA is recommended, in addition to a warm-up period.
        5. **Acute exacerbations** are treated with repetitive or continuous inhaled SABA, a short course of systemic corticosteroids, and supplemental oxygen as needed.

B. **Cystic fibrosis (CF)**
1. **Definition.** CF is a **chronic progressive multisystem genetic disorder with major manifestations in the respiratory, gastrointestinal (GI), and reproductive systems**.
2. **Epidemiology**
    a. CF affects **1 in 3000 Caucasians and is less common in Hispanics, African Americans, and Asians**.
    b. **Five percent of Caucasians are carriers.**
    c. **Median age of survival** has increased to 41 years with CF center–based care.
3. **Etiology.** CF is an **autosomal recessive** disease resulting from genetic mutations on **chromosome 7**. **2000 known mutations cause a wide spectrum of phenotypes ranging**

from mild and atypical to severe and classic.

4. **Pathophysiology**
    a. The **genetic defect** produces an **abnormal cystic fibrosis transmembrane conductance regulator (CFTR) protein** that causes sodium and chloride transport dysfunction in exocrine epithelial cells and submucosal glands.
    b. **In the lungs, abnormal thick, viscous mucus** results in **airway obstruction, inflammation, and infection causing bronchiectasis**.
5. **Clinical features**
    a. **Recurrent** or **chronic respiratory symptoms, steatorrhea, and failure to thrive** (FTT) are typical **presenting features**. Clinical expression is variable. **See Figure 9-3** for the multisystem signs and symptoms of CF.
    b. **Chronic, recurrent sinopulmonary disease includes** chronic productive cough, dyspnea, lung hyperinflation, lung crackles, wheezing, pansinusitis, nasal polyps, digital clubbing, and progressive hypoxemia.
        1. **PFTs** show **decreased respiratory flow rates** (consistent with obstruction) and eventually **decreased lung volumes** (consistent with restriction).
        2. **Pneumonia** develops as the lungs become colonized, first with *Staphylococcus aureus* and later with mucoid *Pseudomonas aeruginosa*.
        3. **Common pulmonary complications** include hemoptysis, pneumothorax, **recurrent pneumonia exacerbations,** severe bronchiectasis, allergic bronchopulmonary aspergillosis, pulmonary fibrosis, cor pulmonale, and eventually respiratory failure.
    c. **GI and nutritional abnormalities, include pancreatic insufficiency** in **90%** of patients, with malabsorption predisposing to malnutrition, deficiencies of vitamins A, D, E, and K, and FTT, with possible later complication of CF-related diabetes mellitus.
    d. **Salt depletion syndromes secondary to sweat electrolyte losses**
    e. **Male urogenital abnormalities, including congenital absence of the vas deferens**
6. **Diagnosis** requires the following:
    a. **One or more** characteristic phenotypic features **or** positive family history **or** increased immunoreactive trypsinogen (IRT) on newborn screen **AND**
    b. **Laboratory evidence** of abnormal CFTR function, including sweat chloride >60 mmol/L **or** two CFTR mutations **or** a characteristic ion transport abnormality across the nasal epithelium
7. **Management. Goals are to preserve the lung function, optimize nutrition, and both prevent and treat complications, while maintaining quality of life.**
    a. **Airway clearance therapies** (e.g., postural drainage and percussion, chest wall oscillating vest) combined with **mucus-altering therapies** (e.g., DNase, hypertonic saline) to remove abnormal secretions
    b. **Antibiotics (inhaled, oral, IV)** to control chronic airway infection and treat acute pulmonary exacerbations
    c. **High-calorie diet, pancreatic enzyme replacement, fat-soluble vitamins** (A, D, E, and K), and **insulin**, if needed, to optimize nutritional status
    d. **Anti-inflammatory therapy** (e.g., high-dose ibuprofen, but not corticosteroids) to treat chronic airway inflammation
    e. **Mutation-specific disease-modifying therapies** (e.g., ivacaftor) to correct gene defects
    f. **Oxygen** as needed for hypoxemia
    g. **Lung transplantation**
    h. **Psychosocial support** for patients and families

C. **Bronchopulmonary dysplasia (BPD; also termed chronic lung disease of infancy [CLDI]; see also Chapter 4, section VI.G.2.a)**
   1. **Definition.** Infants with lung disease of prematurity who require supplemental oxygen ≥28 postnatal days are classified as having mild, moderate, or severe BPD, depending on the level of respiratory support needed.
   2. **Epidemiology.** BPD follows exposure of premature lungs to various antenatal and postnatal insults. Risk increases with increased prematurity and decreased birth weight.
   3. **Etiology and pathophysiology**
      a. Previously, the development of BPD followed treatment with high FiO_2 (fraction of inspired oxygen) and aggressive mechanical ventilation, which resulted in diffuse airway damage, smooth muscle hypertrophy, polymorphonuclear cell (PMN) inflammation, and parenchymal fibrosis.
      b. The current BPD phenotype is manifest primarily by impaired alveolar and vascular development secondary to extreme prematurity. "New" BPD has milder airway injury, inflammation, and fibrosis than "old" BPD because of improved neonatology practices.
      c. Decreased and simplified alveoli result in less surface area for gas exchange.
   4. **Clinical features** vary and range from transient oxygen dependency to a prolonged need for ventilatory support.
      a. **Diminished oxygenation** (decreased PaO_2) and **hypercarbia** (increased $PaCO_2$) are often found on ABG testing.
      b. **Chronic increased work of breathing** with intermittent episodes of tachypnea, wheezing, sputum production, and respiratory distress.
      c. **Frequent respiratory tract infections,** airway hyperreactivity, and pulmonary hypertension may result.
      d. **CXR** is diffusely hazy to coarsely irregular and may remain abnormal for several years.
      e. **Nonpulmonary manifestations** include increased caloric needs, feeding intolerance, delayed growth, and neurodevelopmental sequelae.
   5. **Management**
      a. Goals of treatment are to minimize the lung damage, promote growth of new lung tissue, maintain optimal oxygenation, and prevent complications.
      b. Most important therapy is **supplemental oxygen,** which may be needed after discharge to home.
      c. **Optimize high caloric intake** for growth.
      d. Consider bronchodilators, diuretics, and/or fluid restriction to transiently improve pulmonary function.
      e. **Prevent complicating infections** through avoidance of ill contacts, appropriate immunization practices, and RSV prophylaxis.
      f. **Avoid passive smoke exposure.**
      g. Focus on **early identification and treatment of complications,** such as subglottic stenosis, gastroesophageal reflux disease, and tracheobronchomalacia.
   6. **Prognosis.** Pulmonary symptoms and disease usually **improve with time and lung growth**. Some patients have increased risk of rehospitalization, continued airway hyperreactivity, exercise limitation, delays in development, and poor tolerance of respiratory infections. There is a possibility of risk of developing chronic obstructive pulmonary disease (COPD) during adulthood.

D. **Foreign body aspiration**
   1. **Epidemiology.** Children **3 months–5 years** of age are at greatest risk for small object aspiration.

2. **Etiology. Typical aspirated objects** include seeds, popcorn, hot dogs, candy, grapes, and small toy parts.
3. **Clinical features depend on location and biologic reactivity** of the material aspirated.
    a. **History** may elicit **choking episode** in 50–80% of cases.
    b. **Laryngotracheal foreign bodies** (extrathoracic) result in cough, hoarseness, and **inspiratory stridor**.
    c. **Bronchial foreign bodies** (intrathoracic; right bronchus slightly more common than left)
        1. **Asymmetric findings on auscultation**
        2. **Complete** obstruction with atelectasis, **partial ball-valve** obstruction with unilateral emphysema, **or no obstruction** that initially can be asymptomatic.
        3. **Localized wheezing, persistent pneumonia,** chronic cough, or hemoptysis
    d. **Esophageal foreign bodies may compress the trachea, producing respiratory symptoms.**
4. **Diagnosis** is challenging. **Have a high index of suspicion!**
    a. **A radiopaque object is evident on CXR in only 15% of cases.**
    b. **Consider inspiratory and expiratory films,** or **bilateral decubitus films** in young children who cannot inspire and expire on command, or fluoroscopy to identify air trapping distal to a foreign body.
5. **Management**
    a. **Basic life support** is the initial management for a severe choking episode.
    b. **Natural cough,** if present, is the most effective expulsive mechanism.
    c. **Foreign bodies** that **remain in the airway** must be removed by **bronchoscopy**.

E. **Apnea, apparent life-threatening event (ALTE), Brief resolved unexplained event (BRUE), sudden infant death syndrome (SIDS), and obstructive sleep apnea syndrome (OSAS)**
1. **Definitions**
    a. **Apnea of infancy** is the unexplained **cessation of breathing for ≥ 20 seconds, or a shorter respiratory pause associated with bradycardia, cyanosis, pallor, or hypotonia** in a full-term infant.
        1. **Respiratory pause** may be **central** (no respiratory effort), **obstructive** (efforts at respiration are made but are unsuccessful, usually because of upper airway obstruction), or both.
        2. **Short central apnea** for ≤1**5 seconds is normal** at all ages.
    b. **Apnea of prematurity** is the unexplained cessation of breathing for ≥ 20 seconds in a premature infant (see also Chapter 4, section IX). This usually resolves by 37–40 weeks postconceptual age.
    c. **Periodic breathing** is a normal breathing pattern in young infants with three or more respiratory pauses lasting at least 3 seconds each, with less than 20 seconds of normal respiration in between.
    d. **ALTE/BRUE** is a frightening event characterized by some combination of apnea, color change, change in muscle tone, choking, or gagging, in which recovery occurs only after stimulation or resuscitation.
    e. **SIDS** is the sudden death of a child younger than 1 year of age that is unexplained after a thorough investigation, including a complete autopsy, an examination of the death scene, and a review of the clinical history.
    f. **OSAS** is a disorder of breathing during sleep that is characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns. Obstructive sleep apnea (OSA) is typically worse during rapid eye movement (REM) sleep. Ongoing OSA is associated with risk for neurocognitive

and cardiovascular morbidity.

2. **Epidemiology**
    a. *SIDS* reaches its **peak incidence at 2–4 months** of age, and 95% of cases occur before 6 months of age.
    b. **Risk factors for SIDS**
        1. **Prone sleeping position**
        2. **Soft bedding, overbundling,** and **overheating**
        3. **Prematurity**
        4. Being the **twin of a sibling who died of SIDS**
        5. **Low birth weight** or growth retardation
        6. **Recent illness**
        7. **Lack of breastfeeding**
        8. **Maternal smoking, drug abuse, or infection**
3. **Etiology**
    a. **Apnea of prematurity** is usually caused by **immature central respiratory center control**.
    b. **Obstructive apnea** may be secondary to **craniofacial anomalies, adenotonsillar hypertrophy, obesity, or hypotonia**.
    c. The **cause of SIDS is unknown**.
    d. **No definite cause and effect relationship** has been proven among apnea, ALTE/BRUE, and SIDS.
4. **Differential diagnosis of ALTE/BRUE**
    a. **Seizure disorder**
    b. **Gastroesophageal reflux disease (GERD)**
    c. **Upper airway obstruction**
    d. **Intracranial mass lesion**
    e. **Sepsis or other infections,** including RSV, pertussis, and meningitis
    f. **Metabolic abnormalities, including electrolyte imbalance** and **hypoglycemia**
    g. **Inborn errors of metabolism**
    h. **Arrhythmia,** including **long QT syndrome**
    i. **Abnormal central control of breathing**
    j. **Munchausen by proxy**
    k. **Nonaccidental trauma** (shaken baby syndrome)
5. **Evaluation**
    a. **Detailed history and physical examination,** especially HEENT (head, eyes, ears, nose, and throat), is essential.
    b. **Further testing** is based on clinical impression from the history and physical examination and may include the following:
        1. **Hospital observation** and monitoring
        2. **Blood work**, including complete blood count, ABG, electrolytes, and evaluation for infection
        3. **CXR, electrocardiogram, and electroencephalogram**
        4. **Multichannel recording (sleep study),** which simultaneously evaluates oxygen saturation, airflow, chest wall movement, and cardiac rhythm
        5. **Barium esophagram or pH probe study** to evaluate for **GERD**
        6. **Imaging** studies of the head and neck
        7. **Workup** for **metabolic disease**
6. **Management**
    a. For infant apnea and ALTE**, teach caregivers cardiopulmonary resuscitation techniques**.

b. For moderate–severe OSAS, consider adenotonsillectomy and/or continuous positive airway pressure (CPAP) therapy.
c. *Home cardiorespiratory monitors should not be prescribed to prevent SIDS,* and the following prevention strategies should be followed:
    1. **Sleep on the back**
    2. **Firm bedding without pillows or blankets**
    3. **Avoid overheating**
    4. **Smoke-free environment**
    5. **Early prenatal care and regular well-child care**
    6. **Breastfeed**

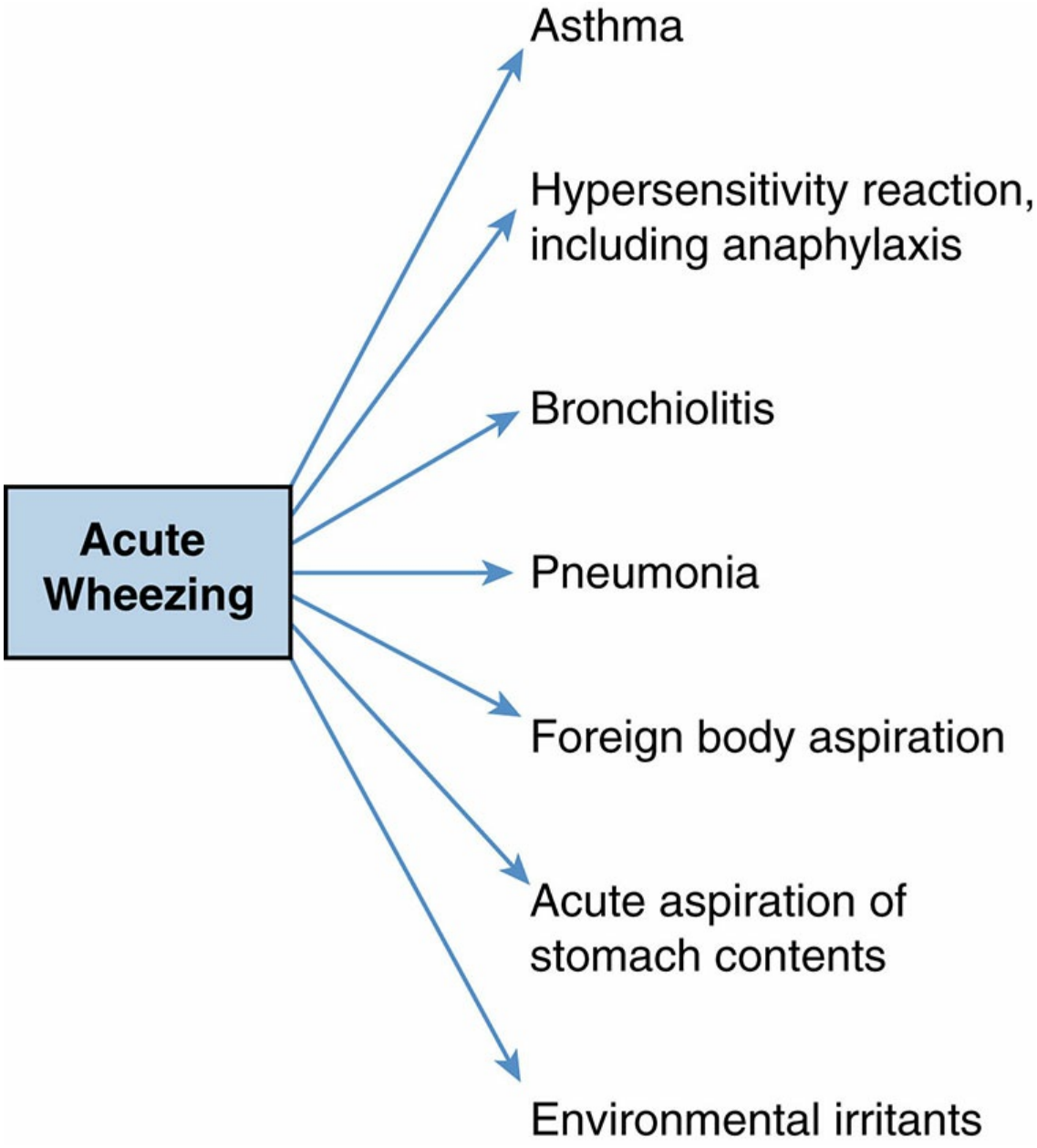

FIGURE 9.1 Differential diagnosis of acute wheezing.

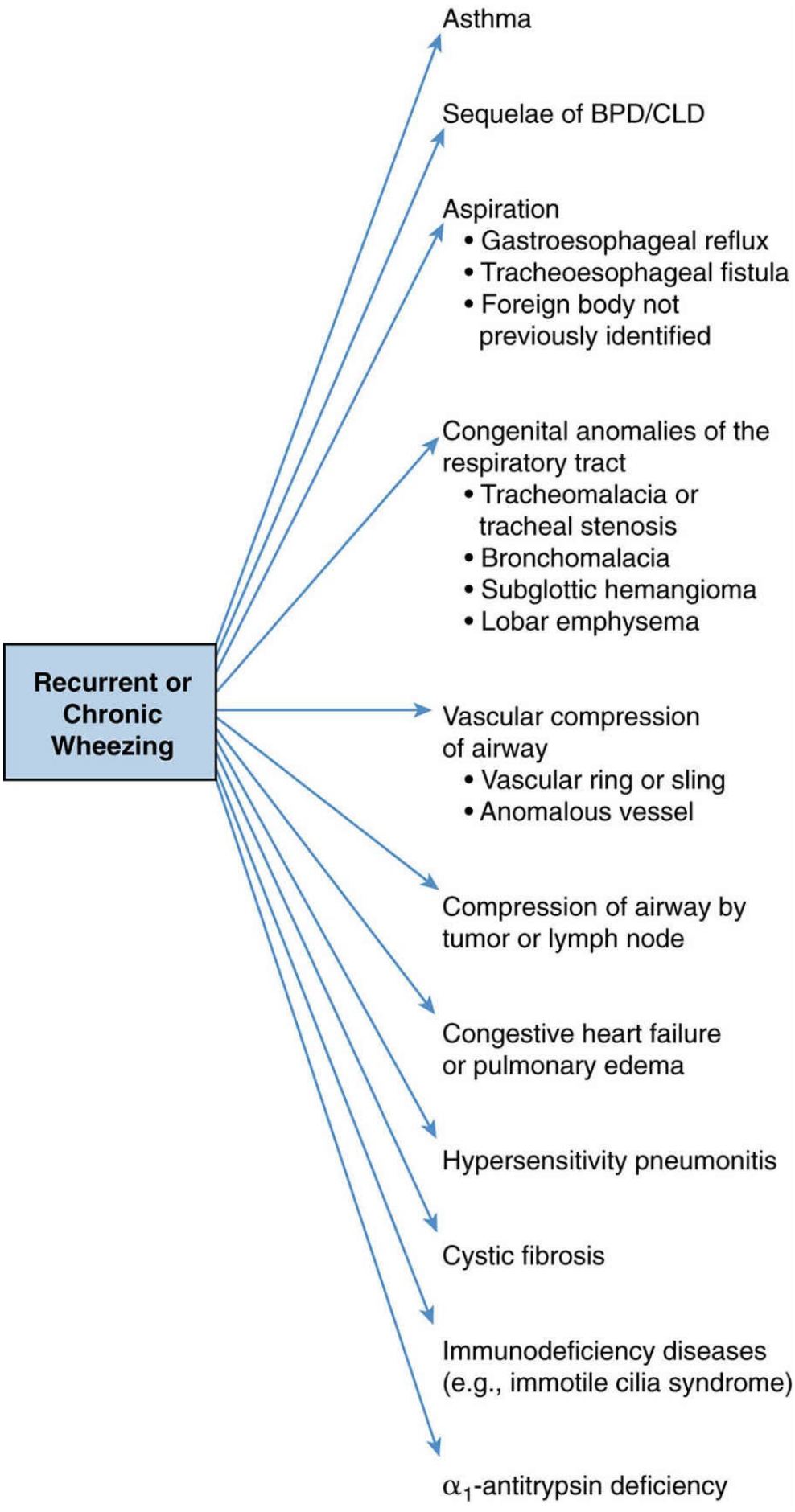
Recurrent or Chronic Wheezing
Asthma
Sequelae of BPD/CLD
Aspiration
• Gastroesophageal reflux
• Tracheoesophageal fistula
• Foreign body not previously identified
Congenital anomalies of the respiratory tract
• Tracheomalacia or tracheal stenosis
• Bronchomalacia
• Subglottic hemangioma
• Lobar emphysema
Vascular compression of airway
• Vascular ring or sling
• Anomalous vessel
Compression of airway by tumor or lymph node
Congestive heart failure or pulmonary edema
Hypersensitivity pneumonitis
Cystic fibrosis
Immunodeficiency diseases (e.g., immotile cilia syndrome)
α1-antitrypsin deficiency

FIGURE 9.2 Differential diagnosis of recurrent or chronic wheezing. *BPD/CLD* = bronchopulmonary dysplasia/chronic lung disease.

Table 9-4
Classifying Asthma Severity and Initiating Therapy in Patients Not Taking Long-Term Controller Medications

Components of Severity	Classifying Asthma Severity							
	Intermittent		Persistent					
			Mild		Moderate		Severe	
	Ages 0–4	**Ages 5–11**	**Ages 0–4**	**Ages 5–11**	**Ages 0–4**	**Ages 5–11**	**Ages 0–4**	**Ages 5–11**
Symptoms	≤2 days per week		>2 days per week but not daily		Daily		Throughout the day	
Night awakenings	0	≤2× per month	1–2× per month	3–4× per month	3–4× per month	>1× per week but not nightly	>1× per week	Often 7× per week
Short-acting beta-agonist: use for symptom control	≤2 days per week		>2 days per week but not daily		Daily		Several times per day	
Interference with activity	None		Minor limitation		Some limitation		Extremely limited	
Lung function: FEV_1 or peak flow	N/A	Normal between exacerbations (>80%)	N/A	>80%	N/A	60–80%	N/A	<60%
Exacerbations	In general, more frequent and severe exacerbations (e.g., hospitalizations, urgent care, intensive care unit admission) indicate greater underlying disease severity							
Recommended step for initiating therapy (see Table 9-5)	Step 1		Step 2		Step 3		Step 3 or 4	

National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US), August 2007:40 and 42.

FEV_1 = forced expiratory volume during the first second of forced breath.

Table 9-5
Stepwise Approach to Managing Asthma Long Term

STEP-UP MEDICATION IF NEEDED (Check Medication Adherence, Inhaler Technique, Other Contributing Factors)						
STEP-DOWN MEDICATION (If Asthma Is Well Controlled for at Least 3 Months)						
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
	Intermittent Asthma			**Persistent Asthma (daily medication)**		
0–4 years	SABA as needed	Low-dose ICS	Medium-dose ICS	Medium-dose ICS + either LABA or montelukast	High-dose ICS + either LABA or montelukast	High-dose ICS + either LABA or montelukast + oral corticosteroids
5–11 years	SABA as needed	Low-dose ICS	Low-dose ICS + either LABA, LTRA or theophylline ***OR*** Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA + oral corticosteroids
>12 years	SABA as needed	Low-dose ICS	Low-dose ICS + LABA ***OR*** Medium-dose ICS	Medium-dose ICS + LABA	High-dose ICS + LABA	High-dose ICS + LABA + oral corticosteroids

Adapted from National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US), August 2007:42.

Quick Relief Medication: SABA as needed for relief of symptoms. Short course of oral steroids may be needed for exacerbations.

SABA = short-acting beta-2 agonist; *ICS* = inhaled corticosteroid; *LABA* = long-acting inhaled beta-2 agonist; *LTRA* = leukotriene receptor antagonist.

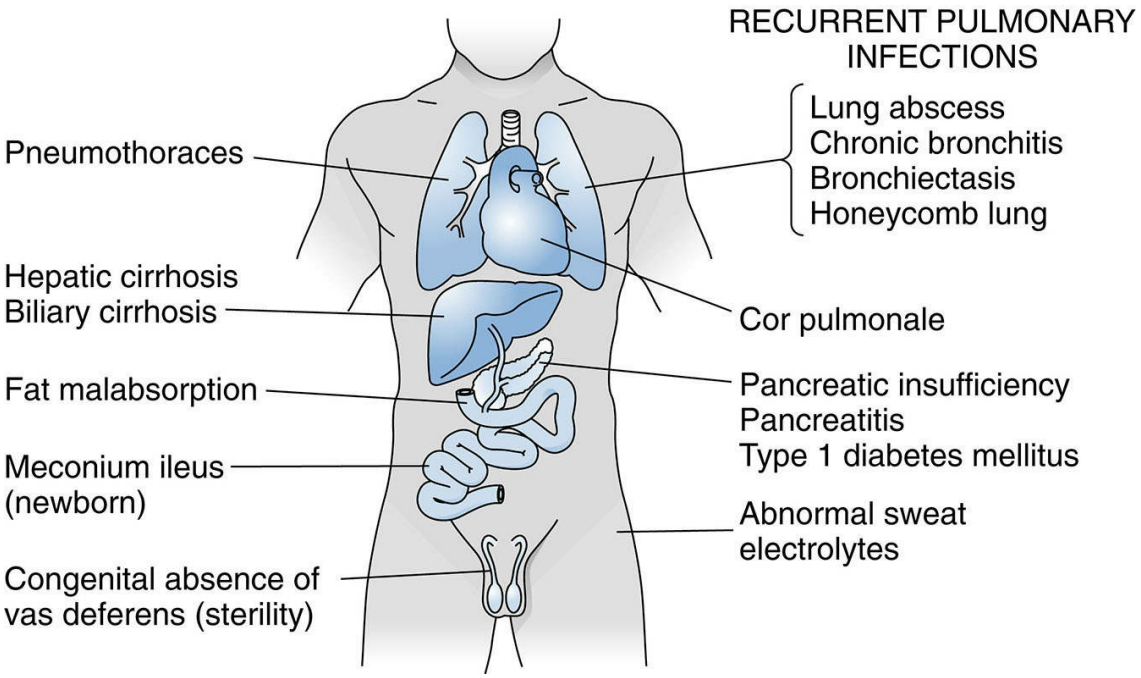

FIGURE 9.3 Features of cystic fibrosis.

Review Test

1. A 2-year-old toddler presents with a 3-day history of increasing inspiratory stridor, cough, and increased work of breathing. On examination, you confirm the inspiratory stridor and also note intercostal retractions and tachypnea with a respiratory rate of 44 breaths/minute. Which of the following is correct regarding the cause and management of the probable diagnosis?
   A. Parainfluenza virus is the most likely cause.
   B. Foreign body aspiration is unlikely because of the absence of a history of choking.
   C. Corticosteroid therapy is contraindicated.
   D. A "thumbprint sign" will be found on a lateral radiograph of the neck.
   E. Antibiotics against *Staphylococcus aureus* are indicated.
2. A 5-month-old female infant in a day care facility develops a low-grade fever (temperature up to 100.8°F [38.2°C]), rhinorrhea, and cough. A few days later, she is brought to the emergency department with tachypnea, chest retractions, diffuse expiratory wheezing, and fine inspiratory crackles bilaterally. Which of the following is correct regarding her likely diagnosis?
   A. Chest radiography will demonstrate decreased lung volumes with bilateral lobar consolidation.
   B. *Chlamydia trachomatis* should be considered as a possible etiologic agent.
   C. Supportive care is the most important management.
   D. Intravenous antibiotics should be started.
   E. Bronchoscopy is indicated.
3. A previously healthy 13-year-old boy presents with a 2-week history of nonproductive cough and low-grade fever. On examination, you note a normal respiratory rate and no evidence of respiratory distress but are surprised to hear inspiratory rales at the bilateral lung bases. Which of the following is the most likely cause of pneumonia in this adolescent?
   A. *Pneumocystis jiroveci*
   B. *Staphylococcus aureus*
   C. Group B streptococcus
   D. *Bordetella pertussis*
   E. *Mycoplasma pneumoniae*
4. A 7-month-old male infant presents with failure to thrive, and he has had two previous episodes of pneumonia. Past medical history is also significant for meconium ileus during the neonatal period. Which of the following is correct regarding his likely diagnosis?
   A. Electrolytes demonstrate hypernatremic, hyperchloremic metabolic acidosis.
   B. His lungs are likely colonized with *Staphylococcus aureus.*
   C. Pulmonary function studies show decreased lung volume consistent with restrictive lung disease.
   D. There is a 50% chance that a subsequent sibling will have the same illness.
   E. Pathophysiology involves abnormal calcium transport.
5. A 5-year-old girl presents with failure to thrive. Workup reveals a sweat chloride level of 90 mmol/L, which is consistent with cystic fibrosis. Which of the following is true regarding this patient's management?
   A. Dietary restriction is the preferred treatment for malabsorption from pancreatic insufficiency.
   B. Antibiotic therapy should be avoided to prevent development of resistant organisms.
   C. Mucus-altering therapies are ineffective in this condition.
   D. Replacement of vitamins A, D, E, and K is necessary.
   E. Chest physical therapy provides little added benefit.

6. A male infant born at 26 weeks' gestation was diagnosed with surfactant deficiency syndrome. He required 3 months of mechanical ventilatory support and oxygen therapy. Now he is ready for discharge from the neonatal intensive care unit and will go home on 0.25 L/minute of oxygen by nasal cannula. Which of the following is correct?
   A. He would be a candidate for palivizumab prophylaxis during respiratory syncytial virus season.
   B. Because of the difficulties breathing and swallowing in young premature infants, his caloric intake should be minimized.
   C. His lung function will continue to deteriorate with time and further growth.
   D. His chest radiograph will be normal because he has improved clinically.
   E. His lung disease should not affect his development.
7. A 3-month-old female infant required stimulation by her mother when she became blue and limp after feeding. In the emergency department, the physical examination is completely normal. Which of the following is correct regarding her presentation, evaluation, and management?
   A. A home apnea monitor should be ordered to prevent sudden infant death syndrome (SIDS).
   B. Consideration should be given for further workup, including possible electroencephalogram to rule out seizure disorder and pH probe study to rule out gastroesophageal reflux.
   C. It is not useful to observe the infant feeding in the emergency department.
   D. It is likely that this infant may later have SIDS.
   E. These parents should now co-sleep with their infant to monitor for any future events.
8. A 3-year-old boy presents with acute onset of fever (temperature up to 103.5°F [39.7°C]), diminished appetite, and drooling. He has been previously well, and inspection of his immunization records reveals that all are up-to-date for his age. On examination, you note that he appears very ill and prefers to sit leaning forward on his hands with his neck hyperextended. His voice is muffled. Which of the following is correct regarding his likely diagnosis?
   A. This patient likely has bacterial tracheitis and should be started on antistaphylococcal antibiotics.
   B. Racemic epinephrine should be administered immediately.
   C. Anesthesiology and otolaryngology should be consulted to visualize his airway and intubate him in a controlled environment (e.g., operating room).
   D. An anterior–posterior radiograph of the neck will show a "steeple sign."
   E. The throat should be examined with a tongue depressor to rule out a retropharyngeal abscess.
9. A 6-week-old female infant presents with increased work of breathing and a staccato-type cough for 3 days. On physical examination you note a temperature of 98.8°F (37.1°C), a respiratory rate of 60 breaths/minute, and bilateral conjunctival erythema. The lungs are clear except for mild wheezing at the bilateral lung bases. Which of the following is correct regarding her likely diagnosis?
   A. Pneumonia is unlikely given the absence of fever, and therefore a noninfectious cause of the patient's symptoms should be sought.
   B. Infection was transmitted by a maternal genital infection.
   C. Blood culture will be positive in 50% of cases.
   D. Corticosteroids are indicated and will improve the patient's clinical course.
   E. Inhaled mucolytics should be considered.
10. A 9-year-old girl with asthma is brought to the office for the first time. On average, she uses her albuterol inhaler three times per week, but for the past 10 days, she has been wheezing

both day and night and is using the inhaler three to four times per day. On examination, you note diffuse wheezing and moderate subcostal retractions. Which of the following is the next step in management?

A. Order a chest radiograph to assess for pneumonia.
B. Refer her to an allergist for allergen immunotherapy.
C. Start an oral leukotriene modifier.
D. Start a low-dose inhaled corticosteroid.
E. Start a short course of systemic corticosteroids.

The response options for statements 11 and 12 are the same. You will be required to select one answer for each statement in the set.

A. Short-acting inhaled β_2-agonist as needed for symptom relief plus daily medium-dose inhaled corticosteroid
B. Short-acting inhaled β_2-agonist as needed for symptom relief
C. Short-acting inhaled β_2-agonist as needed for symptom relief plus daily long-acting β_2-agonist.
D. Long-acting inhaled β_2-agonist as needed for symptom relief plus daily low-dose inhaled corticosteroid
E. High-dose inhaled corticosteroid as needed for symptom relief

For each description of a patient with asthma, select the most appropriate initial pharmacologic therapy.

1. A 8-year-old girl with daily wheezing and nighttime symptoms two times per week.
2. A 4-year-old boy with transient mild wheezing two to three times per year associated with cold symptoms.

Answers and Explanations

1. **The answer is A** [III.B]. Croup is the most common cause of acute stridor with cough in toddlers, and parainfluenza virus causes the majority of these infections. Foreign body aspiration may cause stridor or cough and should be considered as a cause, because in as many as 50% of foreign body aspirations, choking is not witnessed. Corticosteroid therapy is the treatment of choice for symptomatic croup. An anterior–posterior radiograph of the neck will show a "steeple sign" characteristic of subglottic narrowing, while a "thumbprint sign" on lateral neck radiograph is associated with epiglottitis. Antibiotics are not indicated for croup.
2. **The answer is C** [III.E.3–6]. This patient's clinical features are consistent with bronchiolitis, a viral lower respiratory tract infection. Supportive care is the most effective management. Respiratory syncytial virus is the most common cause of bronchiolitis. Chest radiography usually demonstrates hyperinflation and atelectasis. *Chlamydia trachomatis* pneumonia generally occurs in a young infant, 1–3 months of age, and would be very unlikely in a 5-month-old infant. Antibiotics are not effective for viral bronchiolitis. Bronchoscopy would be indicated if foreign body aspiration was suspected, which is less likely in a 5-month-old.
3. **The answer is E** [Table 9-2 and III.F.3]. The most common cause of pneumonia in older children and adolescents is atypical infection with *Mycoplasma pneumoniae* and *Chlamydia pneumoniae.* Pneumonia in immunocompromised patients may be caused by *Pneumocystis jiroveci.* Although pneumonia as a result of *Staphylococcus aureus* may occur in an adolescent, the patient would be more acutely ill. Group B streptococcus is an organism unique to the neonatal period. *Bordetella pertussis* is the cause of whooping cough.
4. **The answer is B** [IV.B.3–5, IV.B.7, and Figure 9-3]. The likely diagnosis is cystic fibrosis (CF). Lung disease eventually develops in all individuals with classic CF; the lungs are initially colonized with *Staphylococcus aureus* and subsequently with mucoid *Pseudomonas aeruginosa.* Neonates with CF may present with meconium ileus, an impaction of inspissated meconium that causes congenital intestinal obstruction. Pulmonary function studies demonstrate decreased respiratory flow rates and air trapping, consistent with obstructive lung disease early in the disease process. Later, restrictive lung disease patterns are present. The autosomal recessive inheritance of CF means that each subsequent sibling has a 25% chance of having the disease. Pathophysiology involves an altered ion-channel regulator (CFTR) protein, resulting in abnormal sodium and chloride transport in epithelial cells, which can cause a hyponatremic, hypochloremic metabolic alkalosis.
5. **The answer is D** [IV.B.7]. Pancreatic insufficiency and malabsorption are very common and require pancreatic enzyme replacement and the administration of fat-soluble vitamins (vitamins A, D, E, and K). Nutritional support is very important, as patients commonly have failure to thrive with difficulty gaining weight, for which high-calorie diets are prescribed. Broad-spectrum antibiotics should be used for the treatment of pulmonary exacerbations. Other effective treatment modalities in cystic fibrosis are mucus-altering agents with aggressive pulmonary toilet, including chest physical therapy to help expectorate thick mucus.
6. **The answer is A** [IV.C]. Prematurity and barotrauma from prolonged mechanical ventilation are significant risk factors for the development of bronchopulmonary dysplasia or chronic lung disease of infancy. These patients are at risk for significant deterioration with respiratory syncytial virus infections during their first year of life, and would therefore benefit from palivizumab (RSV monoclonal antibody) prophylaxis. To meet their metabolic demands and facilitate growth, patients require very high caloric intakes. Pulmonary disease improves with time and lung growth, although chest radiographs may remain abnormal for years. Development is often delayed in children with chronic lung disease.
7. **The answer is B** [IV.E]. This patient had an apparent life-threatening event (ALTE) now more

often referred to as a brief resolved unexplained event (BRUE). The evaluation of an ALTE should include attempts to identify an underlying cause, and workup may include an electroencephalogram to rule out a seizure disorder, an electrocardiogram to rule out a dysrhythmia such as long QT syndrome, electrolytes, a barium esophagogram or pH probe study to rule out gastroesophageal reflux disease, and a sleep study. It might be useful to observe the infant while feeding in the emergency department. The effectiveness of home apnea monitor in preventing sudden infant death syndrome has not been established. In addition, no definitive relationship between ALTE and sudden infant death syndrome (SIDS) has been established. To prevent SIDS or ALTE, co-sleeping is not recommended. SIDS prevention includes firm bedding and sleeping supine.

8. **The answer is C** [III.A.7]. This patient's presentation with fever, toxic appearance, muffled speech, tripod positioning when seated, drooling, and neck hyperextension all suggest epiglottitis as a possible diagnosis. Epiglottitis is now a very uncommon infection as a result of the successful immunization of children against *Haemophilus influenzae* type b; however, epiglottitis may still occur secondary to infection with streptococcal and staphylococcal species. Management includes avoidance of excessive stimulation, such as examination of the pharynx with a tongue depressor, because this may induce respiratory distress. Evaluation of the airway and intubation by experienced personnel in a controlled setting are necessary. Racemic epinephrine is not effective in epiglottitis. A "steeple sign" on a radiograph of the neck is consistent with the diagnosis of croup, not epiglottitis (which demonstrates a "thumbprint sign" on lateral radiograph of the neck). Bacterial tracheitis presents with fever and stridor (rather than a muffled voice), and drooling and neck hyperextension are unlikely to be present.
9. **The answer is B** [III.F.3, III.F.4.c, and Table 9-2]. This patient's clinical features point to a likely diagnosis of pneumonia secondary to infection with *Chlamydia trachomatis,* which is a common perinatally transmitted cause of pneumonia in infants 1–3 months of age. Patients are afebrile, have a characteristic staccato-type cough, and may have a history of conjunctivitis (in 50% of cases). Blood cultures are not positive in this infection. Management includes oral macrolide antibiotics. Neither corticosteroids nor mucolytics are effective treatments for *C. trachomatis* pneumonia.
10. **The answer is E** [IV.A.7 and Tables 9-4 and 9-5]. This patient presents with an acute exacerbation of her chronic asthma and therefore would benefit from a short course of systemic corticosteroids. Both inhaled corticosteroids and leukotriene inhibitors are effective management options for the prevention and chronic management of asthma, and these agents can be considered for her long-term controller therapy. Allergen immunotherapy may also be beneficial but would not be the initial step in management. Chest radiographs are not routinely indicated for asthma exacerbations.
11. **The answers are A and B, respectively** [Tables 9-4 and 9-5 and IV.A.7]. Asthma is graded on a severity scale on the basis of the frequency of asthma symptoms during the day and night, and also on pulmonary function testing. The 8-year-old girl's asthma would be characterized as moderate persistent asthma because of the presence of daily symptoms and nighttime wheezing more often than once per week. The recommended initial treatment for moderate persistent asthma is either a medium-dose inhaled corticosteroid OR a low-dose inhaled corticosteroid with a long-acting inhaled β_2-agonist for the controller, AND an inhaled short-acting β_2-agonist as needed for the reliever. The 4-year-old boy's asthma would be characterized as intermittent asthma. Intermittent asthma only needs a short-acting inhaled β_2-agonist for symptom treatment without need for a long-term controller. Long-acting β_2-agonists should not be used as quick relievers.

CHAPTER 10

Gastroenterology

Dorsey Bass, Lloyd J. Brown

I. Nutrition

A. **General concepts**

1. **Essential nutrients** cannot be synthesized by the body and must be derived from the diet. These include certain vitamins, minerals, amino acids, fatty acids, and a carbohydrate source.
2. **Nonessential nutrients** can be synthesized from other compounds or may be derived from the diet.
3. **Macronutrients** supply energy and essential nutrients needed for growth, development, disease prevention, and activity.
    a. **Carbohydrates** make up approximately 50% of a typical diet and are converted by the body to glucose and other monosaccharides.
    b. **Proteins** are converted to peptides and amino acids. Of the 20 amino acids, 9 are essential. As compared with adults, infants require more protein in their diet (2.2 g/kg during infancy, decreasing to 0.8 g/kg during adulthood).
    c. **Fats** are broken down into fatty acids and glycerol. **Essential fatty acids** play an **important role in infant brain development.** Less than 30% of all calories should come from fats.
    d. **Minerals,** including sodium, chloride, potassium, calcium, phosphorus, and magnesium, are also required daily.
4. **Micronutrients**
    a. **Water-soluble vitamins** include vitamin C and the B-complex vitamins (thiamine, riboflavin, niacin, pyridoxine, folic acid, cobalamin, biotin, and pantothenic acid).
    b. **Fat-soluble vitamins** include vitamins A, D, E, and K.
    c. **Essential trace minerals,** such as iron, iodine, fluorine, zinc, chromium, selenium, and copper, play important roles in metabolism and as enzyme cofactors.
    d. **Certain clinical features are associated with vitamin and mineral deficiencies (Table 10-1).**

B. **Malnutrition**

1. **Marasmus** is the **most common energy depletion state** and is characterized by *near starvation from* **protein and nonprotein calorie deficiencies.** The patient is typically **very thin from loss of muscle and body fat.**
2. **Kwashiorkor** is **less common** and is seen in the parts of the world in which starches are the main dietary staple. This **protein-deficient** state is characterized by **generalized edema, abdominal distension, changes in skin pigmentation, and thin, sparse hair.**
3. Most patients suffering from malnutrition have a combination of energy and protein depletion. The term **protein–energy malnutrition** is used to describe this state.

Table 10-1
Clinical Features of Selected Vitamin and Mineral Deficiencies

Nutrient	Signs and Symptoms
Vitamin A	Night blindness, xerophthalmia (dry conjunctiva and cornea)
Vitamin D	Rickets/osteomalacia, dental caries, hypocalcemia, hypophosphatemia
Vitamin E	Anemia/hemolysis, neurologic deficits, altered prostaglandin synthesis
Vitamin K	Coagulopathy/prolonged prothrombin time, abnormal bone matrix synthesis
Vitamin B_1 (thiamine)	**Beriberi** (cardiac failure, peripheral neuropathy, hoarseness or aphonia, Wernicke encephalopathy)
Vitamin B_6 (pyridoxine)	Dermatitis, cheilosis, glossitis, microcytic anemia, peripheral neuritis
Vitamin B_{12}	Megaloblastic anemia, demyelination, methylmalonic acidemia

(cobalamin)	
Vitamin C	**Scurvy** (hematologic abnormalities, edema, spongy swelling of gums, poor wound healing, impaired collagen synthesis)
Folic acid	Megaloblastic anemia, neutropenia, impaired growth, diarrhea
Niacin	**Pellagra** (diarrhea, dermatitis, dementia), glossitis, stomatitis
Zinc	Skin lesions, poor wound healing, immune dysfunction, diarrhea, growth failure

II. Malabsorption

A. **General concepts about malabsorption**
   1. **Definition.** Malabsorption is the **inadequate absorption of nutrients** and is **most often characterized by diarrhea, abdominal distension, and impaired growth.**
   2. **Normal physiology**
      a. **Digestion** is an intraluminal event requiring digestive enzymes and bile acids for micelle formation.
      b. **Absorption** requires an adequate intestinal mucosal surface and villous brush border with intact transport mechanisms.
   3. **Pathophysiology and etiologies of malabsorption**
      a. **Carbohydrates**
         1. **Undigested sugars are osmotically active** and draw water into the intestinal lumen, causing increased stool volume, increased peristaltic activity, and decreased transit time. This results in diminished digestion and absorption of nutrients.
            a. Unabsorbed sugars are fermented by colonic bacteria, which produce hydrogen gas, carbon dioxide, and acids.
            b. The resulting stool is **watery and acidic** and contains unabsorbed sugars. These unabsorbed sugars are detected as **reducing substances** in the stool by a **positive Clinitest** reaction.
            c. **Another clue to carbohydrate malabsorption is a stool pH below 5.6.**
         2. **Causes** of carbohydrate malabsorption include **isolated congenital enzyme deficiency** (e.g., lactase deficiency) or **mucosal atrophy,** which can cause a loss of enzymes or a disruption of transport mechanisms.
      b. **Proteins**
         1. Dietary proteins are broken down into amino acids or oligopeptides by pepsinogen and pancreatic proteases in the proximal small intestine.
         2. **Causes** of protein malabsorption
            a. **Protein-losing enteropathies** result in hypoproteinemia as a result of transudation of protein from inflamed intestinal mucosa.
            b. **Inflammatory disorders** of the intestinal mucosa, such as Crohn disease (CD) [see section IX] and colitis, may also result in protein loss.
         3. **Clues to protein malabsorption include increased levels of fecal α_1-antitrypsin,** which reflect enteric protein losses, and **low serum albumin** levels seen in protein-losing enteropathies.
      c. **Lipids**
         1. Fats are insoluble in water and must be incorporated into bile salt micelles to be absorbed. Pancreatic lipase is a necessary enzyme that hydrolyzes triglycerides for emulsification.
         2. **Decreased lipase activity** results in **steatorrhea** (fat in stool) and **decreased absorption of fat-soluble vitamins (vitamins A, D, E, and K).**
         3. **Causes** of fat malabsorption
            a. **Exocrine pancreatic insufficiency**
               1. **Cystic fibrosis** (See Chapter 9, section IV.B.)
               2. **Shwachman–Diamond syndrome.** This autosomal recessive disorder is characterized by pancreatic exocrine insufficiency, failure to thrive (FTT), short stature, neutropenia, and sometimes pancytopenia.

3. **Chronic pancreatitis**

b. **Intestinal mucosal atrophy**

c. **Bile acid deficiency**

d. **Abetalipoproteinemia,** an inherited disorder in which beta-lipoproteins are absent, leading to severe fat and fat-soluble vitamin malabsorption. Acanthocytosis of erythrocytes (abnormal star-shaped red blood cells) is seen in abetalipoproteinemia.

4. A *clue to fat malabsorption* may be fecal fat globules seen on examination of stool using the Sudan stain, although the gold standard remains analysis for fecal fat on a 72-hour stool collection. Fecal elastase has a high sensitivity and specificity to detect pancreatic insufficiency.

B. **Protein intolerance leading to malabsorption**

1. **Epidemiology.** Protein intolerance occurs in up to 8% of children. **Cow's milk protein** causes the majority of these reactions. Other causes include soy and egg proteins.
2. **Clinical features.** Protein intolerance is characterized by diarrhea, vomiting, and colicky abdominal pain that occur after exposure to dietary protein. **There are two clinical types of protein intolerance:**
   a. **Enteropathy,** which is characterized by **progressive onset** of diarrhea, vomiting, irritability, and abdominal pain. Chronic blood loss in the stool may lead to anemia, and significant stool protein loss may cause edema and FTT.
   b. **Enterocolitis** implies involvement of the colon, and typically presents **acutely** with diarrhea, rectal bleeding, mucus in the stool, abdominal distension, and irritability. As with enteropathy, hypoproteinemia, edema, and FTT may develop.
3. **Diagnosis** is made by resolution of acute symptoms within a few days after complete withdrawal of the suspected antigen. Chronic symptoms usually resolve within 1–2 weeks.
4. **Management** includes withdrawal and avoidance of suspected dietary protein. **Most protein intolerance is transitory** and resolves by 1–2 years of age.

C. **Celiac disease (gluten-sensitive enteropathy)**

1. **Definition.** This **autoimmune disorder** of the proximal small intestine is characterized by **intolerance to gluten,** which results in mucosal damage.
2. **Epidemiology**
   a. Celiac disease is most common in regions where wheat is a staple in the diet, and associated human leukocyte antigen (HLA) genotypes are found (e.g., North America, Middle East, Europe, Australia). In the United States, the incidence is as high as 1 in 100 individuals.
   b. Celiac disease often presents between **6 months and 2 years of age** when gluten, found in **wheat, rye, barley,** and **oats** (if the oats are harvested in fields that also contain wheat), is introduced into the diet. This age group is more susceptible to overt disease owing to rapid growth. The disease though may present at any age.
   c. Individuals who are susceptible to celiac disease have a **genetic predisposition,** often due to **HLA genotypes HLA-DQ2 or HLA-DQ8.**
3. **Clinical features**
   a. The **primary symptoms** are **diarrhea, vomiting, constipation, bloating, anorexia, and sometimes FTT.** The clinical diagnosis may be challenging, as **short stature** may be the only clinical manifestation and diarrhea may not be present in all patients.
   b. Irritability and developmental regression are common in infants and toddlers.
   c. Abdominal pain and large, foul-smelling stools are also common.
4. **Evaluation**

a. **Small bowel biopsy** is the **gold standard** for diagnosis and demonstrates short flat villi, deep crypts, and vacuolated epithelium with lymphocytes.
b. A **clinical response** with weight gain and resolution of symptoms **when gluten is removed from the diet** also helps confirm the diagnosis.
c. **Serum IgA-endomysial testing** and **serum tissue transglutaminase antibody testing** are extremely sensitive and specific screens for celiac disease, except in individuals with IgA deficiency. Serum antigliadin IgG antibody testing is useful for patients who are IgA deficient.

5. **Management**
   a. A strict **gluten-free diet for life** is necessary and results in complete reversal of intestinal damage. Vitamin and iron supplements may be required.
   b. Dietary changes in children often yield a rapid response, but noncompliance in adolescents is common and may lead to **growth failure** and **delayed sexual maturity.**

D. **Short bowel syndrome**

1. **Definition.** Patients with a **shortened small intestine may have malabsorption resulting in malnutrition and compromised bowel function.**
2. **Etiology**
   a. **Congenital lesions of the gut,** such as gastroschisis, volvulus, or intestinal atresia, may require surgical resection of the small intestine, resulting in an inadequate absorptive surface area.
   b. Infants who have undergone intestinal surgery for necrotizing enterocolitis may develop short bowel syndrome.
   c. Crohn disease, tumors, and radiation enteritis may also lead to short bowel syndrome.
3. **Pathophysiology**
   a. The absorptive capacity of the bowel depends on the length and location of the resected segment and on the condition of the residual gut.
   b. After gut resection, **carbohydrate and fat malabsorption** with **steatorrhea** are common.
   c. Dehydration, hyponatremia, and hypokalemia may all occur if resorptive capacity is limited.
   d. **Distal** small bowel resection (i.e., ileum) limits **vitamin B_{12}** and **bile acid absorption.**
4. **Clinical features** include diarrhea, malabsorption, and FTT.
5. **Management**
   a. Short bowel syndrome was formerly a fatal disorder. The development of **total parenteral nutrition (TPN)** now allows patients to maintain adequate nutrition and significantly improves survival.
   b. **Early enteral feedings** are important to ensure adaptive growth of the remaining small bowel, proper hepatic function, and proper oral motor development.
   c. With proper management, patients may be able to wean off parenteral nutrition and survive. Adaptation of the intestine depends on the length and quality of the residual small bowel and on the presence of an intact ileocecal valve.
   d. **Small bowel transplantation** has been performed but is reserved for patients with coexisting life-threatening TPN-associated liver disease. Liver transplantation may also be required.
6. **Complications** include **TPN cholestasis** with resultant gallstones and cholestatic liver disease, **intestinal bacterial overgrowth, nutritional deficiencies, poor bone mineralization** and **renal stones** from hyperoxaluria, and **secretory diarrhea** as a result

of the osmotic load in the remaining intestine. Treatment at specialized centers can minimize complications and improve outcomes.

III. Gastroesophageal Reflux

A. **Definitions**
   1. **Gastroesophageal reflux (GER)** is the **normal physiologic state** in which stomach contents move retrograde into the esophagus.
   2. **Gastroesophageal reflux disease (GERD)** is a **pathologic state** associated with **gastrointestinal (GI) or pulmonary symptoms and sequelae.** Ten percent of infants with GER have GERD.

B. **Normal physiology.** Normal periodic peristaltic waves of contraction of the esophagus transport ingested food into the stomach. The **lower esophageal sphincter (LES)** is a contracted circular muscle at the distal end of the esophagus that relaxes in a coordinated fashion with the peristaltic wave to allow esophageal contents to enter the stomach.

C. **Pathophysiology of GERD**
   1. **Inappropriate transient lower esophageal sphincter relaxation (TLESR) is the predominant cause of GERD during childhood.** Inappropriate TLESR allows excessive gastric refluxate to enter the esophagus and even the oropharynx. With time, prolonged contact of the esophageal mucosa with gastric contents results in inflammation.
   2. **Gastric emptying delay** may also play a role in GERD by increasing the quantity of gastric refluxate and by increasing gastric distension, which induces more TLESR.

D. **Clinical features of physiologic reflux (GER)**
   1. Infants are often termed "**happy spitters**" because they are without other reflux-associated symptoms. Up to 60% of all infants have episodes of spitting up or vomiting not related to overfeeding or GI disease.
   2. **Emesis is benign,** but often dramatic and traumatic for parents.
   3. **Education and reassurance of parents are vital.** The goal is to avoid aimless formula changes, inappropriate early weaning, medications, homeopathic remedies, or costly seats and straps.
   4. Emesis from physiologic reflux generally resolves by 6–12 months of age.

E. **Clinical features of pathologic reflux (GERD)**
   1. **Infants** may present with the following:
      a. **Emesis** is the **most common presentation.**
      b. Emesis may not always be present, or it may be so severe that it results in suboptimal calorie retention and **FTT.**
      c. **Sandifer syndrome** is a characteristic torticollis with arching of the back caused by painful esophagitis.
      d. **Feeding refusal** with irritability or **constant hunger** may indicate esophagitis. The irritated esophagus may be painful, negatively reinforcing feeding, or the child may desire the buffering action of milk to reduce acid irritation.
   2. **Older children** usually present with the following:
      a. Symptoms of esophagitis, including **midepigastric pain** ("heartburn") that is temporarily relieved with food or antacids and is exacerbated by fatty foods, caffeine, and being in the supine position.
      b. Associated symptoms include nausea (especially on awakening), hoarseness, halitosis, and wheezing.
   3. **Sequelae of GERD**
      a. **Upper and lower airway disease** may be induced or worsened by GERD. Acidic refluxate induces **bronchopulmonary constriction** and can also lead to frank aspiration or microaspiration. Common signs and symptoms include chronic laryngitis, hoarseness, wheezing, the development of vocal cord nodules, and

subglottic stenosis.
    b. **GI** sequelae include FTT, esophageal strictures, and **Barrett esophagus** (conversion of the normal stratified squamous epithelium of the esophagus into columnar epithelium, a condition which may be associated with esophageal adenocarcinoma).
4. Infants who remain symptomatic past 1 year of age and older children are unlikely to have spontaneous resolution of GERD and usually require long-term medical management or surgery.

F. **Diagnosis.** *In many cases the diagnosis of GERD is a clinical one, based on the patient's signs and symptoms. However, in some cases additional diagnostic evaluation* is required, focusing on ensuring normal anatomy and confirming suspected abnormalities.
1. **Barium upper gastrointestinal (UGI) study** examines the **anatomy** of the esophagus, stomach, and duodenum. However, the UGI study is a **poor test for diagnosis of GERD,** even if the refluxate is seen rising up to the oropharynx. Because TLESR is induced during administration of barium through a nasogastric tube, the sensitivity for GERD is high (85–90%) but the specificity is low (50%). Only frank aspiration of barium can be interpreted as GERD.
2. **Gastric emptying study (or scintigraphy)** uses a radioactive marker (e.g., technetium 99m) mixed into age-appropriate foods to measure the rate of gastric emptying. When slow-decay markers are used, radioactive tracer detected in the lungs confirms aspiration.
3. **pH probe measurement** is the **gold standard** for diagnosis but is not indicated for every child with suspected GERD. It is often performed when the diagnosis is unclear, or to correlate reflux with events such as apnea.
    a. The pH of the esophagus is continuously monitored for at least 18 hours.
    b. Diagnosis of GERD is based on the number of acidification episodes, the total duration of esophageal acidification, and the time required for the pH to normalize in the presence of symptoms.
    c. **To interpret the pH probe correctly, results should be correlated with the clinical presentation.**
4. **Endoscopy with biopsy** to detect inflammation may be indicated when the diagnosis is uncertain.
5. **Bronchoscopy with alveolar lavage** may be performed when aspiration is strongly suspected.

G. **Management.** Treatment includes attempts at reducing entry of stomach contents into the esophagus and relieving symptoms.
1. **Conservative management**
    a. **Positioning** in an **upright or sitting position** or raising the head of the bed after feedings or when asleep
    b. **Dietary** recommendations include **frequent small meals** and **thickening of feeds** using infant cereal or a commercial thickener, which decrease the symptoms of GERD by making the stomach contents more viscous.
    c. **Medical Management**
    d. **Acid inhibition** with antacids, histamine H_2-blockers, and proton-pump inhibitors is effective in reducing the irritation caused by the refluxate.
2. **Motility agents** increase the LES tone or increase gastric emptying. The most commonly used agents are erythromycin or metoclopramide**.**
3. **Surgery** may be required for patients who fail conservative and medical management.
    a. The **Nissen fundoplication** wraps the fundus of the stomach around the distal 3.5 cm of the esophagus, resulting in reduction of TLESR in as many as 90% of children.

b. **Pyloroplasty** may be performed to improve gastric emptying.
c. Placement of a **gastrostomy tube** often accompanies a Nissen fundoplication in infants. Reduction in stomach volume by the Nissen procedure requires a period of adaptation and expansion of the stomach that is best assisted with tube feedings. A gastrostomy tube also enables venting of the stomach in cases of uncomfortable bloating.

IV. Intestinal Anatomic Obstructions That Result in Vomiting

A. **Hypertrophic pyloric stenosis**
   1. **Definition.** Thickening of the circular pylorus muscle results in gastric outlet obstruction with projectile vomiting.
   2. **Epidemiology**
      a. Incidence is 2–3.5 in 1000 live births.
      b. **Caucasians** and **first-born male children are affected more commonly.** The male-to-female ratio is 4:1.
   3. **Etiology**
      a. The **etiology is unknown.** Abnormal muscle innervation, breastfeeding, early administration of oral erythromycin, and decreased production of nitric oxide synthase have all been implicated.
      b. Associated conditions include duodenal atresia, tracheoesophageal fistula, trisomy 18, and Cornelia de Lange syndrome.
   4. **Clinical features**
      a. *Vomiting of nonbilious,* milky fluid starts during the second or third week of life.
      b. Vomiting becomes more forceful, is often described as **projectile,** and typically occurs immediately after feeding.
      c. Affected infants may be **irritable but hungry.**
      d. Jaundice occurs in 5% of patients, and it is associated with low levels of the enzyme glucuronyl transferase.
      e. *Dehydration and electrolyte abnormalities from vomiting may occur.*
   5. **Evaluation**
      a. **Physical examination**
         1. The hypertrophied pylorus muscle may be palpable just above and to the right of the umbilicus. It is often referred to as the **"olive."**
         2. Abdominal peristaltic waves may be visible after feeding.
      b. Prolonged vomiting of gastric contents classically results in **hypochloremic, hypokalemic, metabolic alkalosis.**
      c. **Diagnostic studies**
         1. **Ultrasound** is used to measure the pylorus muscle length and thickness and is the **diagnostic method of choice.**
         2. **UGI** study may demonstrate an elongated, narrow pyloric channel **("string sign").**
   6. **Management**
      a. Electrolyte abnormalities and dehydration should be corrected before surgery.
      b. Surgical correction is with a **partial pyloromyotomy,** in which the circular pylorus muscle fibers are transected.

B. **Malrotation and midgut volvulus**
   1. **Definition.** Malrotation is an anatomic abnormality of intestinal rotation that allows the **midgut to twist around the superior mesenteric vessels (i.e., volvulus).** This may obstruct and infarct the bowel.
   2. **Epidemiology**
      a. Incidence of malrotation is 1 in 500 live births, with a 2:1 **male predominance.**
      b. Malrotation is common in patients with heterotaxy, a condition in which the internal organs are abnormally arranged in the chest and abdomen, and may be associated with small bowel atresia, Hirschsprung disease, and intussusception.
   3. **Pathogenesis.** The intestines normally return to the abdomen through the umbilical cord

during the 10th week of gestation and undergo counterclockwise rotation about the axis of the superior mesenteric artery. The intestines are then fixed to the abdominal wall. Malrotation occurs when normal bowel rotation is interrupted.

a. Lack of fixation of the small bowel results in peritoneal bands (**Ladd bands**) that can compress the duodenum, causing mechanical obstruction.
b. The narrow pedicle, which suspends the small bowel and the base of the superior mesenteric vessels, can easily twist, leading to ischemia and midgut volvulus.

4. **Clinical features**
   a. **Bilious vomiting** and **sudden onset of abdominal pain in an otherwise healthy infant** is the classic presentation. Older children may have intermittent, crampy abdominal pain and vomiting.
   b. Anorexia, distension, and blood-tinged stools are common.
   c. Physical examination may initially be normal with peritonitis occurring later. Shock and cardiovascular collapse may occur as bowel ischemia progresses.
5. **Evaluation**
   a. **Abdominal radiographs** may show gastric or proximal intestinal distension and obstruction, often with little or no distal bowel gas.
   b. **Upper intestinal contrast imaging** (UGI study with small bowel follow-through) is the **diagnostic tool of choice,** and demonstrates the abnormal position of the ligament of Treitz to the right of midline, partial or complete duodenal obstruction, and the jejunum to the right of midline.
   c. **Lower intestinal contrast studies** may reveal the cecum in the left abdomen or right upper quadrant.
6. **Management**
   a. Volvulus is a **surgical emergency** requiring immediate exploration, untwisting of the gut, resection of any nonviable segments of intestine, and fixation of the gut to prevent recurrence.
   b. **Fluid resuscitation,** nasogastric suctioning, and broad-spectrum parenteral antibiotics should be administered.
   c. TPN may be required if a large segment of the bowel is resected.

C. **Atresias**

1. **Duodenal atresia and stenosis**
   a. **Definition.** Duodenal atresia is a congenital obstruction of the duodenum caused by failure of the lumen to recanalize at 8–10 weeks' gestation.
   b. **Epidemiology**
      1. Intestinal atresia is the **most common cause of obstruction in the neonatal period.**
      2. Incidence is approximately 1 in 10,000 live births, with a **male predominance.**
      3. One-fourth of cases occur in patients with **Down syndrome.**
   c. **Clinical features**
      1. Diagnosis may be suspected if prenatal ultrasound demonstrates gastric dilation with **polyhydramnios.**
      2. At birth, physical examination of patients with duodenal atresia may reveal a **scaphoid abdomen with epigastric distension.** Infants have feeding intolerance and vomiting.
      3. Duodenal stenosis may present with emesis, weight loss, and FTT.
      4. Other congenital defects (e.g., malrotation, esophageal atresia, congenital heart disease, renal anomalies) may also be present.
   d. **Evaluation**
      1. **Abdominal radiography** shows air in the stomach and proximal duodenum,

creating a **"double bubble"** sign in infants with atresia.

2. **UGI** study is very effective at diagnosing atresia and stenosis.

e. **Management**

1. Nasogastric decompression, hydration, and correction of electrolyte abnormalities (typically hypochloremic metabolic alkalosis) are necessary.
2. Atresia is surgically corrected by duodenoduodenostomy.
3. Exploration for malrotation and other luminal obstructions is also performed at the time of surgical correction.

2. **Jejunoileal atresia**

a. **Definition.** This congenital obstruction of the jejunum or ileum is caused by a mesenteric vascular accident during fetal life.

b. **Epidemiology.** The incidence is approximately 1 in 3000 live births. It is not usually associated with other anomalies.

c. **Clinical features.** Bilious emesis and abdominal distension occur within the first few days of life.

d. **Evaluation.** Abdominal **radiographs** *reveal air–fluid levels,* and **contrast studies** reveal the atresia.

e. **Management.** Patients should undergo nasogastric suctioning and fluid resuscitation before surgical resection and anastomosis of the atretic segment of the small bowel.

D. **Intussusception**

1. **Definition.** Intussusception is the *telescoping or invagination of a more* **proximal portion of the intestine into a more distal portion.**
2. **Epidemiology.** The incidence is 1.5–4 in 1000 live births, with a slight **male predominance.** Peak incidence occurs at **5–9 months of age. Intussusception is the most common cause of bowel obstruction after the neonatal period in infants younger than 2 years.**
3. **Pathogenesis and etiology**

a. Intussusception may occur at a variety of sites within the intestine, but **ileocolic intussusception is the most common location.**

b. Etiology is generally unknown, but a **lead point** such as Meckel diverticulum, polyp, intestinal duplication, Peyer patch, or lymphoma may act to draw the proximal intestine inward. However, a lead point is identified in only 5% of cases and is **more common in older children.**

c. Intussusception causes bowel wall edema and hemorrhage, and may lead to bowel ischemia and infarction.

4. **Clinical features**

a. Previously healthy infants or children may present with **sudden onset of crampy or colicky abdominal pain.** The pain often occurs in intervals followed by periods of calm. Infants may cry and draw their legs toward the chest.

b. Vomiting and **lethargy** are common.

c. Stools may be normal or have a bloody, **"currant jelly"** appearance because of intestinal ischemia and mucosal sloughing.

d. Occasionally, a **sausage-shaped mass** may be palpated in the abdominal right upper quadrant, representing the intussusception.

5. **Evaluation**

a. Initial management should include fluid resuscitation.

b. Radiographs are of limited usefulness but may reveal dilated loops of the bowel, or pneumoperitoneum if perforation has occurred.

c. *Abdominal ultrasound* is the most accurate diagnostic tool in the hands of an

experienced ultrasonographer. **Contrast enema** (barium or Gastrografin) can also be used to both establish the diagnosis and to reduce the intussusception. Contrast enema may show the classic **"coil spring" sign** representing the intussusception.

6. **Management**
    a. **Air or contrast enemas,** often under ultrasound guidance, successfully reduce the intussusception in 80–90% of cases.
    b. If the contrast enema fails to reduce the intussusception, or if the child has signs of peritonitis or pneumoperitoneum, **operative reduction** is indicated.
    c. The **risk of recurrence** is 5% after contrast reduction and 1% after surgical repair.

E. **Hirschsprung disease.** This disorder may also cause vomiting, and it is described in Chapter 4, section XII.D.5.

V. Acute Abdominal Pain

A. **General concepts**
   1. **Definition.** The term **acute abdomen** describes the sudden onset of abdominal pain that requires urgent evaluation, diagnosis, and treatment. Although most acute abdominal pain is self-limited, the pain may result from a serious medical or surgical cause and may require prompt surgical evaluation.
   2. **Etiology (Figure 10-1)**
   3. **Evaluation**
      a. **Complete history** should include questions about recent trauma, prior abdominal pain or surgery, infections, and medication use. **Review of systems** should focus on associated symptoms including fever, vomiting, diarrhea, constipation, anorexia, dysuria, or worsening pain with eating. The timing of symptoms may provide key diagnostic information.
      b. **Physical examination** should include evaluation of the head and neck, chest, abdomen, back, and genitourinary system.
         1. **General assessment.** Restlessness may indicate colicky pain as seen in an obstructed viscus. Abdominal rigidity is seen with a peritoneal process. Constant pain suggests strangulation of the gut or torsion.
         2. **Abdominal examination**
            a. **Intestinal obstruction** may present with high-pitched bowel sounds, abdominal distension, tenderness, and at times, visible peristalsis.
            b. **Peritonitis** presents with diminished or absent bowel sounds, abdominal wall rigidity, involuntary guarding, and often rebound tenderness.
      c. **Diagnostic studies**
         1. **Imaging studies** may include abdominal radiography to identify obstruction, mass, or free air; ultrasound for evaluation of the viscera and fluid; and computer tomography (CT) scan (often with oral, intravenous, and/or rectal contrast) to visualize abdominal anatomy and pathology.
         2. **Laboratory evaluation** should include a complete blood count (CBC), C-reactive protein (CRP), urinalysis, and metabolic panel. Hepatic function tests, amylase and lipase, and testing for pregnancy and sexually transmitted diseases should be performed, if indicated.

B. **Specific causes of abdominal pain**
   1. **Appendicitis**
      a. **Definition.** Appendicitis is obstruction and inflammation of the appendix.
      b. **Epidemiology.** Appendectomy is the **most common pediatric emergency operation.** Peak incidence is **10–12 years of age.**
      c. **Pathophysiology.** The lumen of the appendix is obstructed by either a fecalith or by lymphoid tissue, causing appendiceal distension and ischemia. This distension produces visceral pain referred to the T-10 dermatome or periumbilical region and the release of inflammatory mediators. Without surgical intervention, this process usually leads to perforation within 36–48 hours.
      d. **Clinical features**
         1. **Symptoms** usually **begin with periumbilical pain,** followed by vomiting. Within hours, the pain usually localizes to the **right lower quadrant. Fever and anorexia** are usually present.
         2. **Physical examination** classically demonstrates tenderness to palpation at **McBurney point** (an area two-thirds of the way from the umbilicus to the

anterior superior iliac spine). Voluntary guarding may progress to involuntary guarding and rebound tenderness as peritoneal irritation increases.

3. **Laboratory findings** include **leukocytosis with a polymorphonuclear predominance.**

e. **Diagnosis** may be difficult in children, which contributes to a high rate of perforation (20–50%). Although **abdominal ultrasound or CT scan** often aids in diagnosis, the patient may undergo an appendectomy without having a definitive diagnosis in an attempt to prevent perforation.

f. **Management** consists of fluid resuscitation, perioperative antibiotics, and most often an appendectomy, often by laparoscopy. However, increasing evidence suggests that nonperforated appendicitis can be treated nonsurgically with antibiotics alone. Perforated appendicitis requires drainage of purulent material, irrigation of the peritoneal cavity, and parenteral antibiotics.

2. **Acute pancreatitis**

a. **Definition.** Pancreatitis is an acute inflammatory process of the pancreas that may involve peripancreatic tissues and other organ systems.

b. **Epidemiology.** Pancreatitis is **uncommon** in children.

c. **Pathophysiology.** An initial insult, such as ductal obstruction, abdominal trauma, or viral infection, causes premature activation of pancreatic proenzymes and autodigestion of pancreatic cells. Inflammatory mediators and cytokines damage the pancreas and cause interstitial edema and necrosis. Necrosis of blood vessels may lead to parenchymal hemorrhage.

d. *Etiology.* Causes include **blunt trauma (most common),** infections (e.g., mumps, enterovirus, Epstein–Barr virus [EBV], human immunodeficiency virus [HIV], hepatitis A virus [HAV] and hepatitis B virus [HBV]), drugs and toxins, congenital anomalies, and obstruction. Less commonly, acute pancreatitis may be the result of a systemic illness, such as systemic lupus erythematosus or cystic fibrosis. **Idiopathic pancreatitis accounts for up to 25% of cases in children, and is the second most common cause of pancreatitis during childhood.**

e. **Clinical features**

1. Abdominal pain occurs in the **periumbilical or epigastric area** and may radiate to the back.
2. Fever, anorexia, nausea, and vomiting are common.
3. Physical examination reveals epigastric tenderness, abdominal distension, and decreased bowel sounds. **Grey Turner sign** (bluish discoloration of the flanks) or **Cullen sign** (bluish discoloration of the periumbilical area) may be present in severe cases, caused by blood tracking along fascial planes.
4. Hypotension, tachycardia, hypoxia, and capillary leak may be seen in severe, acute hemorrhagic pancreatitis.

f. **Evaluation**

1. **Serum amylase** levels rise within hours of the onset of pain and remain elevated for 4–5 days. **Serum lipase** level elevation is **more specific** for acute pancreatitis and remains elevated longer than serum amylase levels. It should be noted that other conditions may result in elevated amylase, including gastritis, repeated vomiting (including self-induced vomiting), and renal failure.
2. **Other laboratory abnormalities** may include leukocytosis, hyperglycemia, hypocalcemia, elevated transaminases, and coagulopathy.
3. **Abdominal ultrasound** is the most common method used for diagnosing and monitoring acute pancreatitis. **Abdominal CT scan** is useful in diagnosing

complications, such as abscess, necrosis or **pseudocyst** (described below).

g. **Management**
    1. **Supportive care** includes bed rest, hydration, electrolyte correction, analgesia, and nasogastric suctioning. Oral feedings are usually restricted to minimize pancreatic stimulation.
    2. **In some cases, patients may not be able to tolerate oral feedings for weeks, and TPN** *becomes essential* to prevent protein catabolism. In others, continuous nasogastric or nasojejunal feeds may be used successfully.
    3. **Antibiotics** are indicated for severe, acute necrotizing pancreatitis.
    4. **Surgery** to remove necrotic tissue within and around the pancreas may be indicated. However, surgical intervention for early, acute pancreatitis is controversial.

h. **Complications**
    1. Local complications include abscess formation, necrosis, and **pancreatic pseudocyst.** A pseudocyst is a collection of fluid rich in pancreatic enzymes that arises from pancreatic tissue. A small pseudocyst may resolve on its own. However, a large, persistent pseudocyst may require surgical drainage.
    2. Other complications include respiratory insufficiency, acute respiratory distress syndrome (ARDS), renal failure, shock, and GI bleeding.

3. **Cholecystitis**

a. **Definition.** Inflammation of the gallbladder with transmural edema that may be associated with gallstones or, less commonly, without stones (termed **acute acalculous cholecystitis**)

b. **Epidemiology.** In contrast to adults, acute cholecystitis is uncommon in healthy children. However, it may occur in children with predisposing conditions such as **sickle cell disease,** cystic fibrosis, or prolonged TPN therapy.

c. **Pathophysiology and etiology**
    1. Obstruction of the cystic duct causes increased intraluminal pressure and distension, increased secretion of enzymes and prostaglandins, and progressive inflammation. Infection, necrosis, and perforation may all occur.
    2. Acute acalculous cholecystitis is usually caused by infection (e.g., *Salmonella, Shigella, Escherichia coli*), but may also be seen after abdominal trauma, burns, or vasculitis.

d. **Clinical features**
    1. Abdominal pain is initially diffuse but eventually worsens and localizes to the **right upper quadrant.**
    2. Fever, anorexia, and vomiting are common.
    3. Jaundice may be a late finding.
    4. Physical examination may reveal **Murphy sign** (i.e., palpation of the right upper quadrant during inspiration elicits intense pain and causes the patient to stop inspiratory effort). Guarding and peritoneal signs may also be present.

e. **Evaluation**
    1. Diagnosis is confirmed by **abdominal ultrasound,** which can detect stones and a thickened gallbladder wall.
    2. **Cholescintigraphy** may be useful.
    3. Laboratory findings may include mild elevations of bilirubin and serum transaminases.

f. **Management.** Treatment includes fluid resuscitation, parenteral antibiotics, and analgesia. If the disease progresses or if peritonitis develops, **cholecystectomy** is indicated. This procedure is often performed laparoscopically and may be done

electively after the acute episode resolves.

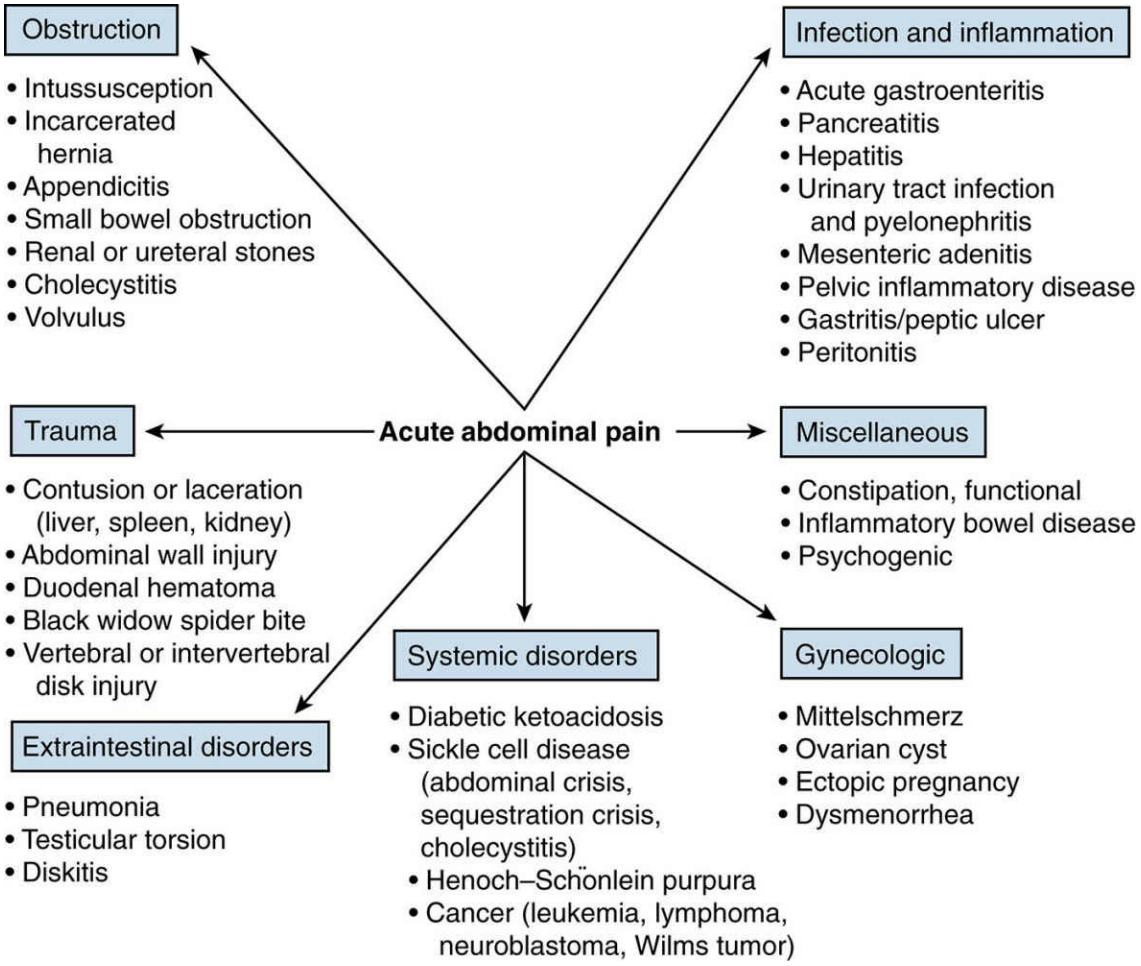

FIGURE 10.1 Etiology of acute abdominal pain during childhood.

VI. Chronic Abdominal Pain

A. **Definitions.** *Chronic abdominal pain (CAP)* is defined as **abdominal pain that occurs each month for at least three consecutive months.**
   1. **Organic CAP** is caused by a disease process or disorder and occurs in *one-third of cases.*
   2. **Nonorganic CAP,** also known as **functional abdominal pain (FAP),** occurs in *two-thirds of cases* and is more common in **females** and in children **older than 5 years.** It is important to highlight that the **patient senses real pain, even in the absence of an underlying organic cause.**

B. **Epidemiology.** *CAP,* occurs in 20–40% of children and adolescents.

C. **Etiology of organic CAP** *(*Table 10-2**)**

D. **Risk factors for nonorganic CAP.** Although the cause is unknown, the following are risk factors that predispose to the development of nonorganic CAP:
   1. **Psychosocial risk factors** include **personality** (e.g., timid, nervous, anxious, overachiever), **birth order** (e.g., first-born and last-born), **life stressors,** including changes in daily routines (e.g., nanny, change in school), **family stressors** (e.g., divorce, separation, parental fighting), and **methods of discipline** that are either too extreme or submissive.
   2. **Risk factors relating to family history** include alcoholism, antisocial or conduct disorders, attention deficit hyperactivity disorder, and family members with functional pain syndromes (e.g., headaches, CAP, musculoskeletal pain).
   3. Some children also have **minor GI disturbances** in motility, or in their sympathetic or parasympathetic nervous systems, which make them susceptible to nonorganic CAP.

E. **Clinical features of FAP**
   1. **Periumbilical pain** is the **classic presentation of FAP.**
   2. The **pain may be varied in character,** including paroxysmal, dull, sharp, or cramping.
   3. The **pain does not interfere with pleasurable activities or sleep** and has no consistent temporal correlation to activity, meals, or bowel patterns.

F. **Evaluation**
   1. **Detailed history and complete physical examination.** A detailed history focusing on symptoms and risk factors for nonorganic CAP, and a comprehensive physical examination with special attention to the abdominal and genitourinary systems, are necessary to exclude organic disease. **The healthier the child appears, the more likely the pain is functional.**
   2. **Laboratory evaluation** should be tempered and based on the clinical symptoms and physical examination.
      a. **Screening laboratories** include CBC, electrolytes, liver function panel, stool for occult blood, stool for parasite screening, urinalysis, and erythrocyte sedimentation rate (ESR) or CRP. If clinical suspicion is high, consider celiac testing.
      b. Screening for ***Helicobacter pylori*** with stool antigen or breath testing should be reserved for children with symptoms of dyspepsia or epigastric pain, because the asymptomatic carriage rate of *H. pylori* is high during childhood.
      c. *Lactose breath hydrogen testing* to rule out lactose intolerance is a reasonable option, because lactose intolerance may be present in as many as 10% of otherwise asymptomatic children.
   3. **Radiographic studies** are not routinely indicated unless warranted by the history or physical examination.

G. **Management**
   1. **Organic CAP** is treated on the basis of the specific diagnosis.

2. **FAP**
    a. **Goals of therapy** include normalization of the child's activities, education of parents as to the nature of the disorder, and development of methods to empower the child and family to control the discomfort.
    b. **Family and individual counseling** are usually necessary.
    c. **Symptomatic medications,** such as antispasmodics, sedatives, or analgesics, are *ineffective.*

H. **Prognosis.** Long-term prognosis of FAP is poor. Only 50% of patients have complete symptom resolution during childhood, and at least 25% of patients go on to have abdominal pain as adults. Poor prognostic factors include male gender, age of onset <6 years, duration of symptoms >6 months, maximum parental education less than high school, lower socioeconomic status, a history of abdominal operations, and having unresolved family issues.

Table 10-2
Organic Causes of Chronic Abdominal Pain

Constipation
Peptic ulcer disease
Carbohydrate intolerance (e.g., lactose, fructose, sorbitol)
Inflammatory bowel disease
Pancreatitis
Celiac disease
***Helicobacter pylori* infection**
Parasitic infection (e.g., *Giardia lamblia* infection)
Genitourinary disorders (e.g., pyelonephritis, hydronephrosis)
Congenital structural abnormalities of the gastrointestinal tract (e.g., malrotation, intestinal duplication, hernia)

VII. Constipation

A. **Definitions**
   1. **Constipation** is defined as a **reduction in defecation** *that causes adverse symptoms,* which may include difficult defecation, painful defecation, abdominal discomfort, and stool retention. Stools are often dry and hard.
   2. Constipation may be associated with **encopresis.** Encopresis is defined as the **developmentally inappropriate release of stool,** unrelated to an organic etiology. **In severe constipation** liquid stool may leak around a hard, retained stool mass and is involuntarily released through the distended anorectal canal.

B. **Epidemiology**
   1. Constipation is **very common** during childhood.
   2. Onset usually occurs during early infancy for organic causes of constipation, and after toilet training for functional constipation [see section VII.D].

C. **Normal stool patterns.** Normal defecation frequency varies with age, with an adult pattern developing by about 4 years of age.
   1. Frequency averages 4×/day during the first week of life, 2×/day by 1 year of age, and 1×/day by 4 years of age.
   2. Adult defecation ranges from 3×/day to 3×/week.
   3. **Breastfed infants defecate more frequently** during the first months of life; however, this decreases rapidly, so that there is no difference in stool pattern between breastfed and formula-fed infants by 4 months of age.

D. **Etiology.** Constipation may be **functional** or **organic.**
   1. **Functional constipation. Functional fecal retention (FFR)** results from inappropriate constriction of the external anal sphincter, and is the **most common form of constipation during childhood.**
      a. **Pathophysiology and etiology. FFR is behavioral.** Infants and toddlers may inappropriately retain stool as a **result of traumatic events** (e.g., hard stool, painful diarrhea, diaper rash, physical abuse) leading to a self-fulfilling cycle of increased fecal mass, fecal hardness, and painful defecation.
      b. **Clinical features.** FFR becomes a behavioral pattern of stool withholding that may lead to large amounts of retained feces with secondary anorectal distension, encopresis, fecal halitosis, abdominal distension and pain, anorexia, urinary tract problems (from pelvic displacement), and psychosocial problems.
   2. **Organic constipation. Organic causes** of constipation represent **fewer than 5%** of cases of childhood constipation and are often present early in *infancy.*
      a. **Hirschsprung disease** is the **most common cause of organic constipation** in an otherwise healthy child (see Chapter 4, section XII.D.5 for details).
      b. See **Table 10-3** for organic causes of constipation.

E. **Evaluation of constipation.** It is necessary to determine if the etiology is organic or whether FFR exists. Although FFR is the most likely cause, a thorough history and physical examination (including a complete neurologic examination) must be conducted to identify the presence of an organic etiology.
   1. **Clues suggesting an organic cause** include delayed meconium passage (>48 hours after birth), onset of constipation during infancy, history of pelvic surgery, encopresis before 3 years of age, and inability to toilet train.
   2. **Clues suggesting FFR** include the development of constipation after toilet training and identification of a **sentinel event** (e.g., change in psychosocial environment, inappropriate toilet training methods, abuse), in the face of continued normal growth

and development.

3. **Diagnostic studies** are only necessary when organic disease is suspected, or if the patient with FFR is failing management. Radiographic studies may include a barium enema, rectal biopsy to rule out Hirschsprung disease, and manometry studies.

F. **Management.** Treatment is based on the suspected cause.

1. Mild, episodic constipation can usually be addressed by ensuring the diet contains adequate **soluble fibers,** and by increasing the amount of water and sorbitol-containing juices.
2. FFR management is based on **cleaning out the fecal mass, softening the stool,** and **educating** the patient and family.
    a. **Stool evacuation** is necessary to begin recovery, and is performed using polyethylene glycol solutions, magnesium salts, mineral oil, enemas, or manual disimpaction.
    b. **Maintenance therapy** most often includes **an osmotic laxative (such as polyethylene glycol)** to soften and lubricate the stool. Mineral oil is useful but should not be used in aspiration-prone infants and children.
    c. **Education is the most important intervention.** Emphasis is placed on identification and correction of triggers, creation of a regular toilet schedule, removal of negative reinforcements, and creation of a positive environment. Individual and family counseling may be helpful.

Table 10-3
Organic Causes of Constipation

Hirschsprung disease
Neuroenteric dysfunction secondary to ischemia, trauma, spinal cord abnormality
Medications (e.g., narcotics, sedatives)
Low-fiber feeding regimens
Anatomic abnormalities (e.g., stricture, adhesion, anteriorly displaced anus)
Systemic disease (e.g., **dehydration, celiac disease**, **hypothyroidism, cystic fibrosis,** diabetes mellitus)
Infant botulism
Lead toxicity
Anorexia nervosa

VIII. Diarrhea

See Chapter 7, section XI.

IX. Inflammatory Bowel Disease (IBD)

A. **Definition.** This is a group of chronic, inflammatory GI disorders that includes **ulcerative colitis (UC)** and **Crohn Disease (CD),** characterized by exacerbations and remissions.

B. **Epidemiology**
   1. The **age of onset is bimodal,** with a peak at 15–20 years of age and a second peak after 50 years of age.
      a. IBD is **increasing in frequency in children,** with 25–30% of all cases of CD and 20% of UC cases presenting before 20 years of age.
      b. Four percent of patients with IBD present before 5 years of age.
   2. Males and females appear equally affected by UC, but there is a 2:1 male-to-female ratio in CD.
   3. Positive family history for IBD is found in approximately 15–20% of patients.

C. **Clinical features**
   1. **Ulcerative Colitis (Table 10-4)**
      a. Inflammation is diffuse, limited to the **mucosa,** and **localized to the colon.** UC usually **begins in the rectum and extends proximally in a contiguous fashion.**
         1. Disease of the rectum only is called **ulcerative proctitis.**
         2. Disease affecting the entire colon is known as **pancolitis.**
      b. **Severity**
         1. **Mild disease,** seen in 60% of cases, presents with rectal bleeding, diarrhea, and abdominal pain.
         2. **Moderate disease,** seen in 30% of cases, presents with nocturnal stooling, cramping, and tenesmus (a continual or recurrent inclination to evacuate the bowels). **Systemic symptoms** of weight loss, anorexia, fever, and anemia may also occur.
         3. **Severe disease,** seen in 10% of cases, presents with more than six stools per day, fever, anemia, leukocytosis, and hypoalbuminemia.
      c. **Extraintestinal manifestations** are less common during childhood and are noted in **Table 10-4**.
      d. *Complications of severe UC*
         1. **Toxic megacolon.** This severe inflammation of the colon leads to decreased intestinal motility, disruption of the mucosal barrier that allows bacteria to enter, and colonic dilatation. Patients present with **fever, abdominal distension,** and **septic shock** and are at risk for perforation and hemorrhage.
         2. **Increased risk of colon cancer**
   2. **Crohn Disease (Table 10-4)**
      a. CD may involve **any segment of the GI tract,** from the mouth to anus.
         1. Unlike UC, the inflammation is eccentric and **segmental** with **"skip lesions."**
         2. Inflammation is **transmural**.
         3. Most children have disease involving the **terminal ileum.**
      b. Intestinal symptoms include abdominal pain, postprandial cramping, diarrhea, and anorexia.
         1. **Initial symptoms may be subtle,** with abdominal pain or decreased growth being the only findings.
         2. Small bowel disease often leads to **malabsorption** with resultant iron, zinc, folate, and vitamin B_{12} deficiencies.
         3. **Perianal disease** often precedes the development of intestinal disease and presents with skin tags, fissures, fistulas, and abscesses.

c. **Extraintestinal complications are more common in CD** than in UC and are noted in **Table 10-4**.
d. **Complications** are caused by the transmural nature of CD and include abscesses, fistulas, strictures, and adhesions.
e. **CD is a chronic** disorder with high morbidity but low mortality. Patients are prone to **frequent exacerbations** despite treatment.

D. **Evaluation.** In addition to a history and physical examination, the following are generally indicated:
1. **Laboratory analyses**
a. **CBC** often shows anemia or leukocytosis.
b. **CRP** is usually elevated.
c. **Serum albumin** and **serum transaminases** to assess nutritional status and liver disease
d. **Stool calprotectin is a very good screen for IBD.**
2. **Stool studies** should be performed to rule out infectious enteropathies.
3. **Abdominal ultrasound** and **CT imaging** can be used to visualize abscesses and thickened bowel walls. **UGI study** with small bowel follow-through can reveal mucosal ulcerations, narrowed lumens, thickened walls, and fistulas.
4. **Colonoscopy with biopsies** of the colon and terminal ileum *confirms the diagnosis.*

E. **Management.** *Treatment* principles include controlling symptoms, reducing recurrences, and optimizing nutrition.
1. **Pharmacotherapy**
a. **Sulfasalazine** and other 5-aminosalicylic acid (ASA) drugs are effective for mild disease, especially for UC, and can also prevent relapses.
b. **Corticosteroids** are often given to calm acute exacerbations and induce remission.
c. **Immunosuppressive agents** are useful in inducing and maintaining long-term remission.
d. **Biologics**, including bioengineered anti-TNF monoclonal antibodies, are quite effective for IBD but are expensive and require parenteral administration.
e. **Metronidazole** is used in the treatment of CD, especially for perianal involvement.
2. **Surgery**
a. **UC can be cured with a total proctocolectomy,** but this is reserved for intractable colitis. Total colectomy is associated with infertility risk in females.
b. Surgical therapy for CD is only considered for persistent obstruction, bleeding, abscesses, and fistulas that do not respond to medical therapy. *Recurrence rate is very high after bowel resection.*
3. **Enteral therapy.** Replacement of normal diet with commercial enteric formulas has been shown to induce and maintain remission in many children with CD and is in wide use worldwide. Total parenteral nutrition may be necessary during flare-ups to ensure adequate growth and healing.

Table 10-4
Differentiation of Ulcerative Colitis and Crohn Disease

Characteristic	Ulcerative Colitis	Crohn Disease
Location	Colon	Any segment of gastrointestinal tract, especially terminal ileum
Rectal bleeding	Frequent	Occasional
Rectal disease	Almost always	Occasional
Perianal disease (skin tags, fistulas, fissures, abscesses)	Rare	Common
Lesions	Contiguous lesions	Skip lesions

Transmural involvement	No	Yes
Extraintestinal manifestations	Uveitis, arthropathy, pyoderma gangrenosum, sclerosing cholangitis	FTT, delayed sexual development, oral aphthous ulcers, erythema nodosum, arthritis, renal stones
Complications	Toxic megacolon	Strictures, fistulas, abscesses
Risk of colon cancer	Significantly increased	Somewhat increased

FTT = failure to thrive.

X. Gastrointestinal Bleeding

A. **Definitions.** Blood loss from the GI tract may occur in several ways, and the presentation may help determine origin of the bleeding.
   1. **Hematemesis** is the vomiting of fresh or old blood, which may have a "coffee ground" appearance from the denaturing of hemoglobin.
   2. **Hematochezia** is bright red blood passed per rectum, usually indicating a lower GI source or a significant rapid bleed from an upper lesion.
   3. **Melena** is dark, tarry stools and often indicates an upper GI bleed **proximal to the ligament of Treitz.**

B. **Laboratory confirmation of GI bleeding.** *Occult bleeding* from the GI tract is confirmed by positive guaiac testing of stool. Guaiac is a colorless dye that changes color from the peroxidase activity of hemoglobin in the presence of hydrogen peroxide developer. Newer occult blood testing uses more specific and sensitive immune assays.
   1. **False-positive** guaiac results may occur because of ingested iron, rare red meats, beets, and foods with high peroxidase content, such as cantaloupe, broccoli, and cauliflower.
   2. **False-negative** guaiac results may occur as a result of large ingested doses of vitamin C.

C. **UGI bleeding**
   1. **Etiology**
      a. Newborns may **swallow maternal blood** during delivery or while nursing from a bleeding nipple. Older children may swallow blood during an episode of **epistaxis** and can present with emesis that mimics a GI bleed.
      b. **Gastritis or ulcers** may occur as a result of severe stress of illness, surgery or burns, or from medications. Ulcers may also develop in children with ***H. pylori*** infection.
      c. Mechanical injury to the mucosa from vomiting (i.e., **Mallory–Weiss tear**) or from foreign body or caustic ingestion may cause UGI bleeding.
      d. **Varices** as a result of portal hypertension or vascular malformations are less common causes.
   2. **Evaluation**
      a. Initial assessment must include a detailed history and physical examination.
         1. Particular attention must be given to the patient's **hemodynamic status.**
         2. Active bleeding is assessed by obtaining a **nasogastric tube aspirate** for fresh blood.
         3. The **nose and oropharynx** should be inspected for non-GI sources of bleeding.
      b. **Laboratory studies** should include hemoglobin and platelet counts, coagulation studies, serum transaminases, and a blood urea nitrogen (BUN) level (suggests a GI bleed if elevated). Patients with active bleeding or hemodynamic changes should have blood sent for type and crossmatch.
      c. **Plain film radiography** has a **limited role** in diagnosis but may be useful if a foreign body or perforation is suspected.
      d. **Upper intestinal endoscopy** for diagnosis and management is indicated for active bleeding with hemodynamic changes.
   3. **Management**
      a. Initial **stabilization** of hypovolemia and anemia is essential. Intravenous access with two large-bore peripheral lines should be established, and a rapid **fluid bolus** of 20 mL/kg of normal saline solution should be given as needed. (See Chapter 20, section II.D for a discussion of the management of shock.)
      b. **Medical therapy** to control UGI bleeding may be useful. Octreotide (vasopressin) can be used to vasoconstrict varices. Ulcers associated with *H. pylori* should be

treated with appropriate antibiotic therapy. Gastritis, esophagitis, and ulcers should also be treated with methods to decrease acid production, such as H_2-blockers or proton pump inhibitors.

c. **Endoscopic therapy** (e.g., photocoagulation, banding, vessel ligation, injection with sclerosing agents) is indicated for active bleeding or if rebleeding is very likely.
d. **Arteriographic embolization** may be used for serious bleeding from vascular malformations.
e. **Surgical treatment** is usually indicated for duodenal ulcers with active arterial bleeding, perforation, or varices.

D. **Lower GI bleeding**

1. **Etiology.** Age is an important factor in determining the cause of lower GI bleeding (**Table 10-5**).
   a. **Necrotizing enterocolitis** should be considered in any newborn who presents with rectal bleeding, feeding intolerance, or abdominal distension (see Chapter 4, section XII.E).
   b. **Juvenile polyps** are the **most common cause** of significant lower GI bleeding beyond infancy. Bleeding is painless, intermittent, and often streaky. Colonoscopy with polypectomy is the definitive treatment.
   c. **Hirschsprung disease** may present with colitis and abdominal distension.
   d. **Allergic colitis** from sensitization to protein antigens in cow's milk, soy milk, or breast milk may develop in neonates and infants.
   e. **Infectious enterocolitis** from bacterial pathogens such as *Salmonella, Shigella, Campylobacter, Yersinia,* and *E. coli* can occur at any age (see Chapter 7, Table 7-6).
   f. **Meckel diverticulum** is an outpouching of the bowel in the terminal ileum that occurs in 2% of infants. It is an important cause of lower GI bleeding in infants and children. The diverticulum contains ectopic gastric mucosa that produces acid. This acid damages adjacent intestinal mucosa, causing the classic presentation of **painless, acute rectal bleeding** in an otherwise healthy child. A nuclear medicine scan identifies the **ectopic gastric mucosa,** and surgical resection is required.
   g. Vasculitis can also cause lower GI bleeding.
      1. **Hemolytic uremic syndrome** is a vasculitis characterized by **microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure**. Intestinal ulceration and infarction of the bowel cause bleeding (see Chapter 11, section VII).
      2. **Henoch–Schönlein purpura** is an IgA-mediated vasculitis that presents with a **palpable, purpuric rash on the buttocks and lower extremities, large joint arthralgias, renal involvement, and GI bleeding** from complications such as intussusception and bowel perforation (see Chapter 11, section V.F.3 and Chapter 16, section I).
   h. **IBD** is an important cause of occult and frank GI bleeding.

2. **Evaluation and management.** As with upper GI bleeding, assessment of hemodynamic status, monitoring for ongoing bleeding, and stabilization are essential. Laboratory studies, intravenous access, and fluid resuscitation are indicated as for upper GI bleeding. Specific management is based on the identified cause.

Table 10-5
Differential Diagnosis of Gastrointestinal Bleeding

Neonate (Birth–1 Month of Age)	Infant/Young Child (1 Month–2 Years of Age)	Preschool Age (2–5 Years)	School Age (>5 Years)	Adolescent (10–21 Years)
Swallowed	Anal fissure	Infectious colitis	Infectious colitis	Infectious

maternal blood Allergic colitis Necrotizing enterocolitis Hirschsprung disease Volvulus	Allergic colitis Infectious colitis Hirschsprung disease Intussusception Meckel diverticulum Intestinal duplication Vascular malformation	Juvenile polyp Meckel diverticulum Hemolytic uremic syndrome Henoch–Schönlein purpura Swallowed blood (e.g., epistaxis) Mallory–Weiss tear	Juvenile polyp Inflammatory bowel disease Swallowed blood (e.g., epistaxis) Mallory–Weiss tear	colitis Juvenile polyp Inflammatory bowel disease Mallory–Weiss tear Peptic ulcer/gastritis

XI. Liver Abnormalities and Hepatitis

A. **General concepts of hepatic injury**
   1.
      a. Direct hepatocellular damage or damage to the biliary system results in derangements in the liver's synthetic ability, excretory function, or detoxification.
      b. Cellular damage also leads to the release of intracellular enzymes characteristic of the originating cell.
      c. Obstruction or damage to the biliary system causes retention of bile enzymes that damage the cells lining the biliary tree and hepatocytes.

B. **Laboratory assessment of liver injury and function**
   1. **Hepatocellular enzymes**
      a. **Aspartate aminotransferase (AST)** elevation is a **sensitive but nonspecific marker** of hepatocyte injury. AST is also found in skeletal muscle, red blood cells, and cardiac tissue.
      b. **Alanine aminotransferase (ALT)** elevation is a **more specific marker of liver disease** but is also found in muscle tissues.
      c. **Lactate dehydrogenase (LDH)** elevation is nonspecific for liver disease, although it may serve as a marker for hepatocellular necrosis.
   2. **Biliary enzymes**
      a. **Alkaline phosphatase** may be elevated in biliary disease, although it may also be elevated in children because of rapid growth; in bone, kidney, and intestinal disease; and in trauma.
      b. **Gamma glutamyl transpeptidase (GGTP) and 5′-nucleotidase (5NT)** are also elevated in biliary disease. 5NT is more specific than GGTP for biliary tract damage.
   3. **Bilirubin** is derived from the breakdown of heme.
      a. **Unconjugated (indirect) bilirubin** is combined with glucuronide by the enzyme **uridine 5′-diphospho (UDP)–glucuronyl transferase** in the liver to form mono- and diconjugates (**conjugated or direct bilirubin**).
      b. **Elevated bilirubin** may be a consequence of **increased heme load** (e.g., hemolysis, polycythemia, hematoma), **decreased capacity for excretion** (e.g., hepatitis, liver failure), or **obstruction to bile flow** (e.g., biliary atresia, choledochal cyst).
   4. **Synthetic function** is assessed by evaluating protein production (e.g., **prealbumin, albumin,** and **prothrombin time**), serum chemistries (e.g., **glucose, cholesterol**), and toxin clearance (e.g., **lactate, ammonia**).

C. **Infant jaundice** (Neonatal jaundice is discussed in Chapter 4, section X.)
   1. **Definitions**
      a. **Infant jaundice** is defined as elevated bilirubin after the neonate period and within the first year of life. Bilirubin collects in the skin, conjunctiva, and mucous membranes and becomes clinically evident when the total bilirubin level exceeds 3 mg/dL.
      b. **Cholestatic jaundice** is defined as **retention of bile within the liver** and occurs clinically when the **direct component of bilirubin is >2 mg/dL or ≥15% of the total bilirubin.**
   2. **Epidemiology**
      a. **As many as 50% of all neonates or infants experience transient jaundice,** the majority of whom have **unconjugated (indirect) hyperbilirubinemia.**
      b. **Conjugated (direct) hyperbilirubinemia** is a marker for cholestasis. Cholestasis occurs in 1 in 10,000–15,000 live births, and more than **50% are caused by neonatal**

hepatitis or biliary atresia [see sections XI.D.2 and XI.D.3].

3. **Clinical features**
   a. Jaundice typically **begins cranially and extends caudally** as bilirubin increases.
   b. Infants often **appear otherwise well.**
4. **Evaluation.** It is important to focus on establishing whether cholestasis exists and whether the problem is isolated to the liver.
   a. **History** should focus on timing of jaundice onset, associated symptoms (e.g., poor growth, bleeding, dark urine), feeding regimen (e.g., breast or bottle, frequency of feedings), and stool quality and color.
   b. **Past medical history** should include prenatal history, medications, infections, and family history of liver disease or jaundice.
   c. **Physical examination** should be comprehensive.
   d. **Laboratory evaluation** should initially include CBC, electrolytes, and assessments of hepatic function. Further testing is directed on the basis of clinical suspicions. **It is difficult to predict the level of bilirubin from the extent of jaundice on physical examination. Measurement of direct and total bilirubin is therefore necessary in all patients with suspected jaundice.**
   e. **Imaging** should include abdominal ultrasound with Doppler evaluation of the hepatic vessels.
   f. **Liver biopsy** is invasive and is reserved for confirmation of diagnosis, for assessment for hepatic injury, or when the evaluation remains inconclusive.
5. **Categories of jaundice**
   a. The differential diagnosis of **unconjugated hyperbilirubinemia** is presented in **Chapter 4, section X.C** and **Figure 4-3.** Two additional causes of unconjugated hyperbilirubinemia are worth noting now:
      1. **Inspissated bile syndrome** is associated with **hemolysis** (e.g., ABO incompatibility) or with a very large **hematoma.** In these cases, the biliary system becomes overwhelmed by the increased bilirubin load. Although unconjugated hyperbilirubinemia predominates early, conjugated hyperbilirubinemia eventually develops as hepatocellular function increases to meet demand.
      2. **UDP-glucuronyl transferase deficiency** can present in three distinct states.
         a. **Gilbert syndrome,** in which **50% of enzyme activity is absent. Mild** *unconjugated bilirubinemia* occurs associated with stress or poor nutrition.
         b. **Crigler–Najjar type 1** is an **autosomal recessive** disorder in which **almost 100% of enzyme activity is absent.** *Kernicterus caused by extremely high bilirubin levels occurs almost universally.*
         c. **Crigler–Najjar type 2** is an **autosomal dominant** disorder in which **90% of enzyme activity is absent.** Bilirubin levels are more variable with a lower likelihood of kernicterus.
   b. The differential diagnosis of **conjugated hyperbilirubinemia** is presented in **Chapter 4, Figure 4-4**.

D. **Cholestatic diseases of infancy**

1. **General concepts**
   a. Cholestasis is characterized by retention of bile within the liver with **prolonged elevation of conjugated (direct) bilirubin.**
   b. **Etiology**
      1. **Infections** (e.g., sepsis, hepatitis, viral infections)
      2. **Metabolic derangements** (e.g., cystic fibrosis, hypothyroidism, galactosemia)
      3. **Extrahepatic mechanical obstruction** (e.g., biliary atresia, bile duct stricture)

4. **Intrahepatic mechanical obstruction** (e.g., paucity of intrahepatic bile ducts, Alagille syndrome)
5. **Idiopathic** (e.g., neonatal hepatitis)
6. **α_1-Antitrypsin deficiency**
7. **TPN-associated disease**

c. **Clinical features of cholestasis**
1. **Jaundice**
2. **Acholic or light stools**
3. **Dark urine**
4. **Hepatomegaly**
5. **Bleeding** (occurs as a result of prolongation of the prothrombin time as a result of diminished hepatic synthetic function)
6. **Failure to thrive**

2. **Neonatal hepatitis**
a. **Definition.** Neonatal hepatitis is **idiopathic hepatic inflammation** during the neonatal period. It is a **diagnosis of exclusion,** and it is the **most common cause of cholestasis in the newborn.**
b. **Epidemiology.** Incidence is 1 in 5000–10,000 live births, with a **male predisposition.**
c. **Clinical features**
1. **Symptoms may range** from transient jaundice and acholic stools to liver failure, cirrhosis, and portal hypertension.
2. **Presenting features in the first week of life include jaundice and hepatomegaly in 50% of patients.** FTT and more significant liver disease occur later in infancy in 33% of patients.
3. The **course of disease is generally self-limited,** with full recovery during infancy in as many as 70% of patients.

d. **Diagnosis** is on the basis of clinical presentation, findings on liver biopsy, and exclusion of other causes of cholestasis.
e. **Management is supportive.**
1. Decreased fat absorption may lead to growth failure and vitamin deficiencies. Increased **nutritional support** with concentrated calories, use of medium-chain triglyceride–containing formulas, and provision of **fat-soluble vitamins A, D, E, and K** are indicated. **TPN** may be needed if growth remains problematic.
2. **Ursodeoxycholic acid,** a bile acid, is used to enhance bile flow and to reduce bile viscosity.
3. **Liver transplantation** may be necessary in cases of severe liver failure.

3. **Biliary atresia**
a. **Definition.** Biliary atresia is a **progressive fibrosclerotic disease** that affects the **extrahepatic biliary tree.** Fifty percent of all pediatric liver transplants are performed for liver failure caused by biliary atresia.
b. **Epidemiology.** Incidence is 1 in 10,000 live births.
c. **Etiology is unknown.**
d. **Clinical features**
1. **Two-thirds of patients present between the ages of 4 and 6 weeks** with jaundice, dark urine, and pale or acholic stools. The remaining one-third of patients present earlier, within the first 2 weeks of life, and therefore the presentation **can be confused with physiologic jaundice.**
2. **Bilirubin levels are moderately elevated.**
3. **Progression of disease is rapid,** with **bile duct obliteration and cirrhosis**

occurring by 4 months of age.

4. Other signs and symptoms include **hepatosplenomegaly,** ascites, poor growth, steatorrhea, peripheral edema, and coagulopathy.
5. Some infants have an associated **polysplenia syndrome** with multiple spleens, bilobed lungs, abdominal heterotaxia, and situs ambiguous. These patients present earlier and progress more rapidly.

e. **Diagnosis must be rapid to affect outcome.**
   1. Abdominal ultrasound and liver biopsy are performed in rapid sequence to rule out other causes of cholestasis.
   2. **Intraoperative cholangiogram with laparotomy, or percutaneous cholangiogram, to examine the biliary tree confirms the diagnosis.**

f. **Management** focuses on supportive care and reestablishing bile duct continuity.
   1. **Kasai portoenterostomy** (Roux-en-Y intestinal loop attached directly to the porta hepatis) is the **treatment of choice to establish bile flow;** however, its success diminishes rapidly with increasing patient age at presentation. **Success is highest if the procedure is performed by 50–70 days of age. Cholangitis** *is a worrisome complication* of the procedure that occurs in as many as 50% of patients, and repeated episodes can stop all bile flow.
   2. **Liver transplantation** is indicated for liver failure and late clinical presentations.
   3. **Supportive care** includes nutrition, fat-soluble vitamin supplementation, and, once bile flow is reestablished, ursodeoxycholic acid.

4. **Alagille syndrome**
   a. **Definition.** This **autosomal dominant** disorder is characterized by **paucity of intrahepatic bile ducts and multiorgan involvement.**
   b. **Epidemiology.** Incidence is 1 in 70,000 live births. Two-thirds of patients have an abnormality on chromosome 20 affecting the JAG 1 gene.
   c. **Clinical features**
      1. Features of **cholestatic liver disease** are indistinguishable from neonatal hepatitis and biliary atresia. Of note, **pruritus in these patients can be debilitating.**
      2. **Unusual facial characteristics** include a broad forehead, deep-set and wide-spaced eyes, a saddle nose with a bulbous tip, pointed chin, and large ears.
      3. **Cardiac disease** often includes **pulmonary outflow obstruction** alone, or as part of tetralogy of Fallot.
      4. **Renal disease** occurs in up to one half of patients.
      5. **Eye anomalies** include **posterior embryotoxon.**
      6. **Musculoskeletal anomalies** include butterfly vertebrae and broad thumbs.
      7. **Growth failure and short stature**
      8. **Pancreatic insufficiency**
      9. **Hypercholesterolemia**
   d. **Diagnosis** is on the basis of clinical features, liver biopsy, and genetic testing to exclude other causes of cholestasis, such as biliary atresia.
   e. **Management** is supportive.

E. **Wilson disease** may cause acute and chronic hepatitis and liver failure. Hepatic involvement is more common than neuropsychiatric symptoms during childhood. See Chapter 5, section XI.A.

F. **Viral hepatitis**
   1. **General concepts**
      a. **Epidemiology.** Incidence varies with the specific virus. The **majority of infections**

in children and adolescents are caused by Hepatitis A infection (HAV) and Hepatitis B infection (HBV).

b. **Pathophysiology**
   1. Liver inflammation associated with viral hepatitis is caused by either hepatotropic viruses discussed below (HAV, HBV, hepatitis C virus [HCV], hepatitis delta virus [HDV], and hepatitis E virus [HEV]) or by other viruses that cause liver inflammation as part of a more widespread disease process (e.g., EBV, varicella-zoster virus, HIV, herpes simplex virus).
   2. Infection results in varying degrees of liver inflammation and swelling. Although hepatocytes are primarily infected, hepatobiliary obstruction results from local swelling. Damage also occurs as a result of the host immune response.

c. **Clinical features. Most infections during infancy and childhood are asymptomatic.**
   1. If present, **symptoms** may include malaise, anorexia, vomiting, fever, diffuse or right upper quadrant abdominal pain, edema, and bruising or bleeding.
   2. **Signs on examination** may include jaundice, hepatosplenomegaly, ascites, increased abdominal vascular markings, caput medusae, spider hemangiomas, and clubbing.

d. **Management** is supportive in the acute phase with specific therapies for chronic disease.

e. **Prevention** of hepatitis A and B is now possible through vaccination. See Chapter 1, sections III.C.1 and III.C.8 for discussions of these vaccinations.

2. **Hepatitis A infection** is caused by HAV, a picornavirus.
   a. **Epidemiology**
      1. **Transmission** is by the **fecal–oral** route through contaminated foods and water or by contact with contaminated individuals (e.g., food handlers). **It is the most common hepatitis virus–causing infection.**
      2. Virus is shed in the stool 2–3 weeks before the onset of symptoms and 1 week after the onset of jaundice.
   b. **Clinical features**
      1. **Incubation period** is **2–6 weeks,** with mean symptom onset at 28 days.
      2. Infection is **asymptomatic in the majority of children** (>70%). Older children and adults are more likely to have symptomatic infection. Jaundice occurs very rarely.
      3. Chronic infection does not occur, although the disease may relapse with return of symptoms in up to 25%.
   c. **Diagnosis is based on serology.** Figure 10-2 describes the time course of infection and the presence of detectable antibodies to HAV.
      1. **Elevated IgM anti-HAV** is present early and can persist for as long as 6 months after infection.
      2. **Elevated IgG anti-HAV** also occurs early in infection and confers lifelong immunity.
   d. **Management** of symptomatic infection is supportive.
3. **Hepatitis B infection** is caused by HBV, a DNA virus.
   a. **Epidemiology. Transmission** is by **perinatal vertical** exposure from an infected mother to her fetus; by the **parenteral** route through exposure to infected blood products, tattooing needles, and intravenous drug use; or by exposure to infected **body secretions.** HBV is found in most body fluids, including blood, tears, saliva, semen, vaginal secretions, urine, feces, and breast milk.

b. **Clinical features**
    1. **Incubation period is 45–160 days** with mean symptom onset of 90 days.
    2. **Acute symptoms of hepatitis** [see section XI F.1.c] occur in <5% of infants, 5–15% of preschool children, and 30–50% of older children and adolescents. **Symptoms are extremely variable,** ranging from asymptomatic infection to nonspecific systemic illness to clinical hepatitis and fulminant liver failure.
    3. **Chronic HBV infection is most common in young infants** who acquire the virus from perinatal exposure but is less common in older children. Chronic HBV infection may result in chronic liver disease with cirrhosis, hepatic fibrosis, portal hypertension, and **increased risk for hepatocellular carcinoma.**
c. **Diagnosis** is on the basis of **serology** (see **Figure 10-3**, which describes the time course of infection and the presence of detectable antigens and antibodies to HBV).
    1. **HBV surface antigen (HBsAg) is pathognomonic for active disease.** It is the antigen used in the hepatitis B vaccine.
    2. **HBV surface antibody (HBsAb)** is **protective** and can result from **vaccination** or **natural infection.**
    3. **HBV core antibody (HBcAb)** results from natural infection (not vaccination) and persists lifelong.
    4. **HBV e antigen (HBeAg)** rises very early in active infection and is therefore useful in diagnosing acute infection.
    5. **HBV e antibody (HBeAb)** rises late in infection.
    6. **HBV polymerase chain reaction (PCR)** may be used for both diagnosis and assessing the response to therapy.
d. **Management** includes supportive care for acute infection and consideration of antivirals for chronic infection.

4. **Hepatitis C infection** is caused by HCV, an RNA virus in the flavivirus family.
    a. **Epidemiology**
        1. **Transmission** is by perinatal vertical route from mother to fetus or by parenteral exposure.
        2. HCV accounts for 90% of transfusion-associated hepatitis and 50% of "non-A, non-B" hepatitis.
    b. **Clinical features.** Acute infection is **rarely symptomatic** (especially in children), although **chronic infection** may result in cirrhosis and hepatic fibrosis. Chronic infection occurs in 80% of infected patients.
    c. **Diagnosis** is by serology demonstrating HCV antibody in the blood. HCV PCR is used as a confirmatory test for chronic infection.
5. **Hepatitis D infection** is caused by HDV, an RNA virus that **requires HBsAg for replication.** Transmission is by parenteral exposure, and infection can occur with or without active hepatitis B infection. Infection may be inconsequential, may cause progression of hepatitis B infection, or may precipitate fulminant liver failure. Diagnosis is by serology demonstrating HDV antigen and antibody.
6. **Hepatitis E infection** is caused by HEV, an RNA virus. Hepatitis E is responsible for **50% of acute hepatitis in young adults in developing countries** and is associated with **20% mortality in infected pregnant women.** Transmission is by **fecal–oral** route. Chronic disease does not occur. Diagnosis is by serology demonstrating HEV antibodies.

G. **Autoimmune hepatitis**
1. **Definition.** This **destructive and progressive** liver disease is characterized by **elevated serum transaminases, hypergammaglobulinemia, and circulating autoantibodies.**
2. **Categories.** Two categories of autoimmune hepatitis are based on autoantibody types.

a. **Type 1 disease** is characterized by the presence of **antinuclear antibody** (ANA) or **anti–smooth muscle antibody.** Type 1 disease is more common than type 2 disease.
b. **Type 2 disease** is characterized by anti–liver kidney microsome antibody or anti–liver cytosol type 1 antibody.

3. **Epidemiology**
   a. Autoimmune hepatitis occurs predominantly in **females with presentation before puberty.**
   b. Other **nonhepatic autoimmune diseases** (e.g., UC, vasculitis, vitiligo) occur in 20–40% of patients with autoimmune hepatitis.
4. **Clinical features**
   a. **Fifty percent** of patients present with **acute hepatitis,** mimicking viral hepatitis, and **50%** of patients present with **chronic liver disease.**
   b. **Jaundice** is usually mild to moderate.
   c. **Nonhepatic signs and symptoms** include fatigue, anorexia, arthritis, rash, nephritis, and vasculitis.
5. **Diagnosis** is on the basis of clinical presentation, typical laboratory findings, and exclusion of other liver diseases. A **high degree of suspicion** is required in patients with a family history of autoimmune disease, in those with nonhepatic autoimmune disease, and in those with chronic liver disease.
   a. **Laboratory studies** reveal **elevated serum transaminases, hypergammaglobulinemia, and circulating autoantibodies.**
   b. **Liver biopsy** is generally performed to evaluate for cirrhosis, to grade disease activity, and to exclude other diagnoses.
6. **Management** includes supportive care, **corticosteroids** for initial control of hepatic inflammation, and **immunosuppressive agents,** such as azathioprine or 6-mercaptopurine. Liver transplantation is indicated for severe liver disease.

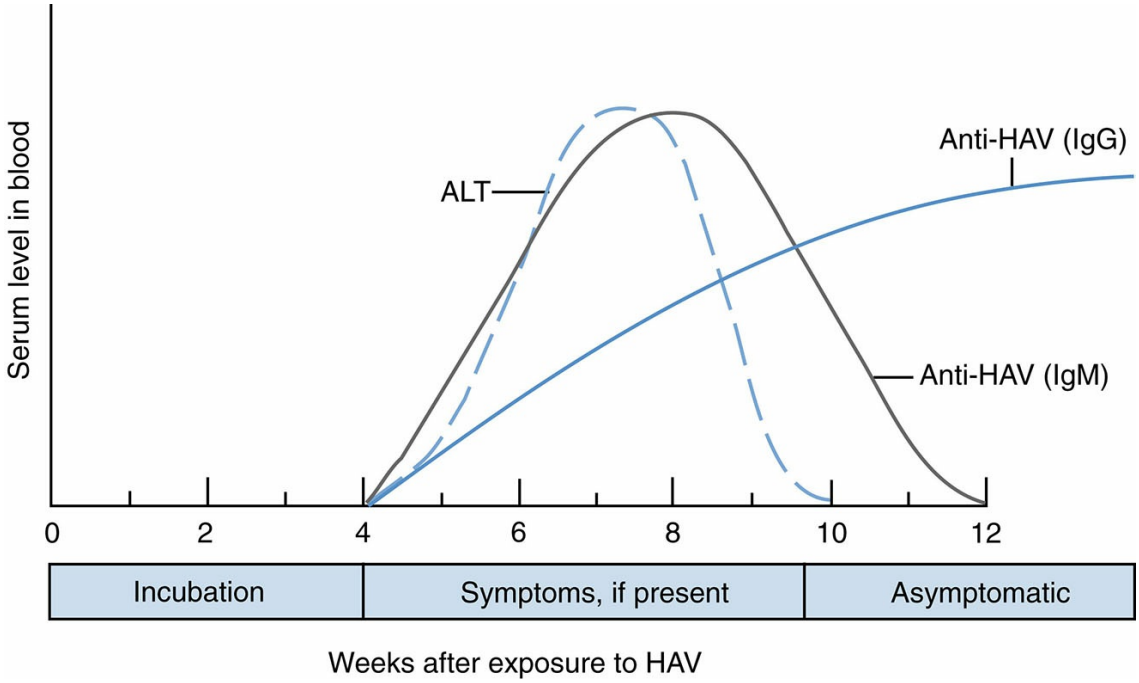

FIGURE 10.2 Time course of hepatitis A infection and the presence of detectable antibodies to hepatitis A. *Anti-HAV (IgM)* = IgM antibody to hepatitis A; *Anti-HAV (IgG)* = IgG antibody to hepatitis A; *HAV* = hepatitis A virus; *ALT* = alanine aminotransferase.

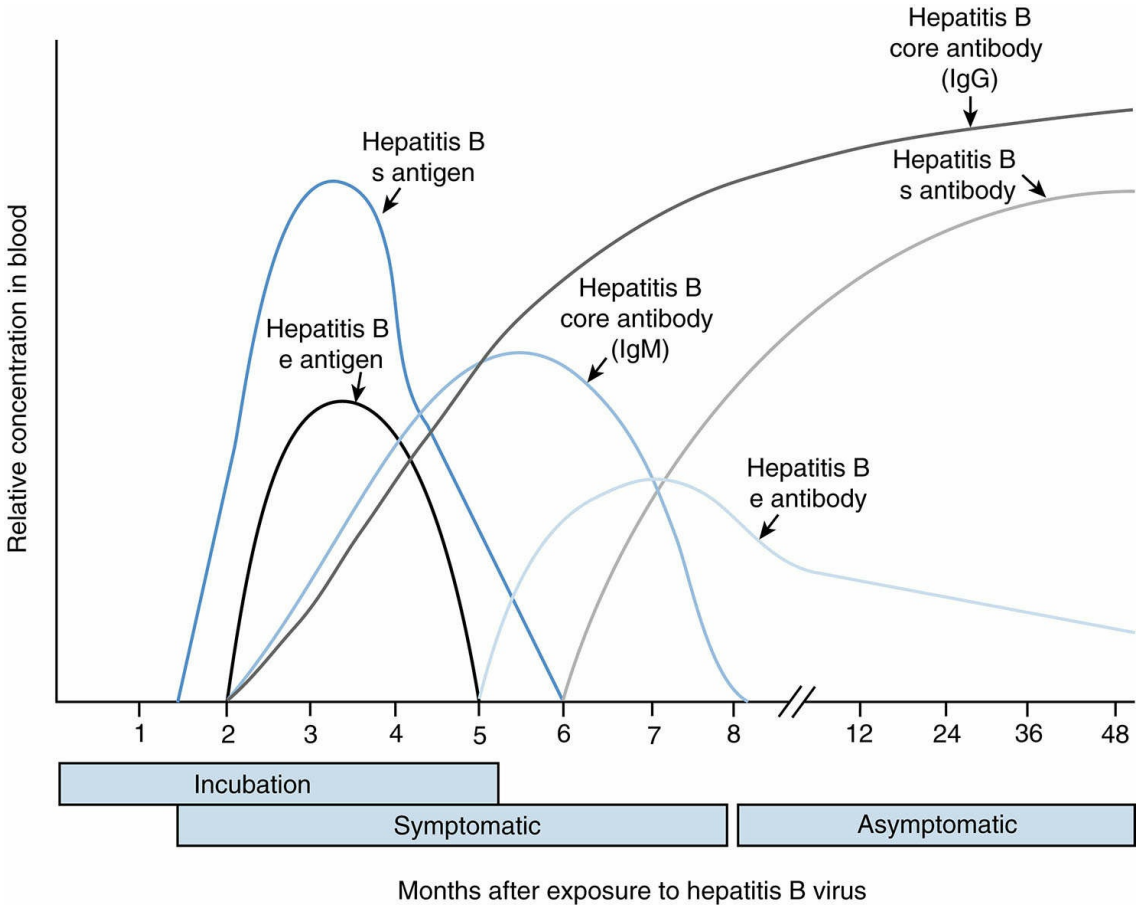

FIGURE 10.3 Time course of acute hepatitis B infection and the presence of detectable antigens and antibodies to hepatitis B.

Review Test

1. A 2-month-old female infant presents with acute onset of crying and bilious vomiting. On examination, her abdomen is tender and distended. Upper intestinal contrast imaging demonstrates intestinal malrotation with midgut volvulus. Which of the following conditions is also associated with this diagnosis?
   A. Hypertrophic pyloric stenosis
   B. Ulcerative colitis
   C. Renal anomalies
   D. Down syndrome
   E. Heterotaxy
2. A 6-week-old male infant is admitted to the pediatric ward with vomiting and dehydration. The parents note that their child has been vomiting for the past 3 weeks with increasing severity and frequency. Initially, he would spit up a small amount after every other feeding. However, for the past week, he has vomited forcefully after each breastfeeding. To the parents, it seems like he vomits the entire feeding. He has remained hungry, with no fever and no diarrhea. During the past 2 days, he has had only two wet diapers per day. After admission, serum electrolytes are drawn. Based on the most likely diagnosis, which of the following would be the most likely electrolyte pattern?
   A. Hypernatremic, hypokalemic metabolic acidosis
   B. Hypernatremic, hypokalemic metabolic alkalosis
   C. Hypochloremic, hypokalemic metabolic alkalosis
   D. Hyperchloremic, hypokalemic metabolic alkalosis
   E. Hypochloremic, hypokalemic, metabolic acidosis
3. You are called to evaluate a newborn in the nursery who has been vomiting after every feeding. The prenatal history is notable for polyhydramnios, and the physical examination is significant for a scaphoid abdomen and paucity of bowel sounds. Which of the following is the most likely diagnosis?
   A. Congenital diaphragmatic hernia
   B. Hypertrophic pyloric stenosis
   C. Intestinal malrotation
   D. Duodenal atresia
   E. Hirschsprung disease
4. An 8-year-old girl is brought to the emergency department with a 3-day history of periumbilical abdominal pain that radiates to the back, as well as nausea, vomiting, and anorexia. The girl's mother denies any recent travel, ill contacts, and trauma to her abdomen. Laboratory assessment reveals an elevated white blood cell count, mild hyperglycemia, and elevated amylase and lipase. Which of the following is the most likely underlying cause of her disorder?
   A. Idiopathic
   B. Sepsis
   C. Viral infection
   D. Drug or toxin exposure
   E. Congenital anomalies of the pancreas
5. A previously healthy 9-month-old girl is brought to the emergency department with an 18-hour history of intermittent, inconsolable crying interspersed with periods of lethargy. She has vomited twice and has had one bowel movement that the mother describes as bloody. Based on the clinical presentation, which of the following is the most appropriate diagnostic procedure at this time?

A. Plain abdominal radiography
B. Upper gastrointestinal imaging with small bowel follow-through study
C. Barium enema
D. Surgical exploration
E. Abdominal ultrasound

6. A 3-year-old boy is brought to the office by his parents, who are concerned because he has hard, painful stools. For the past 4 months, their son defecates every 3–4 days and cries during the stooling. The resulting stool is very hard. Physical examination of the child is normal. Which of the following is correct regarding his constipation?
   A. His constipation is unlikely to lead to encopresis.
   B. A barium enema should be ordered to evaluate for Hirschsprung disease.
   C. His constipation likely resulted from a traumatic triggering event, such as a severe, painful diaper rash or painful diarrhea.
   D. Abdominal radiographs should be ordered to evaluate for an underlying organic cause of his constipation.
   E. The parents should be instructed to encourage their son to drink juice with each meal, and the boy should be reevaluated in 3–4 months.
7. A 4-week-old, formula-fed male infant has a history of blood-tinged stools with mucus for the past few days. His mother reports that he has been fussier than usual lately but has had no fever, vomiting, or cold symptoms. Physical examination reveals mild abdominal distension but is otherwise normal. You suspect cow's milk protein allergy. Which of the following is the most appropriate next step to confirm diagnosis?
   A. Abdominal radiographs
   B. Small bowel biopsy
   C. Allergen skin testing
   D. Stool-reducing substances and pH
   E. Change his diet to an alternative protein source

The response options for statements 8 and 9 are the same. You will be required to select one answer for each statement in the following set.

A. Celiac disease
B. Crohn disease
C. Ulcerative colitis
D. Irritable bowel syndrome
E. Lactase deficiency

For each patient, select the likely diagnosis.

1. A 15-year-old girl presents with abdominal cramps and diarrhea for 2 weeks. Examination reveals two perianal skin tags and pubertal delay.
2. A 10-year-old boy has a history of bloody diarrhea and abdominal pain. He now presents with high fever, low blood pressure and abdominal distension.
3. A 4-year-old girl is brought to the urgent care center with an acute onset of vomiting blood. Her parents report that her symptoms began abruptly 3 hours ago, and since then she has had four episodes of bloody emesis. Vital signs reveal a heart rate of 152 beats/minute and a blood pressure of 110/56 mm Hg. Which of the following is the most appropriate first step in management?
   A. Begin intravenous H_2-blockers.
   B. Order urgent upper endoscopy.
   C. Order a complete blood count to assess the patient's hemoglobin.

D. Place two large-bore peripheral lines and administer a 20 mL/kg normal saline fluid bolus.
E. Place a nasogastric tube and aspirate to assess for blood.

4. A 12-month-old female infant with failure to thrive is brought to the office. Her parents note that she is very fussy and often spits up after feedings. She also has two loose foul-smelling stools each day. Serologic testing reveals elevated serum tissue transglutaminase antibody. Which of the following foods can she eat safely without aggravating or inducing her symptoms?
   A. Rice
   B. Wheat
   C. Oats
   D. Barley
   E. Rye
5. A 4-month-old female infant has gastroesophageal reflux disease confirmed by pH probe. She has failed to respond to conservative management that included positioning and thickened feeds. Which of the following is the most appropriate next management step?
   A. Initiation of medical therapy
   B. Changing her diet to a hydrolyzed amino acid formula
   C. Nissen fundoplication
   D. Gastric antroplasty
   E. Gastrostomy tube feedings
6. A 5-week-old male infant has been brought to the clinic by his parents, who have concerns about jaundice. He was born at full-term, weighing 8 pounds, 9 oz, and he had an uncomplicated delivery and neonatal course. Today, his weight is 9 pounds, 1 oz, and his vital signs are normal. On examination, his liver is enlarged and 4 cm below the right costal margin. Jaundice is present. Laboratory evaluation reveals a total bilirubin of 12.9 mg/dL with a direct component of 5.9 mg/dL. Which of the following is the next most appropriate step in management?
   A. Begin phototherapy to treat the patient's jaundice.
   B. Refer the patient for a liver transplant.
   C. Begin ursodeoxycholic acid to enhance bile flow.
   D. Order an urgent abdominal ultrasound and refer for a liver biopsy.
   E. Reassure the parents that no treatment is required as he likely has neonatal hepatitis.
7. A 5-year-old girl has a 4-day history of nausea, vomiting, diarrhea, and loss of appetite. On physical examination, her conjunctiva are icteric and the right upper quadrant of her abdomen is tender. You suspect hepatitis A infection. Which of the following is correct regarding this diagnosis?
   A. The presence of jaundice is unusual in a child of her age with hepatitis A infection.
   B. She should also be tested for hepatitis D infection, which may occur in association with hepatitis A.
   C. Chronic infection occurs in 25% of patients.
   D. She is likely to be noninfectious at this point in her illness.
   E. Serologic testing at this point in her illness will reveal elevated IgM antibody to hepatitis A only; IgG antibody to hepatitis A rises late in infection.
8. A 10-year-old girl is in the office for follow-up of abdominal pain that first occurred 5 months ago. The pain is periumbilical in location and is described vaguely as sometimes sharp, sometimes dull, and sometimes burning. The pain occurs only during the day; she denies waking up at night secondary to pain. She is able to participate in her soccer practice and games after school and on weekends. Fever, vomiting, diarrhea, and dysuria are all absent. Examination is normal, except for very mild abdominal tenderness on palpation of her

periumbilical region. She is otherwise a very healthy-appearing girl with normal growth and development. You suspect functional abdominal pain. Which of the following is correct regarding this likely diagnosis?

A. Almost all patients have resolution of their symptoms by adulthood.
B. Most cases of chronic abdominal pain have an organic cause.
C. Your counseling should include making sure the patient understands that her pain is not real but imagined.
D. Even though her pain is functional, she may also have a minor disturbance in her sympathetic or parasympathetic nervous system that has put her at risk for pain.
E. Given the degree of pain, she should be given permission to miss school when the pain is present.

Answers and Explanations

1. **The answer is E** [IV.B.2]. Malrotation is the result of abnormal rotation and fixation of the intestines in utero. In heterotaxy, the intestines begin their rotation from an already abnormal position, and this results in final fixation in a variable position. This variable rotation and final position can lead to twisting of the intestines and volvulus. Pyloric stenosis is a thickening of the pylorus muscle that results in projectile vomiting. Intestinal malrotation is not present in this disorder. Ulcerative colitis is a type of inflammatory bowel disease in which many intestinal manifestations may be present, including rectal bleeding, diarrhea, abdominal pain, and toxic megacolon, but not intestinal malrotation. Patients with Down syndrome may have duodenal atresia but are at no increased risk for malrotation. Renal anomalies are not associated with malrotation.
2. **The answer is C** [IV.A.4 and IV.A.5]. The infant's symptoms are the classic presentation of hypertrophic pyloric stenosis. Forceful vomiting of stomach contents develops, and the vomiting persists unless it is corrected surgically. This persistent vomiting causes a progressive loss of hydrogen ions and chloride, resulting in hypochloremia and a metabolic alkalosis. If hydrogen ion loss is severe, hypokalemia often develops as well.
3. **The answer is D** [IV.C.1]. Duodenal atresia is a congenital anomaly that develops because of failure of the intestinal lumen to recanalize early in gestation. As a result, the fetus is unable to swallow significant amounts of amniotic fluid, and this may lead to polyhydramnios. Postnatally, duodenal atresia leads to vomiting, epigastric distension (proximal to the obstruction), and absence of intestinal bowel gas that causes a scaphoid appearance to the abdomen. Although the abdomen may be scaphoid in appearance with congenital diaphragmatic hernia, polyhydramnios is not associated with this condition, and these infants present with severe respiratory distress at birth. Pyloric stenosis, malrotation, and Hirschsprung disease are not associated with a scaphoid abdomen or polyhydramnios.
4. **The answer is A** [V.B.2.d]. The clinical presentation is most consistent with pancreatitis. In children, approximately 25% of cases of pancreatitis are idiopathic (without identifiable cause). Idiopathic pancreatitis is second only to blunt abdominal trauma, which is the leading cause of acute pancreatitis during childhood. Sepsis, viral infections, and drug or toxin exposure are other important causes of pancreatitis in children but are less common than trauma or the idiopathic category. Congenital anomalies of the pancreas and biliary tree are also less common causes.
5. **The answer is E** [IV.D.5]. This infant's history is consistent with intussusception, in which the intestine telescopes into itself, causing bowel wall edema, mucosal injury, and eventually necrosis. The child typically presents with colicky abdominal pain, often accompanied by vomiting, lethargy, and bloody stools. The most appropriate initial test to diagnose intussusception is an abdominal ultrasound. Experienced radiologists may also then perform the potentially therapeutic contrast enema under ultrasound guidance. Surgical exploration is indicated for intussusception that fails to reduce with contrast enema or if peritonitis is suspected. Plain radiography is not generally sensitive for this diagnosis. Upper gastrointestinal imaging with small bowel follow-through will not show most cases of intussusception, which most commonly occurs in the ileocolic location.
6. **The answer is C** [VII.D.1]. This patient's constipation is most likely functional or nonorganic (functional fecal retention). Functional constipation results from an inappropriate constriction of the external anal sphincter. Most commonly, toddlers retain stool purposely because of a traumatic event, such as a painful diaper rash, painful diarrhea, or even physical or sexual abuse. Encopresis may be associated with severe constipation and could eventually result in this patient. Organic causes of constipation (e.g., Hirschsprung disease, hypothyroidism,

infant botulism) account for less than 5% of constipation seen during childhood. Therefore, radiographic studies are not indicated unless suggested on the basis of history or physical examination. Because this patient's constipation is associated with pain, management should include stool evacuation using osmotic laxatives, enemas, or other modalities. Recommendations for increased dietary fiber, water, and juice are important adjuncts to treatment but alone are insufficient for this patient whose constipation is significant and resulting in very hard stools and crying during defecation.

7. **The answer is E** [II.B.3]. Protein intolerance occurs in up to 8% of all infants and is usually caused by cow's milk protein or soy protein allergy. Protein intolerance may present with vomiting, diarrhea, irritability, rectal bleeding, and weight loss. Diagnosis of protein intolerance is made up on resolution of symptoms after a complete withdrawal of the suspected antigen. Symptoms usually resolve within 1–2 weeks of stopping the offending protein. Because this approach to treatment and diagnosis is noninvasive and effective, abdominal radiographs, small bowel biopsy, and allergy testing are not necessary and are overly invasive for this 4-week-old. In addition, radiographs are not diagnostic, and this infant is too young for a response to allergy skin testing. Stool-reducing substances and an abnormal acidic pH are found in carbohydrate malabsorption, not protein malabsorption.
8. **The answers are B and C, respectively** [IX.C and Table 10-4]. Patients with Crohn disease, like the girl in question 8, may present with diarrhea, abdominal cramping, and loss of appetite. Perianal skin disease, such as skin tags, fissures, and fistulas, may precede intestinal symptoms. Patients with Crohn disease may also have poor growth and delayed puberty. Patients with ulcerative colitis, like the boy in question 9, often present with rectal bleeding, diarrhea, and abdominal pain. In addition, his presentation with fever, abdominal distension and low blood pressure may be consistent with toxic megacolon, a severe complication of ulcerative colitis. In contrast, celiac disease presents with bloating, foul-smelling stools, diarrhea, and vomiting. Delayed sexual maturity is unusual, stools are nonbloody, and perianal disease is not usually present. Irritable bowel syndrome is associated with bloating, cramping, and alterations in stool patterns. Lactase deficiency is a disorder of carbohydrate absorption and presents with bloating and diarrhea.
9. **The answer is D** [X.C.3.a]. Before further investigation or definitive therapy, the most important step in any patient who may have hypovolemia or significant or worsening anemia is initial stabilization, including the ABCs (airway, breathing, and circulation). This includes placement of two large-bore intravenous lines for fluid resuscitation. Because the heart rate is elevated, suggesting hypovolemia, a normal saline solution bolus would also be an appropriate initial step in management. After stabilization, placement of a nasogastric tube to confirm upper gastrointestinal bleeding and ordering a complete blood count to assess the patient's hemoglobin are appropriate. Intravenous H_2-blockers are used if gastritis, esophagitis, or ulcer disease is suspected. Upper endoscopy would also likely be needed to diagnose the cause of the bleeding, but after the patient has been initially stabilized.
10. **The answer is A** [II.C.2.b and II.C.5]. This patient presents with the classic features of celiac disease (gluten-sensitive enteropathy). Signs and symptoms usually develop between 6 months and 2 years of age when gluten is introduced into the diet. The treatment of celiac disease is restriction of gluten from the diet. Wheat, barley, and rye all contain gluten. Oats also usually contain gluten because most oats are harvested in fields that also contain wheat. Rice is the only food listed that does not contain gluten and can be eaten safely by patients with celiac disease.
11. **The answer is A** [III.G.2]. Gastroesophageal reflux disease results from inappropriate transient lower esophageal sphincter relaxation that allows gastric contents to reflux into the esophagus, and manifests as vomiting, irritability, arching of the back, poor weight gain, and pulmonary symptoms (e.g., wheezing). After a trial of conservative management that includes positioning

and thickened feeds, medical management with antacids, H_2-blockers, or proton-pump inhibitors is indicated. Dietary changes would be ineffective at this time. Nissen fundoplication with gastric antroplasty and gastrostomy tube feedings may be required should medical management fail.

12. **The answer is D** [XI.C.1, XI.C.4.e, and XI.C.4.f]. This patient has cholestasis, or retention of bile within the liver, manifested by the elevated conjugated (direct) bilirubin. In addition, the findings of hepatomegaly and poor growth (he has only gained 8 oz since birth) are consistent with the diagnosis of cholestasis. The causes of cholestasis are many, and biliary atresia and choledochal cyst must always be considered and ruled out rapidly in any infant who presents with conjugated hyperbilirubinemia. This evaluation includes an abdominal ultrasound and liver biopsy in rapid sequence. Should biliary atresia not be identified promptly (by 50–70 days of age), liver transplantation may be the only treatment option. Phototherapy is not indicated for direct hyperbilirubinemia. Neonatal hepatitis is a possible cause of this patient's symptoms, but biliary atresia must first be ruled out. Ursodeoxycholic acid enhances bile flow, but it is recommended only once biliary obstruction has been excluded.
13. **The answer is A** [XI.F.2 and Figure 10-2]. Hepatitis A infection is the most common hepatitis virus infection and usually occurs through fecal–oral contamination. Only 30% of children infected with the hepatitis A virus have symptoms of hepatitis (the majority of hepatitis A infections are asymptomatic during childhood), but even those with hepatitis symptoms very rarely have jaundice. Hepatitis D infection requires the presence of hepatitis B surface antigen (HBsAg) for replication, not hepatitis A virus. Chronic hepatitis A infection does not occur, but up to 25% can have a relapse of symptoms at some point after recovery from the initial infection. Patients shed virus in the stool for 2–3 weeks before the onset of any symptoms and for 1 week after the onset of symptoms. Serologic testing confirms the diagnosis. Both IgM and IgG antibodies to hepatitis A virus rise early in infection.
14. **The answer is D** [VI.C and Table 10-2]. Nonorganic or functional abdominal pain is much more common than organic abdominal pain in children. However, although the pain is nonorganic, some children do have minor disturbances in gastrointestinal motility or in their parasympathetic or sympathetic nervous systems that make them susceptible to the pain. It is important to understand that the pain is real to the patient, and therefore, management should focus on empowering the child and family to overcome the discomfort. In addition, the child must resume and normalize all activities, including attending school even when pain is present. Although 50% of patients have resolution of symptoms during childhood, at least 25% still have pain as adults.

CHAPTER 11

Nephrology and Urology

Elaine S., Kamil, Lee Todd, Miller

I. Fluids, Electrolytes, and Dehydration

A. **General principles**
   1. The **most common cause of acute fluid and electrolyte imbalance is acute diarrhea with dehydration.**
   2. Worldwide, acute diarrheal diseases are among the leading causes of childhood morbidity and mortality.

B. **Total body fluid requirement** *is the sum of a patient's maintenance fluid needs, replacement of prior fluid losses (i.e., deficits), and replacement of ongoing losses,* if any.
   1. **Maintenance water and electrolyte calculations** are designed to balance the usual daily losses of water and salts that occur as a result of normal daily metabolic activities. These losses take both measurable forms (**sensible losses**), such as urinary losses, and less readily measurable but still clinically significant forms (**insensible losses**), such as losses from the skin, lungs, and gastrointestinal (GI) tract.
      a. **Maintenance water requirement is** approximately **1500 mL/m^2/day** for children. Water requirements for infants and premature infants vary with the birth weight and postnatal age.
      b. **Maintenance water requirement may alternatively be calculated** from the patient's weight.
         1. **100 mL/kg/day** for the first 10 kg of body weight
         2. **50 mL/kg/day** for the second 10 kg of body weight
         3. **20 mL/kg/day** for each kg above the first 20 kg of body weight
      c. **Maintenance fluids should be increased** if the patient has **increased insensible losses,** such as **respiratory distress and fever (i.e., about a 10% increase for every degree of temperature).**
      d. **Maintenance sodium (Na^+) requirement is approximately 2–3 mEq/kg/day.**
      e. **Maintenance potassium (K^+) requirement is approximately 2 mEq/kg/day.**
   2. **Deficit fluid calculations** are designed to replace **abnormal losses of water and salts** caused by pathologic states, such as diarrhea and vomiting. Deficit fluids are calculated as follows: **Fluid deficit (L) = pre-illness weight (kg) − current weight (kg).**
   3. **Ongoing loss calculations** are designed to replace additional losses of water and salts after the patient's initial evaluation (e.g., ongoing vomiting or diarrhea, nasogastric tube aspirate). These ongoing losses are replaced milliliter for milliliter.

C. **Dehydration** *may be classified* by both the **initial serum Na^+ level and by the degree of dehydration.**
   1. **Classification by serum sodium concentration**
      a. **Hyponatremic** dehydration **(Na^+ < 130 mmol/L)**
      b. **Isonatremic** dehydration **(Na^+ = 130–150 mmol/L)**
      c. **Hypernatremic** dehydration **(Na^+ > 150 mmol/L)**
   2. **Classification by degree of dehydration**
      a. **Mild dehydration (3–5%)** is associated with normal pulse rate and quality, flat fontanelle, dry mucous membranes, normal skin turgor, normal capillary refill, and normal to decreased urine output.
      b. **Moderate dehydration (7–10%)** is associated with mild tachycardia with a weak pulse, flat fontanelle, deep set eyes, reduced tears, dry mucous membranes, skin tenting, and capillary refill of about of 2 seconds, in a patient with decreased urine output.
      c. **Severe dehydration (≥10%)** is associated with tachycardia and feeble pulse, sunken fontanelle, sunken eyes, no tears, parched and cracked lips and buccal mucosa,

clammy skin, and capillary refill >3 seconds, in a patient with lethargy and anuria.

D. **Parenteral rehydration** should occur in **two phases:**
   1. **Emergency phase**
      a. **The goal of the emergency phase** is to restore or maintain the intravascular volume to ensure perfusion of vital organs.
      b. The emergency phase is **the same for all patients,** regardless of the patient's initial serum sodium level.
      c. **20 mL/kg boluses** of intravenous (IV) solutions with a high enough oncotic load (e.g., **normal saline** or **lactated Ringer solution**) are commonly used.
   2. **Repletion phase**
      a. The **goal of the repletion phase** is a more gradual correction of the patient's water and electrolyte deficits.
      b. Patients with the **acute onset of hyponatremic or isonatremic dehydration** generally have their fluid and electrolyte deficits replaced **over 24 hours.** Chronic hyponatremia should be corrected much more slowly.
      c. Patients with **hypernatremic dehydration** generally have their fluid and electrolyte deficits replaced more slowly, usually **over 48 hours,** to minimize **the risk of cerebral edema** that may accompany rapid fluid correction.

E. **Oral rehydration therapy (ORT)**
   1. **ORT may be an effective, safe, and inexpensive alternative** to IV rehydration therapy.
   2. **Oral rehydration salt (ORS) solutions** are **balanced mixtures of glucose and electrolytes** for use in treating and preventing dehydration, potassium depletion, and base deficits caused by diarrhea.
   3. ORT is based on the principle that the intestinal absorption of sodium and other electrolytes is enhanced by the active absorption of glucose (**coupled cotransport mechanism**). This coupled cotransport process of intestinal absorption **continues to function normally during secretory diarrhea,** whereas other pathways of intestinal absorption of sodium are impaired.
   4. **ORT is inappropriate** for patients with severe life-threatening dehydration, for patients with paralytic ileus or GI obstruction, and for patients with extremely rapid stool losses or repeated severe emesis losses.

II. Hematuria

A. **Definition.** Hematuria is defined as the presence of red blood cells (RBCs) in the urine. Hematuria may be seen on voiding (**gross hematuria**) or only on urinalysis (**microscopic hematuria**). **Microscopic** hematuria is defined as ≥5–6 RBCs per high-power field (HPF) detected on two or more consecutive samples.

B. **Epidemiology.** Approximately 5% of school children have microscopic hematuria detected on a single voided urine sample, but only 0.5–2% have persistent microscopic hematuria.

C. **Clinical significance.** Microscopic hematuria may be an indicator of a serious medical condition such as a tumor or chronic glomerulonephritis or may be of no serious medical consequence. Discolored urine may not be from blood in the urine. See **Figure 11-1** for clues regarding the causes of discolored urine. The **differential diagnosis of hematuria** is outlined in **Figure 11-2**.

D. **Evaluation** (**Figure 11-1**)**.** Detection of hematuria may be by urinary dipstick or by microscopy. **Urinary dipstick** detects the presence of hemoglobin or myoglobin in the urine. **False-negative results** may occur with **ascorbic acid** (vitamin C) ingestion. **Microscopic urinalysis may also provide helpful clues.** When RBCs are present on microscopic examination, **careful examination of RBC morphology and identification of other urine elements, such as casts or bacteria, may be extremely helpful** in determining the cause of the hematuria.

1. **RBC morphology**
   a. RBCs originating in the glomerulus are dysmorphic in character, often with blebs in the RBC membrane.
   b. RBCs that appear to be normal biconcave disks usually originate in the lower urinary tract.
2. **RBC casts** are diagnostic of glomerular bleeding, which usually occurs in acute or chronic glomerulonephritis.
   a. **Crystals** may be indicative of renal stone disease.
   b. Large numbers of RBCs (especially in the presence of dysuria) may indicate **acute hemorrhagic cystitis,** which may result from bacterial infections, viral infections (e.g., adenovirus), or chemotherapeutic agents (e.g., cyclophosphamide).

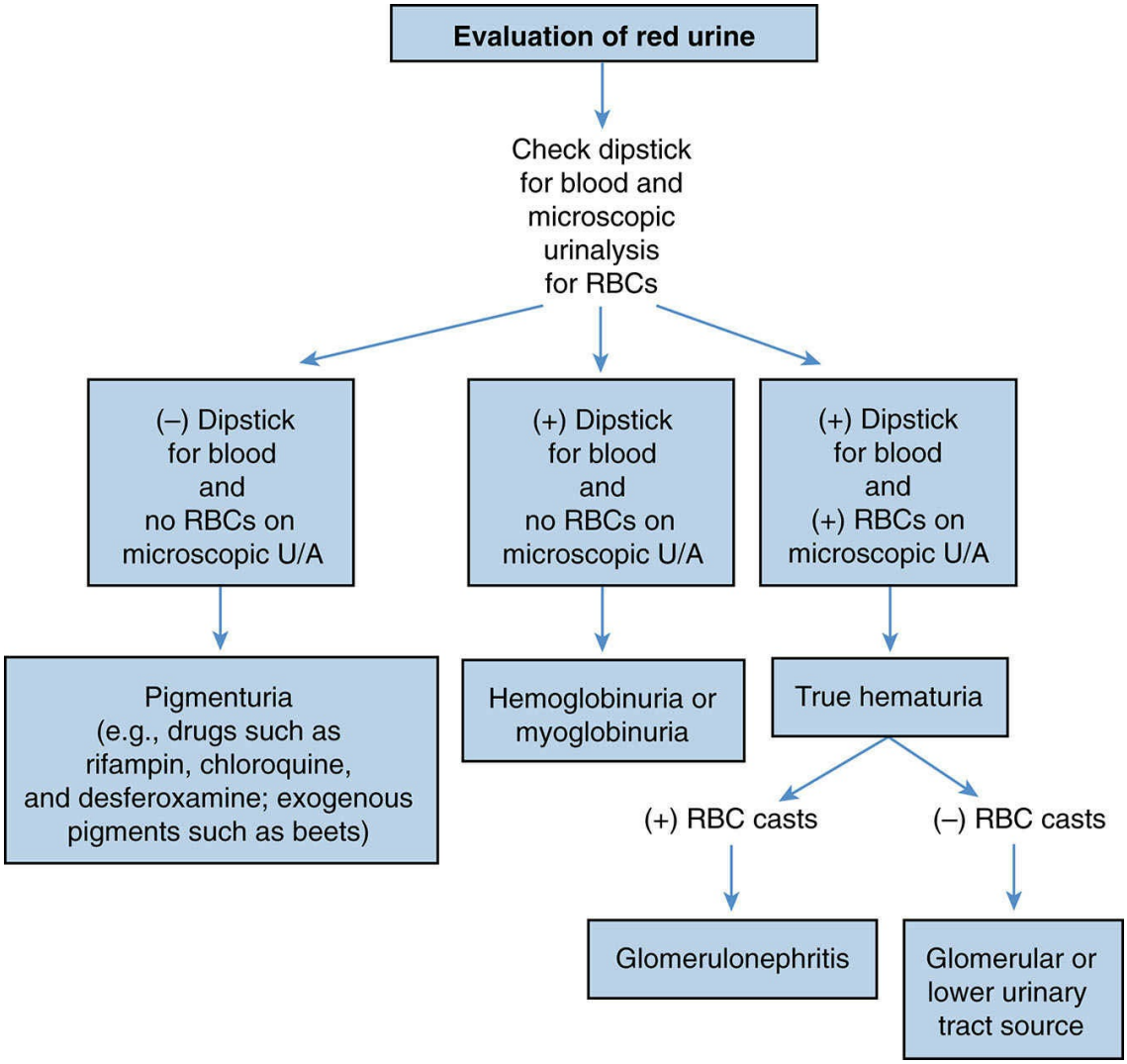

FIGURE 11-1 An approach to red urine. *RBC* = red blood cell; *U/A* = urinalysis.

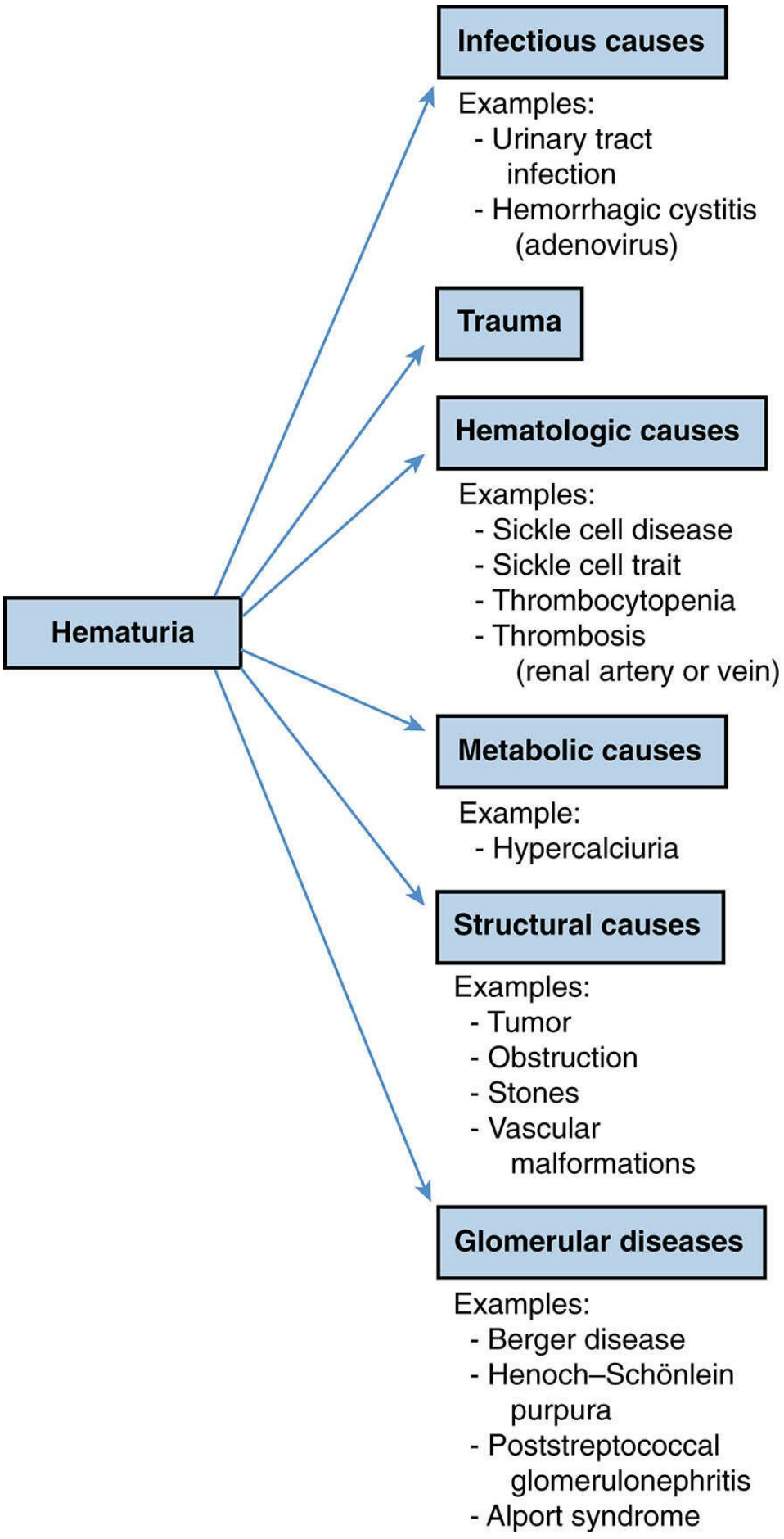
Hematuria
Infectious causes
Examples:
- Urinary tract infection
- Hemorrhagic cystitis (adenovirus)
Trauma
Hematologic causes
Examples:
- Sickle cell disease
- Sickle cell trait
- Thrombocytopenia
- Thrombosis (renal artery or vein)
Metabolic causes
Example:
- Hypercalciuria
Structural causes
Examples:
- Tumor
- Obstruction
- Stones
- Vascular malformations
Glomerular diseases
Examples:
- Berger disease
- Henoch–Schönlein purpura
- Poststreptococcal glomerulonephritis
- Alport syndrome

FIGURE 11-2 Differential diagnosis of hematuria.

III. Proteinuria

A. While a small amount of protein is normally present in the urine, **proteinuria greater than 100 mg/m^2/day** or an elevated urine total protein/creatinine ratio are considered pathologic.

B. **Detection**

1. **Urinary dipstick** is the most frequently used method of screening for proteinuria and detects variable levels of **albuminuria.**
    a. **False positives** may result if the urine is very concentrated (specific gravity > 1.025) or alkaline (pH ≥ 7.0), or if the patient has received certain medications (e.g., penicillin, aspirin, IV contrast imaging agents, oral hypoglycemic agents).
    b. **False negatives** may result if the urine is very dilute.
2. **Twenty-four–hour urinary protein collection** (normal is <100 mg/m^2/day) **is the most accurate method of detecting proteinuria** but is very difficult to obtain in children. Instead, a **random spot urine total protein-to-creatinine ratio (TP/CR)** is usually performed. An early morning sample correlates well with 24-hour urinary protein excretion.
    a. Normal urine TP/CR for infants of age 6–24 months is <0.5.
    b. Normal urine TP/CR for children of age >2 years is <0.2.

C. **Epidemiology.** Up to 10% of children have a single positive dipstick test for proteinuria at some point; however, <1% have persistent proteinuria on repeated dipstick evaluations.

D. **Classification**

1. **Benign transient proteinuria.** Increased urinary protein excretion may sometimes be associated with vigorous exercise, fever, dehydration, and congestive heart failure (CHF).
2. **Orthostatic proteinuria**
    a. Certain children and adults (especially athletic individuals) have increased urinary protein excretion while upright but not while supine.
    b. Orthostatic proteinuria is usually a **benign condition,** and its confirmation eliminates the need for further workup.
    c. The presence of orthostatic proteinuria is diagnosed with an elevated afternoon urine TP/CR and a normal first morning urine TP/CR.
3. **Persistent pathologic proteinuria**
    a. Persistent pathologic proteinuria may be associated with significant renal disease and is considered a marker for progression of renal disease.
    b. Generally, **the greater the magnitude of the proteinuria, the more serious the renal disease.** The greatest amounts of proteinuria are seen in patients with nephrotic syndrome [see section VI].
    c. Persistent pathologic proteinuria may have a **glomerular** origin or a **tubular** origin. Glomerular proteinuria is more common.
        1. **Glomerular proteinuria** is caused by increased permeability of the glomerular capillaries to large molecular weight proteins, as seen in glomerulonephritis [see section V] and in minimal change nephrotic syndrome.
        2. **Tubular proteinuria** results from decreased reabsorption of low molecular weight proteins by the tubular epithelial cells, or by the addition of inflammatory proteins to the tubular urine.
            a. **Examples of tubular proteinuria** include interstitial nephritis, ischemic renal injury (acute tubular necrosis, acute kidney injury [AKI]), and tubular damage resulting from nephrotoxic drugs.
            b. **Laboratory findings** include elevated levels of **urinary β_2-microglobulin,**

a good marker for tubular proteinuria among others. This small molecule, which is freely filtered at the glomerulus, is normally almost completely reabsorbed by the tubular epithelial cells. Its presence therefore signifies tubular injury. **Glucosuria** and **aminoaciduria** may also accompany diffuse injury to the tubular epithelial cells.

E. **Evaluation of proteinuria** *(*Figure 11-3**)**

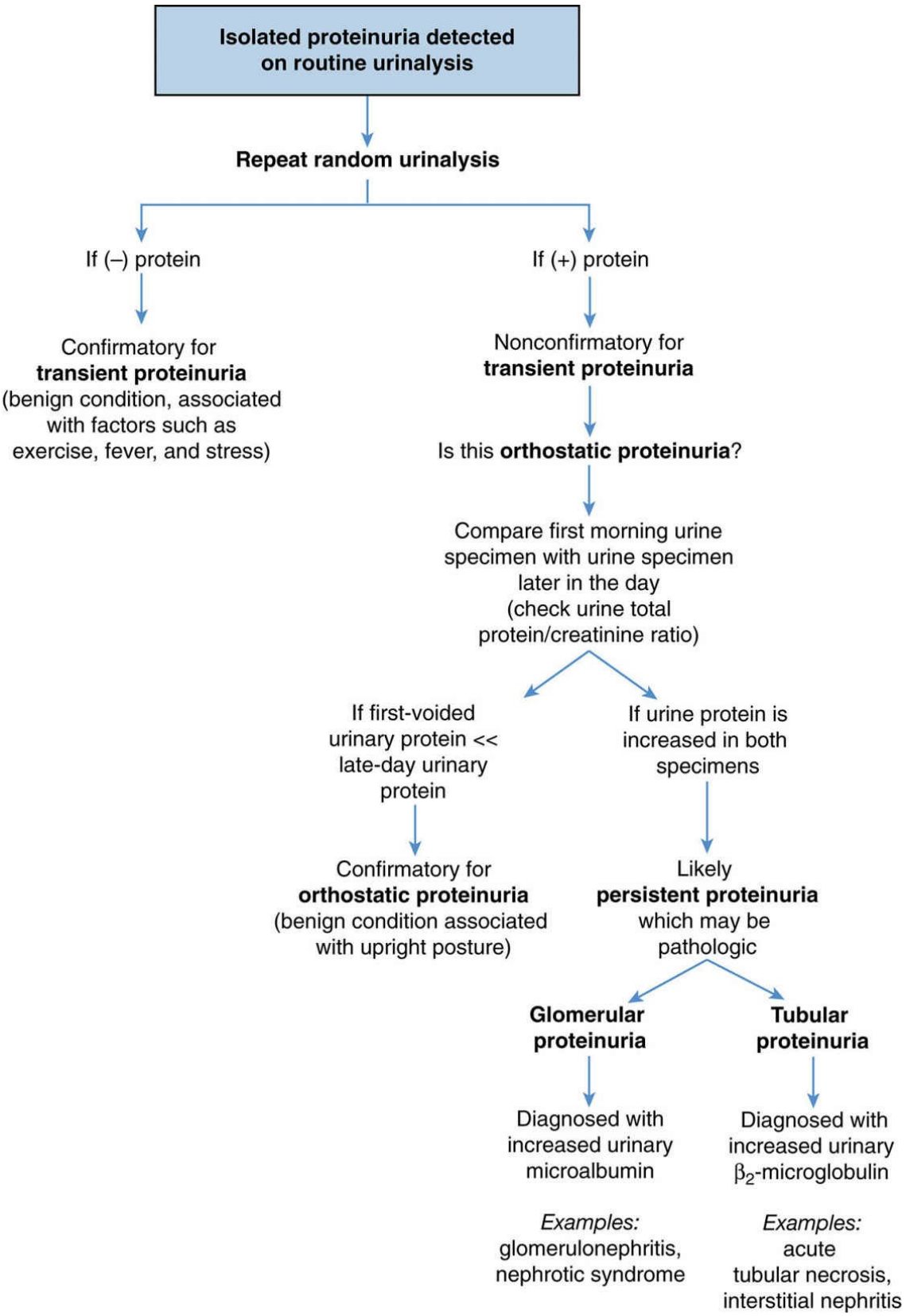

FIGURE 11-3 Evaluation of proteinuria.

IV. Hypertension

A. **Definitions**
   1. **Normal blood pressures** during childhood depend on the child's age, sex, height, and weight. Standards are based on upper arm blood pressures (blood pressures in the legs are generally higher than in the arms).
   2. **Normal systolic and diastolic blood pressures** are defined as blood pressure **less than the 90th percentile.**
   3. Prehypertension is **between the 90th and 95th percentiles** for age.

B. **Classification.** Hypertension is divided into categories based on severity and etiology.
   1. **Hypertension** is defined as the average of three separate blood pressures that are **greater than the 95th percentile** for age.
   2. **Stage 1 hypertension** is defined as systolic or diastolic **blood pressures between the 95th and 99th percentiles + 5 mm Hg.**
   3. **Stage 2 hypertension** is defined as systolic or diastolic **blood pressures > 99th percentile + 5 mm Hg.**
   4. **Malignant hypertension** is hypertension associated with evidence of end organ damage, such as retinal hemorrhages, papilledema, seizures, and coronary artery disease (in adults).
   5. **Essential hypertension** is defined as hypertension without a clear etiology.
   6. **Secondary hypertension** is hypertension that has a recognizable cause (e.g., renal parenchymal disease, coarctation of the aorta). **Most hypertension in childhood is secondary hypertension.**

C. **Measurement**
   1. **Blood pressure cuff size**
      a. **It is critical to use the proper size cuff.** A cuff that is **too small** will give **factitiously elevated blood pressures,** and a cuff that is **too large** will give **falsely depressed blood pressures.**
      b. The cuff bladder should measure two-thirds of the length of the arm from the shoulder to the elbow.
   2. **Position**
      a. Blood pressure in infants should be measured in the supine position.
      b. Blood pressure in children and adolescents should be measured in the seated position with the fully exposed right arm resting on a supportive surface at heart level.

D. **Etiology** *(***Table 11-1****)**. The causes of hypertension vary with the child's age.
   1. In **neonates and young infants,** the most common causes include renal artery embolus after umbilical artery catheter placement, coarctation of the aorta, congenital renal disease, and renal artery stenosis.
   2. In **children 1–10 years of age,** the most common causes include renal diseases and coarctation of the aorta.
   3. In **adolescents,** the most common causes include renal diseases and essential hypertension.

E. **Clinical features.** *Clinical presentations of hypertension* also vary with the child's age. **Some children, like some adults, are asymptomatic.**
   1. **Infants** may present with nonspecific signs and symptoms including irritability, vomiting, failure to thrive, seizures, or even CHF if the hypertension is severe.
   2. **Children** with malignant hypertension, especially of **acute onset,** may develop headaches, seizures, and stroke.

3. **Children** with **chronic hypertension** may have growth retardation and poor school performance.

F. **Evaluation.** Because most children with hypertension have secondary hypertension, the cause of the hypertension is usually identified through a careful history (including family history and birth history), physical examination, and diagnostic testing. Testing is guided by the most likely causes of hypertension on the basis of the child's age and clinical presentation.
   1. **Physical examination**
      a. All children should undergo an assessment of growth and careful, accurate measurements of **four-limb blood pressures** to evaluate for coarctation of the aorta (see Chapter 8, section III.F). In coarctation, hypertension is usually noted in the right arm with lower blood pressures in the legs.
      b. In children, a careful **fundoscopic examination** may show retinal hemorrhages, papilledema, or in long-standing hypertension, arteriovenous nicking.
      c. Other important physical findings include signs of CHF, café-au-lait spots as seen in neurofibromatosis, abdominal masses, abdominal bruits, and ambiguous genitalia.
   2. **Laboratory evaluation and imaging**
      a. **Initial evaluation** should include a complete blood count (CBC), electrolyte panel, blood urea nitrogen (BUN) and creatinine, urinalysis, plasma renin and aldosterone levels, thyroid panel, chest radiograph, and renal ultrasound. A urine microalbumin/creatinine ratio is useful in detecting early glomerular injury from the hypertension as a sign of end organ damage. (Note that the microalbumin/creatinine ratio is a very sensitive test for detecting proteinuria and is used to detect early glomerular proteinuria in hypertension. The protein/creatinine ratio becomes positive when a patient has more overt proteinuria and is therefore an indicator for more severe damage.)
      b. If the initial evaluation is suggestive, further studies may include plasma catecholamines, measurement of plasma and urinary steroids, and echocardiography. Computer tomography (CT) angiography, especially in the setting of discrepant kidney sizes, can be performed to rule out renal artery stenosis.
      c. Ambulatory blood pressure monitoring is very useful to rule out anxiety ("white coat hypertension") before embarking on more expensive or invasive diagnostic testing.

G. **Management.** The treatment of hypertension should be aimed at curative therapies, whenever possible. **In chronic hypertension, the ultimate goal is to maintain the child's blood pressure below the 90th percentile for age.**
   1. If a specific, treatable cause of hypertension is identified, directed management, such as surgical correction of a coarctation of the aorta, treatment of hyperthyroidism, or removal of a catecholamine-secreting tumor, is performed as a cure.
   2. If the child appears to have **essential hypertension,** the initial approach is conservative through implementation of a diet with no added salt, and if appropriate, weight loss. This approach requires frequent monitoring and encouragement.
   3. If the child has **underlying renal disease** or more significant hypertension (e.g., stage 2), or if conservative hypertension treatment has failed, antihypertensive medications are used.
   4. **Hypertensive emergencies** (e.g., seizures, severe headache, stroke, fundoscopic changes, CHF) require prompt therapy with IV antihypertensives.

Table 11-1
Etiology of Hypertension in Children

Essential hypertension*	• No identifiable cause, but heredity, salt sensitivity, obesity, and stress all may play a role
Renal diseases	• Glomerulonephritis • Reflux nephropathy • Renal dysplasia • Polycystic kidney disease • Renal trauma • Obstructive uropathy • Hemolytic uremic syndrome
Renal vascular lesions	• Renal artery stenosis or embolus • Renal vein thrombosis • Vasculitis • Neurofibromatosis
Cardiac disease	• Coarctation of the aorta
Endocrine disorders	• Neuroblastoma • Pheochromocytoma • Congenital adrenal hyperplasia • Hyperthyroidism • Hyperparathyroidism • Hyperaldosteronism • Cushing syndrome
Central nervous system disorders	• Increased intracranial pressure (e.g., hemorrhage, tumor) • Encephalitis • Familial dysautonomia
Drug-related causes	• Corticosteroids • Illicit drugs (e.g., amphetamines, cocaine, PCP) • Anabolic steroids • Cold remedies • Oral contraceptives
Genetic causes	• Liddle syndrome • Gordon syndrome • Apparent mineralocorticoid excess syndrome • Glucocorticoid remediable • Aldosteronism
Miscellaneous causes	• Wilms tumor • Blood pressure cuff too small • Anxiety • Pain • Fractures and orthopedic traction • Hypercalcemia

*Essential hypertension is rare in young children. All children with hypertension should have a careful evaluation to determine the cause of the hypertension.

PCP = phencyclidine.

V. Glomerulonephritis

A. **Definition.** Glomerulonephritis refers to a group of diseases that cause inflammatory changes in the glomeruli.

B. **Etiology.** Causes are varied but generally involve **immune-mediated injury** to the glomerulus. Various antigens can stimulate immune complex deposition or formation within the glomerulus.

C. **Classification**

1. **Primary glomerulonephritis** refers to a disease process limited to the kidney.
2. **Secondary glomerulonephritis** refers to a disease process that is part of a systemic disease (e.g., systemic lupus erythematosus [SLE]).

D. **Clinical features.** The presentation of glomerulonephritis is **variable.**

1. Some patients present with an **acute "nephritic" syndrome** which is characterized by **gross hematuria, "cola-colored" urine, hypertension, and occasionally signs of fluid overload from renal insufficiency.**
2. Some patients may present with glomerulonephritis associated with **nephrotic syndrome** with heavy proteinuria, hypercholesteremia, and edema.
3. Some patients may be relatively **asymptomatic,** in whom glomerulonephritis is only detected as part of the evaluation of microscopic hematuria, proteinuria, or hypertension.

E. **Laboratory evaluation.** Laboratory studies should be performed promptly to avoid missing key transient abnormalities (e.g., transient decrease in serum complement is seen in poststreptococcal glomerulonephritis [PSGN]).

1. **Initial evaluation** should include **urinalysis** (to look for casts and to evaluate RBC morphology), **urinary TP/CR** (to quantify proteinuria), **blood chemistries** (including electrolyte panel, BUN, creatinine, serum albumin, liver enzymes, and cholesterol), **serum complement components, antibody testing** (antinuclear antibody [ANA], antineutrophil cytoplasmic antibody panel [ANCA], antistreptolysin O [ASO] and anti-DNase B [ADB]), and an **IgA level** if IgA nephropathy is suspected.
2. **Additional evaluation,** should the history be suggestive, may include human immunodeficiency virus (HIV) testing and hepatitis C and hepatitis B serologies to evaluate for causes of postinfectious glomerulonephritis.

F. **Common types of glomerulonephritis in children**

1. **Post-Streptococcal Glomerulonephritis (PSGN)**
   a. **Epidemiology. PSGN** is the **most common form of acute glomerulonephritis** that occurs in school-age children. (Note that some of the other less common causes of postinfectious glomerulonephritis include malaria, HIV, hepatitis B and C, and congenital syphilis.) PSGN is rare before 2 years of age.
   b. **Clinical features**
      1. PSGN typically develops **8–14 days after an infection of the skin or pharynx** with a **nephritogenic strain of group A β-hemolytic streptococcus.** The latency period after impetigo may be as long as 21–28 days.
      2. **Hematuria** (often gross hematuria), **proteinuria** (rarely of nephrotic proportion), and **hypertension** with signs of fluid overload (e.g., edema) are common clinical features.
      3. **Low serum complement** (C3) is present but transient and normalizes within 8–12 weeks.
      4. The degree of impairment of renal function is variable and usually normalizes within 6–8 weeks. Severe renal failure is rare.
   c. **Diagnosis.** Diagnosis is on the basis of clinical features and laboratory findings,

including evidence of prior streptococcal infection.

1. **Detection of prior streptococcal infection**
    a. **ASO titer** is positive in 90% of children after streptococcal pharyngitis, but is positive in only 50% of patients with impetigo.
    b. **ADB titer** is reliably positive after respiratory or skin infections with streptococcus.
2. **Other diagnostic tests** should include urinalysis, serum complement levels, renal ultrasound, tests of renal function, serum albumin, and serum cholesterol if the serum albumin is depressed.
3. **Renal biopsy** is indicated only if the patient has significant renal impairment or nephrotic syndrome, or if the serum complement fails to normalize within 12 weeks. **Biopsy** typically shows mesangial cell proliferation and increased mesangial matrix, as well as very large subepithelial deposits (humps) on electron microscopy, and C3 and IgG deposits on immunofluorescent microscopy.

d. **Management.** Treatment is supportive in most cases and includes fluid restriction, antihypertensive medications, and dietary restriction of protein, sodium, potassium, and phosphorus, as dictated by the level of renal functional impairment.
e. **Prognosis** is excellent with complete recovery in most patients.
f. **Prompt antibiotic treatment of infections with nephritogenic strains of group A β-hemolytic streptococcus does not reduce the risk of PSGN, although it will reduce the risk of rheumatic fever** (see Chapter 16, section VI and Chapter 7, section IX.A.5.f).

2. **IgA nephropathy (Berger disease)**
    a. **Epidemiology**
        1. IgA nephropathy is the **most common type of chronic glomerulonephritis worldwide.** It typically presents in the second or third decade of life.
        2. It is more prevalent in **Asia** and **Australia** and in **Native Americans**, and it is rare in African Americans.
    b. **Etiology.** The cause is poorly understood but may relate to abnormal clearance and formation of IgA immune complexes containing IgA molecules that are abnormally glycosylated.
    c. **Clinical features.** Clinical findings classically include **recurrent bouts of gross hematuria associated with respiratory infections.** However, not all patients experience gross hematuria. Transient acute renal failure may occur in some patients. Microscopic hematuria is present in between the bouts of gross hematuria. The presence of heavy proteinuria and elevated serum creatinine are poor prognostic signs.
    d. **Diagnosis. Renal biopsy,** which shows mesangial proliferation and increased mesangial matrix on light microscopy, is the basis of diagnosis. Immunofluorescent microscopy reveals mesangial deposition of IgA as the dominant immunoglobulin. Approximately 50% of patients have elevated serum levels of IgA. In more advanced cases there may be crescents, glomerular scarring, and tubular atrophy.
    e. **Management.** Treatment is supportive and includes regular follow-up for the development of hypertension. Hypertension may eventually worsen proteinuria and renal function. Medications (angiotensin-converting enzyme [ACE] inhibitors, steroids, and immunosuppressants such as mycophenolate mofetil) are usually recommended for patients with associated pathologic proteinuria, renal insufficiency, or more significant glomerular inflammation on renal biopsy.
    f. **Prognosis** is variable. Twenty to forty percent of patients eventually develop end-

stage renal disease (ESRD).

3. **Henoch–Schönlein purpura (HSP) nephritis** (see Chapter 16, section I)
    a. **Definition.** HSP is an **IgA-mediated vasculitis** characterized by **nonthrombocytopenic "palpable purpura" on the buttocks, thighs, and lower arms, in addition to abdominal pain, arthritis or arthralgias, and gross or microscopic hematuria.**
    b. **Clinical features.** Clinical findings related to renal involvement include the following:
        1. In the majority of patients, the renal features of HSP are self-limited with complete recovery within 3 months. One to five percent of patients develop chronic renal failure.
        2. If proteinuria and marked hematuria are present, there may be severe glomerular inflammation. Renal biopsy is indicated for significant proteinuria or if there is an elevated serum creatinine.
        3. The renal biopsy in HSP nephritis is indistinguishable from that of a patient with IgA nephropathy.
4. **Membranoproliferative glomerulonephritis (MPGN)**
    a. **Definition.** MPGN is a term used for three forms of histologically distinct glomerulonephritis that share similar features. MPGN is characterized by lobular mesangial hypercellularity and thickening of the glomerular basement membrane.
    b. **Clinical features**
        1. Patients typically present with acute nephritic syndrome or with nephrotic syndrome accompanied by microscopic or gross hematuria.
        2. Hypertension is common.
        3. Seventy-five percent of patients have low serum complement levels.
        4. Clinical course is variable, although most patients ultimately develop ESRD.
    c. **Management.** There is no standardized treatment for MPGN, although some patients may respond to corticosteroids or mycophenolate mofetil. ACE inhibitors may slow disease progression.
5. **Membranous nephropathy (MN)** is a rare form of glomerulonephritis in young children, although it may be seen in children and adolescents. MN presents with heavy proteinuria and may progress to renal insufficiency. MN is the most common cause of nephrotic syndrome in adults in the United States. It is an autoimmune disease sometimes associated with hepatitis B infections and SLE.
6. **SLE nephritis** (see Chapter 16, section IV.D.8)

VI. Nephrotic Syndrome (NS)

A. **Definition.** NS is a condition characterized by **heavy proteinuria (>50 mg/kg/24 hours or by a urine total protein/creatinine ratio ≥3.5**), hypoalbuminemia, hypercholesterolemia, and edema.

B. **Epidemiology**
   1. Two-thirds of cases in children present before 5 years of age.
   2. In young children, the ratio of boys to girls is 2:1. By late adolescence, both sexes are equally affected.

C. **Classification.** There are **three categories of NS:**
   1. **Primary NS,** which refers to cases that are not a consequence of systemic disease. Primary NS accounts for **90% of all childhood cases of NS.** The **most common cause of primary NS in children is minimal change disease (MCD),** which accounts for 95% of NS cases among young children and 50% of cases in older children and adolescents.
   2. **NS that results from other primary glomerular diseases,** including focal segmental glomerulosclerosis (FSGS), MPGN, IgA nephropathy, and PSGN
   3. **NS that results from systemic diseases,** including SLE and HSP

D. **Pathophysiology**
   1. The basic physiologic defect is a loss of the normal charge- and size-selective glomerular barrier to the filtration of plasma proteins.
   2. Excessive urinary protein losses lead to the hypoproteinemia of NS.
   3. Hypercholesterolemia is a consequence of the hypoproteinemia.
      a. Reduced plasma oncotic pressure induces increased hepatic production of plasma proteins, including lipoproteins.
      b. Plasma lipid clearance is reduced because of reduced activity of lipoprotein lipase in adipose tissue.

E. **Clinical features**
   1. Most children present with **edema,** which can range from mild periorbital edema to scrotal or labial edema to widespread edema. The edema often **follows an upper respiratory infection (URI).** Pleural effusions and hypotension may also occur.
   2. Patients may rarely be asymptomatic at the time of diagnosis. In these patients, NS is diagnosed during an evaluation for asymptomatic proteinuria, and they are less likely to have MCD.
   3. Patients are **predisposed to thrombosis** secondary to hypercoagulability. Rarely, patients may present with stroke or other thrombotic events such as renal vein thrombosis, deep vein thrombosis, and sagittal sinus thrombosis.
   4. Patients are also at an *increased risk for infection with encapsulated organisms,* such as ***Streptococcus pneumoniae,*** and therefore may present with **spontaneous bacterial peritonitis, pneumonia, or overwhelming sepsis.**
   5. The clinical course for the child with MCD follows periods of relapses and remissions. About one-third of patients have only one episode, one-third have infrequent relapses, and one-third will have frequent relapses. For the latter two groups, the nephrotic syndrome is a chronic illness in which the side effects of medications have to be weighed against the complications of the disease.
   6. Many, but not all, children with MCD achieve a sustained remission by adolescence.

F. **Diagnosis.** Diagnosis is on the basis of clinical features and on the following studies:
   1. **Urinalysis** typically reveals 3^+ to 4^+ protein, sometimes microscopic hematuria, and a very elevated urinary TP/CR. *The presence of RBC casts indicates a cause other than MCD.*
   2. **CBC** may show an elevated hematocrit as a result of hemoconcentration resulting from

the hypoproteinemia. The platelet count may also be elevated.

3. **Routine chemistries** (electrolytes) may demonstrate metabolic acidosis, which may be caused by *acquired* renal tubular acidosis (in severe cases the heavy proteinuria of nephrotic syndrome may cause RTA). Hypoalbuminemia and elevated serum cholesterol are present. BUN and creatinine should be measured to assess for renal impairment.
4. **C3, ANA, and antistreptococcal antibodies** are indicated during an initial evaluation to rule out causes of NS other than MCD.
5. **Renal ultrasound** often shows enlarged kidneys.
6. **Renal biopsy** is rarely indicated in the young child with typical NS, unless the creatinine clearance is impaired or initial management with corticosteroids is ineffective.
7. Genetic testing for mutations associated with nephrotic syndrome may be indicated in the child who presents with nephrotic syndrome before their first birthday and in the steroid-resistant child.

G. **Management.** Treatment is dictated by the underlying cause of the NS.

1. Most children are hospitalized for initial treatment, although a relatively asymptomatic child with a reliable caregiver can be followed carefully as an outpatient.
2. If the child has widespread edema, scrotal or labial edema, hypotension, or symptomatic pleural effusions, IV infusions of **25% albumin** should be given initially to achieve a diuresis and to maintain the intravascular volume.
3. The **diet** should consist of meals with **no added salt.**
4. **Most patients with MCD respond to therapy with corticosteroids.** Steroid-dependent and frequently relapsing children may achieve a prolonged remission during treatment with **cyclophosphamide**, mycophenolate mofetil, tacrolimus, or cyclosporine. For the steroid-resistant patient a prolonged course of tacrolimus plus steroids may induce a remission.
5. **Because of the risk of pneumococcal infection, if the child is febrile,** evaluation should include blood culture, urine culture, and chest radiograph. If peritonitis is suspected, paracentesis for Gram stain, culture, and cell count of the ascites fluid is indicated. Empiric broad-spectrum IV antibiotic coverage should be initiated.

H. **Prognosis** varies according to the underlying cause. **Mortality approaches 5%,** almost exclusively in children who are steroid-resistant and almost always from **overwhelming infection** or **thrombosis.**

VII. Hemolytic Uremic Syndrome (HUS)

See Chapter 13, section I.F.2.b.(3) and Chapter 7, Table 7-6.

A. **Definition.** HUS is a condition characterized by **acute kidney injury (AKI) in the presence of microangiopathic hemolytic anemia and thrombocytopenia.**

B. **Subtypes.** There are three different subtypes of HUS, which differ in their known etiology, treatments, and prognoses: Shiga-like toxin HUS, pneumococcal HUS, and atypical HUS.

C. **Shiga-like toxin–associated HUS (STEC-HUS)**

1. **Epidemiology.** STEC-HUS is the most **common subtype seen in childhood.**
2. **Etiology**
   a. STEC-HUS occurs as a result of an intestinal infection with a **toxin-producing bacterial strain.** In North America, the most common pathogen is ***Escherichia coli* 0157:H7.** Other pathogens include other strains of *E. coli* and *Shigella dysenteriae* type 1. Testing the stool with cultures for enteropathogenic *E. coli* and for Shiga toxin is informative.
   b. Known sources of bacterial contamination include undercooked beef, unpasteurized milk, produce, and contaminated fruit juices. Human-to-human transmission has been described.
3. **Pathogenesis**
   a. **Vascular endothelial injury by the Shiga-like toxin is the key to the pathogenesis of injury in STEC-HUS.**
   b. The toxin binds to endothelial cells, causing endothelial cell injury, most especially in the renal vasculature. This leads to platelet thrombi formation and renal ischemia from the microthrombi.
4. **Clinical features.** The clinical presentation includes a **diarrheal prodrome** (often bloody and may be severe) followed by the sudden onset of **hemolytic anemia, thrombocytopenia, and AKI.**
5. **Management. Treatment is supportive.**
   a. Transfusions as needed for severe anemia and thrombocytopenia.
   b. AKI is managed as described in section X.E.
   c. **The use of antibiotics is controversial in treating diarrhea due to HUS-associated bacteria.** Although **antibiotic treatment of *E. coli* hemorrhagic colitis with certain antibiotics may increase the likelihood that the patient will eventually develop HUS,** there is some preliminary evidence that fosfomycin may be protective and could be considered during outbreaks of *E. coli*–associated diarrhea.
6. **Prognosis.** The prognosis is generally **favorable** and depends on the severity of the presentation.
   a. **Poor prognostic signs** for renal recovery include a **high white blood cell (WBC) count** on admission and **prolonged oliguria.**
   b. A minority of patients die during the acute phase from the complications of colitis, such as **toxic megacolon,** or from central nervous system complications, such as cerebral infarctions.

D. **Pneumococcal HUS**

1. Pneumococcal HUS is triggered by infection with pneumococcus and accounts for about 5% of the cases of HUS.
2. It is mediated by neuraminidase, which functions as a toxin in the presence of a *S. pneumoniae* infection. Plasma infusions may worsen the symptoms in this type of HUS, and if plasma exchange is considered, albumin should be used instead of plasma.
3. It often carries a worse prognosis than STEC-HUS because of necrotizing pneumonia.

E. **Atypical HUS (aHUS)**

1. **Epidemiology.** aHUS is much less common than STEC-HUS.
2. **Etiology**
    a. **Drugs** (e.g., oral contraceptives, cyclosporine, tacrolimus) or pregnancy may cause aHUS.
    b. **Inherited** aHUS occurs with both autosomal dominant and autosomal recessive inheritance patterns, although not all patients have identifiable mutations. These genetic mutations cause chronic, excessive activation of complement, which also leads to platelet activation, endothelial cell damage, and systemic thrombotic microangiopathy.
3. **Clinical features.** Clinical findings are similar to those of STEC-HUS. Diarrhea may also be present, and severe proteinuria and hypertension are more consistently found. The clinical course is generally more severe with multiorgan damage.
4. **Management. Treatment is supportive.** Inciting medications, if any, must be stopped immediately.
5. **Prognosis.** Some patients have a chronic relapsing course (**recurrent HUS**). All patients with aHUS have a higher risk of progression to ESRD than patients with STEC-HUS.

VIII. Hereditary Renal Diseases

A. **General concepts.** Because many inherited renal diseases present in childhood, **a careful family history is critical** in all children with renal disease.

B. **Alport syndrome**

1. **Definition.** Alport syndrome is a form of **progressive hereditary nephritis** that is secondary to defects in the side chains of **type IV collagen** within the glomerular basement membrane.
2. **Etiology. Inheritance** is usually **X-linked dominant,** although autosomal dominant and autosomal recessive variants exist.
3. **Clinical features**
    a. **Renal manifestations** initially include hematuria, often gross hematuria, and sometimes hypertension. ESRD often occurs in males with X-linked Alport syndrome as early as adolescence, but the age of onset of ESRD differs between kindreds. Women who carry the gene are less likely to develop ESRD, but it may occur. Autosomal dominant and autosomal recessive Alport syndrome may also lead to ESRD.
    b. **Hearing loss** typically begins in childhood and progresses; approximately 50% of adults have some loss of hearing, ranging from mild to severe.
    c. **Ocular abnormalities** involving the lens and retina occur in 25–40% of patients.
4. **Management.** Therapy includes treatment of hypertension, use of ACE inhibitors (even in patients who have proteinuria without hypertension), sometimes with the addition of an angiotensin receptor blocker to slow the progression of renal disease, and eventually renal transplantation.

C. **Multicystic renal dysplasia.** This condition is the **most common cause of a renal mass in the newborn,** occurring in 1 in 4300 live births, and is most often unilateral. The inheritance is not clear, but it appears to be a sporadic occurrence. See section XII.D.2 for more details.

D. **Autosomal recessive polycystic kidney disease (ARPKD) or infantile polycystic kidney disease**

1. **Epidemiology.** ARPKD is uncommon, occurring in approximately 1 in 10,000–40,000 live births.
2. **Clinical features**
    a. The most severely affected infants have a maternal history of **oligohydramnios** secondary to nonfunctioning or poorly functioning kidneys in utero. This leads to **pulmonary hypoplasia, which may be incompatible with life.**
    b. **Greatly enlarged cystic kidneys**
    c. **Severe hypertension** is common.
    d. **Liver involvement** of variable clinical severity is a constant finding, including cirrhosis with portal hypertension.
3. **Prognosis.** Although the degree of renal insufficiency in infancy may range from mild to severe, ARPKD is **progressive** and ultimately all patients require renal transplantation.

E. **Autosomal dominant polycystic kidney disease (ADPKD) or adult polycystic kidney disease**

1. **Epidemiology.** ADPKD is a common genetic disorder (affecting about 1 in 500 individuals) that usually presents in **adulthood** (20–40 years of age). There are two gene mutations that cause ADPKD; ADPKD1 mutations are more common and cause an earlier onset of disease than ADPKD2 mutations.
2. **Clinical features.** Clinical findings are variable and include abdominal pain, flank masses, urinary tract infection (UTI), gross or microscopic hematuria, hypertension, or

renal insufficiency. Associated cerebral aneurysms may occur, with early death.

3. **Prognosis.** Most patients develop severe hypertension and renal insufficiency, eventually requiring transplantation.

F. **Medullary sponge kidney.** This condition occurs sporadically or may have autosomal dominant inheritance. Patients may be asymptomatic or have hematuria, UTI, or nephrolithiasis.

G. **Nephronophthisis.** This is a ciliopathy that occurs in several forms. The **infantile, juvenile, and adolescent forms** are autosomal recessive and lead to ESRD in childhood or young adulthood, and there are often significant associated extrarenal manifestations in 10–15% of patients, including retinal degeneration, cerebellar vermis hypoplasia, occipital encephalocele, hepatic fibrosis, situs inversus, bronchiectasis, and skeletal defects. More than 13 mutated genes have been described that lead to nephronophthisis.

IX. Renal Tubular Acidosis (RTA)

A. **Definition.** RTA refers to a group of congenital or acquired disorders that result from the **inability of the kidney to maintain normal acid–base balance because of defects in bicarbonate conservation or because of defects in the excretion of hydrogen ions.**

B. **Etiology** (Table 11-2)
   1. **Congenital forms** of RTA are caused by mutations in various transporters in the proximal or distal tubular cells.
   2. **Acquired forms** of RTA may be caused by nephrotoxic drugs (e.g., amphotericin) or systemic diseases (e.g., autoimmune disorders).

C. **Clinical features** (Table 11-2). **Symptoms vary with the type of RTA** and with the patient's **age.**
   1. **Infants and young children** tend to present with **growth failure and vomiting**, and, at times with life-threatening metabolic acidosis.
   2. **Older children and adults** may have recurrent calculi, muscle weakness, bone pain, and myalgias.
   3. Some forms of RTA result in **nephrocalcinosis,** which in turn may lead to polyuria from urinary concentrating defects.
   4. **The classic electrolyte presentation** is a **hyperchloremic metabolic acidosis** with a **normal serum anion gap.**

D. **Types of RTA** (Table 11-2)

E. **Evaluation.** RTA should be considered in patients who present with a non–anion gap hyperchloremic metabolic acidosis. Acidosis should be confirmed by a venous blood gas.
   1. **Initial laboratory studies** should include serum potassium, phosphorus and uric acid, urine pH, and urinalysis to evaluate for proteinuria and glucosuria. Calculation of the **urine anion gap** (urine Na^+ + urine K^+ − urine chloride) is important; a **positive urine anion gap is seen in Types I and IV RTA and may be seen in Type II RTA.**
   2. If there are signs of a diffuse tubular disorder (manifested by hypokalemia, hypophosphatemia, and aminoaciduria), the patient should be evaluated for **Fanconi syndrome** by performing more extensive testing of other tubular functions.

Table 11-2
Types of Renal Tubular Acidosis (RTA)

Type of RTA	Characteristic Features	Causes or Associations	Clinical Presentation	Treatment
Distal RTA (Type I)	• Inability of the distal renal tubular cells to excrete acid (H^+)	• Isolated inherited defect • Associated with nephrotic syndrome, sickle cell anemia, connective tissue disorders • Associated with toxins, drugs (amphotericin)	• Vomiting • Growth failure • Acidosis • Nephrocalcinosis and nephrolithiasis	• Small doses of oral alkali
Proximal RTA (Type II)	• Impaired bicarbonate reabsorption by the proximal renal tubular cells	• Isolated inherited defect • Intoxication (heavy metals) • Prematurity • Drugs (gentamicin) • Associated with more global defects in tubular reabsorption (Fanconi syndrome*)	• Vomiting • Growth failure • Acidosis • Muscle weakness	• Large doses of oral alkali

Type IV RTA	• **Transient** acidosis in infants and children • *Hyperkalemia is the hallmark*	• Associated with renal disorders such as obstructive uropathy and interstitial nephritis • Diabetes mellitus • Associated with mineralocorticoid deficiency states	• Patients may be asymptomatic or may present with failure to thrive	• Furosemide to lower serum potassium; oral alkali

*Findings associated with Fanconi syndrome: proximal RTA, hyperphosphaturia, aminoaciduria, glucosuria, and potassium wasting.

X. Acute Kidney Injury

A. **Definition.** *AKI* is defined as an abrupt decrease in the ability to excrete nitrogenous wastes.
B. **Etiology** *(*Table 11-3**)**
C. **Clinical features**
   1. Systemic signs and symptoms depend on the cause and severity of the renal insult but often include lethargy, nausea, vomiting, respiratory distress, hypertension, and sometimes seizures.
   2. The clinical presentation may be oliguric (diminished urine output) or nonoliguric (normal urine output). In children, **oliguria** is defined as a **urine output < 1 mL/kg/hour.**
D. **Evaluation**
   1. **Laboratory tests** should include serum electrolytes, BUN, creatinine, urinalysis, and urinary protein and creatinine levels, as well as a more specific investigation for the cause of kidney injury, such as testing for ANCA or drug levels of nephrotoxic medications based on the clinical history.
   2. **Imaging studies** may include a renal or pelvic ultrasound and a nuclear renal scan to evaluate renal function.
E. **Management**
   1. If possible, the specific cause should be addressed (e.g., removal of a nephrotoxic drug).
   2. If the patient is intravascularly volume depleted, **the intravascular volume should be restored first with appropriate IV fluids, and then total fluid intake should be restricted to the patient's insensible losses (approximately 300 mL/m^2/day) plus output (urine, stool) replacement.**
   3. **Electrolyte intake should be matched to estimated electrolyte losses.** Typically, sodium, potassium, and phosphorus intake are restricted.
   4. **Protein intake should be restricted** to the recommended dietary allowance (RDA) of protein for age. Caloric intake should also be at the RDA for age.
   5. **Patient monitoring** should include daily weights, frequent blood pressure measurements, calculation of intake and output, and monitoring of electrolytes.
   6. **Dialysis therapy** (peritoneal dialysis, hemodialysis, or continuous renal replacement therapy) is used when conservative management fails to maintain the patient in safe biochemical, nutritional, and fluid balance.

Table 11-3
Etiologies of Acute Kidney Injury (AKI)

Categories of AKI	Causes of Renal Failure	Specific Examples	Laboratory Findings
Prerenal	Caused by a reversible ↓ in renal perfusion that leads to a ↓ in GFR	Dehydration	↑ BUN/Creat ratio > 20
Hemorrhage	↑ Urine SG ≥ 1.030		
Congestive heart failure	Urine osmolality > 500		
Septic shock	Urine Na^+ < 20		
Hypoproteinemic states	$^*Fe_{Na}$ < 1% in older children, <2.5% in neonates		
Renal parenchymal	Damage to glomerulusDamage to tubules (acute tubular necrosis)Damage to interstitium (acute interstitial nephritis)	PSGN	Hematuria
Lupus nephritis	Proteinuria↑ Urinary β_2-microglobulin		
HUS			

hypoperfusionDrugs (semisynthetic penicillins)	neonates		
Eosinophilia, eosinophiluria			
Postrenal	Obstruction of urine flow from either a solitary kidney, from both kidneys, or from the urethra	Stones	Dilation of renal collecting system on renal ultrasound
Tumor			
Ureterocele			
Urethral trauma			
Neurogenic bladder			
Posterior urethral valves in males			
Vascular	↓ Perfusion of the kidneys	Renal artery embolus (especially in the presence of an umbilical artery catheter)	↓ Renal blood flow on nuclear renal scan
Renal vein thrombosis, presenting with sudden-onset gross hematuria and a unilateral or bilateral flank mass, with ↑ incidence in infants of diabetic mothers			

*

HUS = hemolytic uremic syndrome; *PSGN* = poststreptococcal glomerulonephritis; Fe_{Na} = fractional excretion of sodium; *SG* = specific gravity; *GFR* = glomerular filtration rate; *Creat* = creatinine; *BUN* = blood urea nitrogen.

XI. Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD)

A. **Etiology**
   1. The **most common causes** include glomerular diseases (e.g., FSGS), congenital or inherited kidney diseases (e.g., renal dysplasias or obstructive uropathies), reflux nephropathy, collagen vascular diseases, cystic kidney diseases, interstitial nephritis, and HUS.
   2. The cause is unknown in up to 10% of cases.
   3. Determining the cause of the child's chronic kidney disease may have implications for the child and his or her family, especially important in cases of inherited disorders. Specific therapies may modify disease progression, some genetic diseases may occur in siblings or offspring, and some diseases may recur in transplanted kidneys.

B. **Clinical features.** Clinical findings may include short stature, anemia, failure to thrive, polyuria and polydipsia, lethargy, and rickets.

C. **Evaluation**
   1. Investigation for the causes of CKD
   2. Careful family history
   3. Assessment of growth and nutrition
   4. Evaluation for renal osteodystrophy (i.e., bone disease secondary to renal failure)
   5. Serologic testing for collagen vascular diseases
   6. Renal imaging to look for structural kidney abnormalities
   7. Renal biopsy (in some cases)

D. **Management**
   1. **Medical**
      a. **Nutritional management** includes assurance of adequate caloric intake and avoidance of high phosphorus, high sodium, and high potassium foods. Patients are also given oral phosphate binders and vitamin D analogues to prevent renal osteodystrophy. Protein intake should be at the RDA for age.
      b. **Biochemical management** includes monitoring and management of serum electrolytes, BUN, creatinine, calcium, and alkaline phosphatase.
      c. **Blood pressure** monitoring and management are critical.
      d. **Anemia** is treated with iron and recombinant erythropoietin therapy.
      e. **Growth** is closely monitored, and patients may require recombinant human growth hormone if their growth fails to normalize with other medical interventions.
   2. **Dialysis** is initiated or **transplantation** is considered when the **glomerular filtration rate is <10% of normal,** or **earlier if the child is symptomatic.**
      a. **Peritoneal dialysis** is generally the **preferred dialysis modality in infants and children.**
      b. **Chronic hemodialysis** may also be performed in children and requires vascular access via an indwelling catheter or an arteriovenous fistula. This is technically very difficult in an infant.
      c. **Kidney transplantation** is the **preferred treatment for children with ESRD.**
         1. Living related donors and living unrelated donors are preferred over deceased donors because of better kidney transplant outcomes. Graft outcome varies with donor source. Approximately 80% of living donor kidneys and 65% of deceased donor kidneys remain functioning 5 years after transplant.
         2. Kidney transplantation requires lifelong immunosuppression with increased risks of infection and subsequent malignancies.

3. The **most common causes of transplant loss** include acute and chronic rejection, noncompliance with medications, technical problems during surgery, and recurrent disease.

XII. Structural and Urologic Abnormalities

A. Structural and urologic abnormalities are **common,** occurring in 6–10% of children.

B. **Congenital obstructive abnormalities** may occur at any level in the urinary tract. Bilateral lesions threaten renal function.

1. **Ureteropelvic junction obstruction** may occur as a result of kinks, fibrous bands, or overlying aberrant blood vessels.
2. **Ureterovesical junction obstruction** may occur as a result of ureterocele, primary megaureter, or abnormal insertion of the ureter into the bladder.
3. **Bladder outlet obstruction** may occur as a result of **posterior urethral valves in males**, may be secondary to polyps or tumors, and may be associated with **prune belly syndrome** (i.e., absence of rectus muscles, bladder outlet obstruction, and, in males, cryptorchidism). Bladder outlet obstruction is typically associated with impairment in renal function.
4. Any form of congenital obstruction, if severe in utero, may lead to abnormal renal development (**renal dysplasia**). Severe impairment of renal function from any in utero cause may lead to oligohydramnios, which results in pulmonary hypoplasia that may be incompatible with life.

C. **Acquired obstruction** may occur as the result of renal calculi [see section XIII], tumors, or strictures.

D. **Renal abnormalities**

1. **Renal agenesis** occurs as a result of the failure of development of the mesonephric duct or the metanephric blastema, and may be associated with severe congenital anomalies in other organ systems (e.g., **heart and hearing**).
   a. **Unilateral renal agenesis** occurs in 0.1–0.2% of children.
   b. **Bilateral renal agenesis** is very rare. Infants die in the perinatal period secondary to associated pulmonary hypoplasia.
2. **Renal dysplasia** is much more common than renal agenesis.
   a. **Pathologically,** renal dysplasia is associated with altered structural organization of the kidney, ranging in severity from mild to severe.
   b. **Functionally,** renal dysplasia is associated with concentrating defects, RTA, and varying degrees of decreased kidney function.
   c. Patients with relatively mild renal dysplasia and its associated renal functional abnormalities at birth may experience improved kidney function in later infancy and childhood, only to deteriorate in late childhood or adolescence.
   d. Severe renal dysplasia results in a nonfunctional kidney.
      1. **The most common abdominal mass discovered in newborns is the multicystic dysplastic kidney,** which is usually associated with an atretic ureter.
      2. If bilateral and severe, multicystic dysplastic kidneys are incompatible with life. These infants are usually born with the stigmata of Potter syndrome (see Chapter 5, section IV.I.6).
3. **Other structural abnormalities** include **horseshoe kidney** (fusion of the lower poles of the kidneys), **renal ectopia** (kidney located outside of the renal fossa, such as in the pelvis), and **duplication anomalies.**

E. **Vesicoureteral reflux (VUR)**

1. **Definition.** VUR is defined as urine refluxing from the urinary bladder into the ureters and the renal collecting system.
2. **Epidemiology.** It is estimated that at least 0.5% of healthy infants have some degree of

VUR.

3. **Etiology**
    a. **VUR** is caused by **abnormalities of the ureterovesical junction,** most commonly a short submucosal tunnel in which the ureter inserts through the bladder wall. It also is associated with dysfunctional voiding patterns in infants and children.
    b. VUR has been described to have multiple inheritance patterns, including autosomal dominant inheritance with variable expression, autosomal recessive, or X-linked inheritance.
4. **Classification.** VUR is graded from grade 1 to grade 5 **(Figure 11-4)**.
5. **Clinical features**
    a. **Most children with lower grades of VUR eventually have spontaneous resolution of the reflux.**
    b. **VUR may predispose to episodes of pyelonephritis,** and severe pyelonephritis in turn may lead to renal scarring, especially in infants and young children.
    c. **Severe in utero VUR may lead to renal hypoplasia/dysplasia and compromised kidney function.**
    d. **Reflux nephropathy** is the pathologic entity resulting from severe VUR. Kidneys show segmental scars, contraction, and interstitial nephritis, and this may lead to ESRD and hypertension.
6. **Diagnosis.** VUR is diagnosed by **voiding cystourethrogram (VCUG)** in which contrast is introduced into the urinary bladder via a urinary catheter. The bladder and kidneys are imaged under fluoroscopy during filling of the bladder and during voiding.
7. **Management**
    a. **Low-dose prophylactic antibiotics** were previously routinely prescribed to reduce the incidence of UTI until the child outgrew the VUR. However, more recent studies have suggested that the benefits of prophylactic antibiotics may not outweigh the risks, especially in older children with low-grade VUR. The infant with high-grade VUR (e.g., grades 4 or 5) and a history of febrile UTI is still a candidate for prophylactic antibiotic therapy and close follow-up.
    b. Children with grade 4 or 5 reflux should be referred to a pediatric urologist for consideration of surgical reimplantation of the ureters.

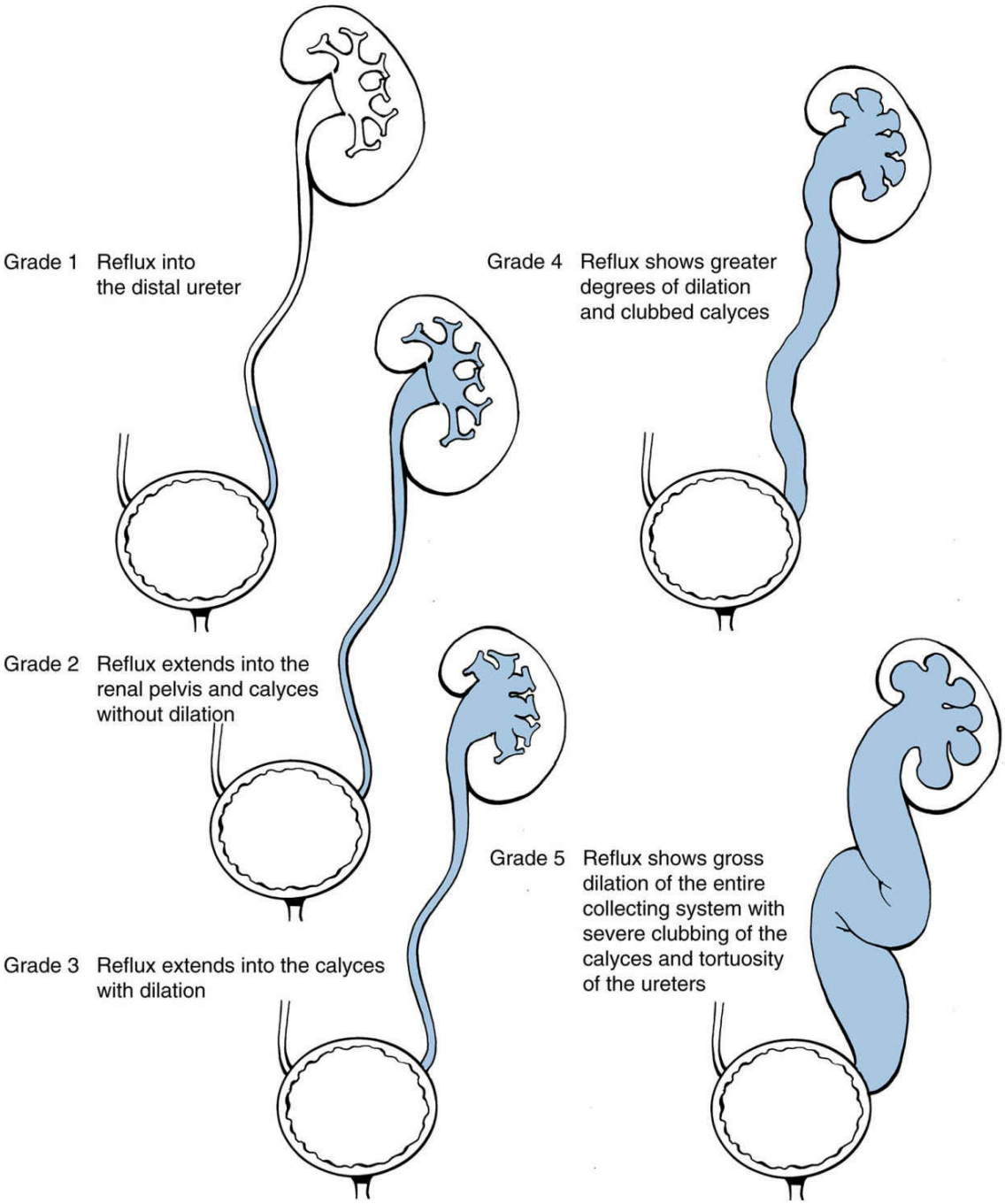

FIGURE 11-4 Classification of vesicoureteral reflux.

XIII. Urolithiasis

A. **Epidemiology.** Renal stones are uncommon in children, and predisposing metabolic disorders should be sought in any child presenting with urinary calculi. There is a higher incidence in overweight and obese children.

B. **Etiology.** The **most common stones seen in childhood** include stones of calcium salts, uric acid, cysteine, or magnesium ammonium phosphate (struvite). Conditions associated with urolithiasis that should be considered include the following:
   1. **Hypercalciuria,** which predisposes to calcium-containing stones. Hypercalciuria may be idiopathic or caused by hypercalcemia, familial hypercalciuria, or furosemide use (especially in premature infants).
   2. **Hypocitraturia,** which predisposes to calcium-containing stones and is an inherited condition.
   3. **Hyperoxaluria,** which may be inherited or secondary to malabsorption from the GI tract (e.g., inflammatory bowel disease)
   4. **Distal RTA**
   5. **Hyperuricosuria,** which may occur during the treatment of leukemia or lymphoma, with Lesch–Nyhan syndrome or with primary gout
   6. **Cystinuria,** which is an **autosomal recessive** disorder that may lead to radiopaque renal stones
   7. **UTI,** especially with *Proteus mirabilis*
   8. **Hyperparathyroidism**

C. **Clinical features.** Clinical findings include flank or abdominal pain, gross or microscopic hematuria, or symptoms of cystitis or pyelonephritis.

D. **Diagnosis and evaluation.** Because of the possibility of an underlying metabolic disorder, children with urolithiasis should have a careful evaluation, including the following:
   1. **Laboratory testing** should include electrolytes, BUN, creatinine, calcium, phosphorus, parathyroid hormone (PTH) level, uric acid level, and venous blood gas to rule out RTA.
   2. **Urine testing** should include urinalysis with microscopy, urinary oxalate-to-creatinine ratio to identify hyperoxaluria, random first morning urine for calcium-to-creatinine ratio to identify hypercalciuria and uric acid-to-creatinine ratio to identify hyperuricosuria, urine culture, and testing for cystinuria. Twenty-four–hour urine collections are important to measure 24-hour urinary excretion of creatinine, oxalate, uric acid, citrate (low urinary citrate predisposes to stone formation), calcium, phosphorus, magnesium, and cysteine.
   3. **Imaging studies,** including a plain radiograph of the abdomen and renal ultrasound, are necessary to confirm and identify the stone(s). Sometimes a high-resolution abdominal CT scan can identify the stone.
   4. **Stone fragment analysis,** if a fragment is collected.

E. **Management.** Management is aimed first at hydration and the relief of any obstruction, treating any associated UTI, and then specific therapy on the basis of the underlying predisposing cause of the urolithiasis. On an on-going basis, patients should have, increased water intake at least to the maintenance fluid range, as well as reduced sodium intake. Patients with hypocitraturia can be treated with increased fluids that contain citrate.

XIV. Urinary Tract Infection (UTI)

A. **Epidemiology.** *UTI is one of the most common bacterial infections in children.*
   1. **Incidence** of symptomatic UTI during infancy is 0.4–1%.
   2. Until 6 months of age, UTIs are twice as common in infant boys than girls. After 6 months of age, UTIs are much more common in girls.
   3. Before 6 months of age, UTIs are 10 times more common in **uncircumcised boys** as compared with boys who are circumcised.

B. **Etiology.** The vast majority of UTIs are caused by enteric bacteria, especially ***E. coli***. Other pathogens include *Klebsiella*, *Pseudomonas*, *Staphylococcus saprophyticus* (especially in adolescent females), *Serratia*, *Proteus* (associated with a high urinary pH), and *Enterococcus.*

C. **Pathogenesis**
   1. Most bacteria enter the urinary tract by **ascending** through the urethra.
   2. Bacterial properties that promote the adherence of bacteria to the urothelium increase the likelihood of UTI (such as the presence of P fimbria on *E. coli*).

D. **Clinical features.** *UTI symptoms vary with the age of the child.*
   1. **In neonates,** symptoms are nonspecific and include lethargy, fever or temperature instability, irritability, and jaundice.
   2. **In older infants,** symptoms include fever, vomiting, and irritability. **Pyelonephritis is difficult to diagnose in young nonverbal children but should be suspected if fever or systemic symptoms are present.**
   3. **In young children** who were previously toilet-trained or dry at night, UTI may present with nocturnal enuresis or daytime wetting.
   4. **In older children, cystitis** (lower tract infection) is diagnosed when children present with only low-grade or no fever and with complaints of dysuria, urinary frequency, or urgency. **Pyelonephritis** (upper tract infection) is associated with back or flank pain, high fever, and other symptoms and systemic signs such as vomiting and dehydration.

E. **Diagnosis and evaluation**
   1. Diagnosis depends on the proper collection of the urine specimen.
      a. **In neonates and infants,** urine for culture must be collected by suprapubic aspiration of the urinary bladder or via a sterile urethral catheterization. A clean "bagged" urine sample is adequate for a screening urinalysis but **not** for culture.
      b. **In older children** who can void on command, a careful "clean-catch" urine sample is adequate for culture.
      c. Because bacteria multiply exponentially at room temperature, it is crucial that the urine be cultured immediately or at least refrigerated immediately until it can be cultured.
   2. **Urinalysis findings suggestive of UTI** include the presence of leukocytes on microscopy (>5–10 WBCs/HPF) and a positive nitrite or leukocyte esterase on dipstick. Note however that not all bacteria produce nitrites (e.g., enterococcus), which may lead to a negative nitrite test.
   3. **Urine culture** remains the **"gold standard"** for diagnosis. **Significant colony counts** depend on the culture method:
      a. Any growth on urine collected by suprapubic aspiration
      b. ≥10,000 colonies in samples obtained by sterile urethral catheterization
      c. ≥50,000–100,000 colonies of a single organism in urine collected by clean-catch technique
   4. **Imaging**
      a. Imaging is indicated in selected children with UTI, because children with UTI have

an increased incidence of structural abnormalities of the urinary tract (e.g., vesicoureteral reflux).

b. All children with pyelonephritis, all children with recurrent UTI, prepubertal males, and girls younger than 2 years of age with cystitis should have an imaging evaluation, which should include a renal ultrasound and consideration for a VCUG.

F. **Management**

1. **Empiric antibiotic therapy** should be started in symptomatic patients with a suspicious urinalysis while culture results are pending. Commonly used oral antibiotics include trimethoprim–sulfamethoxazole or cephalexin.
2. **Neonates** with UTIs are admitted to the hospital for initial IV management, which commonly includes ampicillin and gentamicin.
3. **Toxic-appearing children** with high fever and children with dehydration should also be admitted to the hospital for initial IV antibiotics and hydration. Patients can be transitioned to oral antibiotics once the child has shown clinical improvement and sensitivities are available.
4. Duration of treatment for cystitis is usually 7–10 days, and for pyelonephritis, 14 days.

Review Test

1. A 3-week-old uncircumcised male infant presents with a 2-day history of very poor feeding. He now takes only 1 oz of formula every 3 hours, instead of the usual 2–3 oz. The parents state that their son has become increasingly irritable, and they deny fever, vomiting, or other symptoms. You perform a laboratory evaluation to look for evidence of infection. A urinalysis demonstrates 25–50 white blood cells per high-power field. You suspect that the infant has a urinary tract infection (UTI). Which of the following statements regarding UTI in this infant is correct?
   A. There would be no significant difference in his risk of UTI had he been circumcised.
   B. During infancy, the risk of developing a UTI is the same as that of an infant girl.
   C. A clean "bagged" urine sample is adequate for culture in this febrile infant with no obvious source of infection.
   D. If diagnosed with a UTI, this infant has an increased risk of having vesicoureteral reflux as compared with an infant without a UTI.
   E. This infant should be treated empirically with oral antibiotics on an outpatient basis and reevaluated within 24 hours.
2. A 5-year-old boy is brought to your office by his parents, who noticed that when their son urinated earlier in the day, his urine appeared red. Dysuria, urinary frequency, and fever are absent, and he is well appearing on examination. Which of the following statements regarding this patient's presentation and subsequent workup is correct?
   A. This patient may be diagnosed with microscopic hematuria if there are ≥10 red blood cells (RBCs) per high-power field on a single urine sample.
   B. On urinalysis, RBCs that appear as biconcave disks indicate that they originated in the glomerulus, and this suggests that he has glomerulonephritis.
   C. Because of his presentation with hematuria at a young age, this patient will likely have persistent microscopic hematuria.
   D. This patient's red-colored urine may have resulted from eating beets the previous day.
   E. This patient's urinary dipstick for blood may be falsely positive if he has recently ingested ascorbic acid (vitamin C).
3. A 4-year-old girl who recently returned from Southeast Asia presents with a history of watery diarrhea, vomiting, and decreased urine output. She is irritable and is crying, although she stops crying when held by her parents. Examination reveals tachycardia with a normal blood pressure, dry mucous membranes, and good peripheral perfusion with normal skin turgor. Which of the following statements regarding rehydration of this child is correct?
   A. The goal of the emergency phase of intravenous rehydration is to restore or maintain intravascular volume to ensure perfusion of the vital organs. The type of intravenous fluids administered depends on the serum level of sodium in the blood.
   B. Appropriate bolus fluids in the emergency phase of intravenous rehydration should include 20 mL/kg of one half–normal saline solution.
   C. If this patient is isonatremic or hypernatremic, her fluid deficits should be replaced over 24 hours, but if she is hyponatremic, her fluid deficits should be replaced over 48 hours.
   D. If stool losses continue, these losses should not be replaced until all the deficit fluids are replaced.
   E. Oral rehydration therapy may be effective even if this child has a secretory diarrhea.
4. A 5-year-old boy has a 3-day history of headache, "puffiness," and dark-colored urine. Physical examination reveals hypertension and periorbital and peripheral edema. Urinalysis reveals hematuria with red blood cell casts and 2+ proteinuria. The diagnosis of poststreptococcal glomerulonephritis is suspected pending further evaluation. Which of the

following statements regarding this patient's diagnosis is correct?

A. If diagnosed with poststreptococcal glomerulonephritis, this patient would be expected to have mild to moderate impairment of renal function and normal serum complement levels.
B. This patient is likely to have had an infection of the skin or pharynx with a nephritogenic strain of group A β-hemolytic streptococcus 60–90 days before the current presentation.
C. A negative antistreptolysin O titer would rule out the diagnosis of poststreptococcal glomerulonephritis in this patient.
D. Antibiotic treatment with penicillin for streptococcal pharyngitis would have prevented this patient's glomerulonephritis.
E. If the diagnosis of poststreptococcal glomerulonephritis is confirmed, the prognosis for this patient is excellent; complete recovery usually occurs.

5. A previously healthy 3-year-old girl presents with a 2-week history of progressive facial edema. You suspect nephrotic syndrome. Which of the following statements regarding this patient's presentation, evaluation, and management is correct?

A. This patient's nephrotic syndrome is most likely a consequence of a primary glomerular disease, such as IgA nephropathy.
B. This patient's age of presentation is atypical; the peak age of presentation of nephrotic syndrome is between the ages 5 and 15 years.
C. This patient should undergo renal biopsy to confirm the diagnosis and to establish an appropriate approach to management.
D. If this patient develops a high fever, she should be empirically treated with antibiotics to cover possible pneumococcal peritonitis.
E. Discovery of heavy proteinuria, hypoalbuminemia, and hypocholesterolemia on laboratory testing would confirm the diagnosis.

6. A previously healthy 3-year-old boy presents with lethargy, pallor, and bloody diarrhea. He has had bloody stools for 4 days, and in the past 2 days he has developed fatigue and pale skin. He is drinking less than normal, and his urine output is somewhat decreased. The parents deny any travel or medication use. Physical examination reveals mild hypertension, pale mucous membranes, abdominal tenderness, and a petechial skin rash on the trunk and extremities. Hemolytic uremic syndrome (HUS) is suspected. Which of the following statements regarding the suspected diagnosis is correct?

A. Given the nature of this patient's symptoms and his young age, he is most likely to have atypical HUS.
B. Parenteral antibiotic treatment with gentamicin is indicated for the treatment of suspected *Escherichia coli* hemorrhagic colitis.
C. Although he has a petechial rash, his platelet count will be normal.
D. The prognosis is poor; he will likely have a chronic relapsing course, with a high chance of end-stage renal disease.
E. The renal impairment is caused by toxin binding to renal vascular endothelial cells.

7. A 14-year-old Japanese American boy has 3+ protein and 4+ blood with red blood cell casts on a routine screening urinalysis conducted as part of a health maintenance evaluation. Further questioning reveals two prior episodes of "brown-colored urine" concurrent with upper respiratory tract infections during the last 3 years. Which of the following is the most likely diagnosis?

A. Membranous nephropathy
B. Systemic lupus erythematosus nephritis
C. IgA nephropathy
D. Membranoproliferative glomerulonephritis
E. Henoch–Schönlein purpura nephritis

8. A 3-year-old girl has a 2-day history of fever, irritability, and emesis. Urine culture grows >100,000 colonies/mL of *Escherichia coli.* She is treated with cephalexin and returns 10 days later for an imaging evaluation to rule out a structural abnormality of the urinary tract. A voiding cystourethrogram reveals grade 2 vesicoureteral reflex (VUR), but her renal ultrasound is normal. Which of the following statements regarding VUR is correct?
   A. Inheritance of VUR is most likely to be autosomal recessive.
   B. The chance of developing chronic renal insufficiency as a result of VUR is 50%.
   C. Referral to a pediatric urologist for ureteral reimplantation is appropriate.
   D. The VUR is likely caused by a short submucosal tunnel in which the ureter inserts through the bladder wall.
   E. Because this patient has grade 2 VUR, she should be placed on prophylactic antibiotics.
9. A 1-year-old boy has a 2-day history of irritability, decreased oral intake, decreased urine output, occasional watery diarrhea, and tactile fever. On physical examination, he is nontoxic and moderately dehydrated and has a temperature of 38.3°C (101°F). You admit him for intravenous rehydration because of his dehydration. Which of the following statements regarding his maintenance fluid and electrolyte requirements is correct?
   A. His maintenance sodium requirement is approximately 1 mEq/kg/day.
   B. His maintenance water requirement is 1000 mL/m^2/day of body surface area.
   C. His fever will result in increased insensible losses, and maintenance fluids should therefore be increased by 5% for every degree of temperature above 38°C.
   D. His maintenance fluid calculations need to be adjusted for increased ongoing losses should he develop protracted vomiting or profuse watery diarrhea.
   E. Maintenance fluid calculations for this child take into account both sensible and insensible losses.
10. A 4-day-old male infant has gross hematuria. His parents noticed the bleeding today when they changed his diaper. Perinatal history is remarkable for a term gestation complicated by gestational diabetes mellitus. Physical examination reveals hypertension and a right-sided flank mass. In addition, the infant appears very sleepy, and his mucous membranes are dry. Which of the following is the most likely explanation for his hematuria?
   A. Maternal systemic lupus erythematosus nephritis
   B. Adenovirus infection
   C. Sickle cell disease
   D. Hypercalciuria
   E. Renal vein thrombosis
11. A 6-month-old female infant with a 2-week history of vomiting is brought to your office by her parents. The vomiting occurs three to four times per day, and her parents report she has been very fussy. Review of her growth records reveals very poor growth consistent with failure to thrive. A complete blood count is normal, but an electrolyte panel shows metabolic acidosis. Which of the following laboratory findings would be most consistent with suspected renal tubular acidosis?
   A. Hypokalemia
   B. Hyperphosphatemia
   C. Hyperchloremia
   D. Elevated serum anion gap
   E. Hypocalcemia

The response options for statements 12–14 are the same. You will be required to select one answer for each statement in the following set.

A. Autosomal dominant
B. Autosomal recessive

C. Sporadic
D. X-linked

For each patient, select the likely mode of inheritance of the disease.

1. A 6-month-old girl with bilateral abdominal masses and severe hypertension, whose older sister died as a neonate after being diagnosed with oligohydramnios.
2. A 12-year-old boy who has three renal cysts on a renal ultrasound that was performed for the evaluation of microscopic hematuria. The patient's paternal grandfather died of a stroke at 32 years of age, and the patient's father has hypertension.
3. A 15-year-old boy who has mild hearing loss, mild hypertension, hematuria, and proteinuria.

Answers and Explanations

1. **The answer is D** [XIV.A, XIV.E.1, and XIV.F]. Infants with urinary tract infections (UTIs) have an increased risk of having underlying structural abnormalities, including vesicoureteral reflux. A structural abnormality of the urinary tract, such as vesicoureteral reflux, predisposes a child to developing a UTI. Before 6 months of age, UTIs are twice as common in boys, but after 6 months of age, UTIs are more common in girls. Before 6 months of age, UTIs are 10 times more common in uncircumcised boys as compared with circumcised boys. In neonates and infants, urine for culture must be collected by suprapubic aspiration of the urinary bladder or by a sterile urethral catheterization. Bagged specimens obtained from an infant are inappropriate for culture as they are very likely to be contaminated. Outpatient management for older nontoxic children with suspected UTI may be appropriate. However, toxic-appearing children, neonates, and patients who have significant dehydration should be hospitalized and administered intravenous antibiotics initially.
2. **The answer is D** [Figure 11-1]. Patients may develop red-colored urine from the ingestion of exogenous pigments, such as those found in beets, and from medications, such as phenytoin and rifampin. Such patients have negative urine dipsticks for blood. Although 4–5% of school children may have microscopic hematuria on a single voided urine sample, only 0.5–2% have persistent microscopic hematuria on retesting. The diagnosis of microscopic hematuria may be made if ≥6 red blood cells (RBCs) are noted per high-power field on three or more consecutive urine samples. Patients with positive dipsticks for blood should have microscopic evaluations of fresh urine specimens. RBCs that appear as normal biconcave disks usually originate in the lower urinary tract, unlike dysmorphic RBCs, which are more likely to originate in the glomerulus. False-negative results on dipstick for blood may occur with ascorbic acid (vitamin C) ingestion.
3. **The answer is E** [I.D, I.E]. Oral rehydration therapy has been shown to be a safe and inexpensive alternative to intravenous rehydration and effective even in the face of secretory diarrhea, such as would be seen in cholera. Patients with secretory diarrhea still maintain their ability to absorb fluid and electrolytes through an intact, coupled cotransport mechanism. However, oral rehydration therapy should not be used for patients with severe life-threatening dehydration, paralytic ileus, or gastrointestinal obstruction. In patients with these problems, parenteral rehydration is more appropriate. The goal of the first phase of parenteral rehydration (emergency phase) is to restore or maintain the intravascular volume to ensure perfusion of vital organs, and this phase is the same for all patients (regardless of the patient's initial serum sodium level). Appropriate fluids for use in the emergency phase include isotonic crystalloids, such as normal saline or lactated Ringer solutions in boluses of 20 mL/kg. One quarter– or one half–normal saline is not an appropriate intravenous fluid for the emergency phase. The subsequent repletion phase, or the more gradual correction of fluid and electrolyte deficits, should occur over 24 hours for patients with isonatremic and hyponatremic dehydration, and over 48 hours for patients with hypernatremic dehydration. There is a risk of cerebral edema if deficit replacement occurs too quickly in patients with hypernatremic dehydration. Ongoing losses should be replaced on a "milliliter for milliliter basis" concurrent with the replacement of deficits.
4. **The answer is E** [V.F.1]. The most common form of acute glomerulonephritis in school-age children is poststreptococcal glomerulonephritis. Patients usually present with hematuria, proteinuria, and hypertension after an infection of the skin (sometimes up to 28 days after impetigo) or pharynx (usually 10–14 days after pharyngitis) with a nephritogenic strain of group A β-hemolytic streptococcus. The prognosis for children with poststreptococcal glomerulonephritis is excellent, and affected children usually recover completely; renal failure

is rare. Laboratory features consistent with the diagnosis include transient low serum complement levels. The antistreptolysin O titer is positive in 90% of children after a respiratory infection but in only 50% of patients who have had skin infections. Antibiotic treatment of streptococcal pharyngitis or impetigo does not reduce the risk of poststreptococcal glomerulonephritis, although the risk of rheumatic fever is reduced.

5. **The answer is D** [VI.A, VI.B, VI.E, and VI.G.5]. Nephrotic syndrome in children is defined as heavy proteinuria (>50 mg/kg/24 hours), hypoalbuminemia, hypercholesterolemia, and edema. Patients with nephrotic syndrome are susceptible to infections with encapsulated organisms, such as pneumococcal infections, and are at risk for developing peritonitis, pneumonia, and overwhelming sepsis. Patients with nephrotic syndrome and fever should therefore be treated empirically with antibiotics pending culture results. The most common form of nephrotic syndrome in children is minimal change disease, which comprises 90% of all cases. Primary glomerular disease (e.g., IgA nephropathy) and systemic diseases (e.g., systemic lupus erythematosus) are less common causes of nephrotic syndrome in children. Most cases of childhood nephrotic syndrome (two-thirds) occur in children younger than 5 years of age. Renal biopsy to establish the diagnosis or to determine a management approach is not indicated for most patients with nephrotic syndrome. However, it is indicated for patients who have impaired creatinine clearance or for those who do not respond to initial management with corticosteroids.
6. **The answer is E** [VII.C.3]. There are three subtypes of hemolytic uremic syndrome (HUS), a Shiga toxin–associated form (the most common form in childhood), pneumococcal- associated form, and an atypical form caused by medications or complement system dysregulation which is often inherited. Shiga toxin–associated HUS occurs as a result of intestinal infection with a toxin-producing bacterial strain, most commonly *Escherichia coli* 0157:H7. The toxin binds to vascular endothelial cells, especially in the renal vasculature, causing platelet thrombi and resultant renal ischemia. Patients with HUS have a microangiopathic hemolytic anemia, renal impairment, and thrombocytopenia, which may result in visible petechiae on the skin. The prognosis for patients with Shiga toxin–associated HUS is generally good, although poor prognostic signs include elevated white blood cell count on admission and prolonged oliguria. Antibiotic treatment of the *E. coli* hemorrhagic colitis is controversial and may actually increase the likelihood that a patient will go on to develop HUS.
7. **The answer is C** [V.F.2]. This patient's clinical presentation and ethnicity are consistent with IgA nephropathy (Berger disease), the most common form of chronic glomerulonephritis in the world. Patients with IgA nephropathy typically present in the second or third decade of life with recurrent bouts of gross hematuria associated with respiratory infections. IgA nephropathy is most common in Asia and Australia and in Native Americans. Membranoproliferative nephritis, membranous nephropathy, and nephritis as a result of systemic lupus erythematosus during childhood are all less common causes of glomerulonephritis in children. This patient's clinical presentation is not consistent with Henoch–Schönlein purpura, which is characterized by abdominal pain, palpable purpura on the buttocks and thighs, and joint symptoms.
8. **The answer is D** [XII.E]. Vesicoureteral reflux (VUR) is caused by abnormalities of the ureterovesical junction, most commonly a shortened submucosal tunnel in which the ureter inserts through the bladder wall. The inheritance pattern is most commonly autosomal dominant with variable expression but autosomal recessive inheritance has also been described. The majority of children with VUR eventually outgrow the reflux, although a minority develop severe renal impairment owing to reflux nephropathy from severe VUR. Patients with grade 4 or 5 VUR should be referred to a pediatric urologist for consideration of ureteral reimplantation. Although previously recommended, low-dose prophylactic antibiotics to decrease the risk of urinary tract infection in low risk patients is not indicated.

9. **The answer is E** [I.B and I.C]. Maintenance water and electrolyte calculations are designed to balance the usual daily losses of water and salts as a result of normal daily metabolic activities. These losses include both measurable forms (sensible losses), such as urinary losses, and less readily measurable but still clinically significant forms (insensible losses), such as losses from the skin, lungs, or gastrointestinal tract. The maintenance sodium requirement is approximately 2–3 mEq/kg/day for infants and children. When calculating maintenance fluids using the surface area method, the maintenance water requirement for children is 1500 mL/m^2/day. Fever will result in increased insensible losses, and maintenance fluids should be increased by about 10% for every degree of temperature above 38°C. Maintenance fluid calculations should not be adjusted for increased ongoing losses, such as profuse watery diarrhea. Instead, any increased stool losses should be replaced on a "milliliter per milliliter" basis.
10. **The answer is E** [Figure 11-2 and Table 11-3]. This patient likely has a renal vein thrombosis, which presents in infancy with the sudden onset of gross hematuria and unilateral or bilateral flank masses. Acute renal failure may result. Infants of diabetic mothers have a greatly increased risk of renal vein thrombosis. Maternal systemic lupus erythematosus (SLE) would not result in hematuria in the infant; however, maternal SLE is associated with infant heart block. Adenovirus infection is a cause of hemorrhagic cystitis, which often causes hematuria; however, this would be very unusual in a neonate. Similarly, although sickle cell disease also causes hematuria, it would be an uncommon presentation in a neonate. Hypercalciuria is a common cause of hematuria; however, a flank mass would not be a presenting sign.
11. **The answer is C** [IX.E and Table 11-2]. The classic electrolyte presentation seen in renal tubular acidosis (RTA) is a hyperchloremic metabolic acidosis with a normal serum anion gap. Hypokalemia is not specifically associated with RTA; however, type IV RTA is associated with hyperkalemia. Patients with Fanconi syndrome may present with proximal (type II) RTA with glucosuria, aminoaciduria, and hyperphosphaturia (therefore low serum phosphorus levels, not high serum phosphorus levels). Hypocalcemia is not a feature of RTA.
12. **The answers are B, A, and D, respectively** [VIII.D, VIII.E, and VIII.B]. Infantile polycystic kidney disease *(question 12)* is an autosomal recessive disorder characterized by greatly enlarged cystic kidneys, severe hypertension, and variable degrees of liver involvement. Severe cases are associated with oligohydramnios, pulmonary hypoplasia, and early neonatal death. Although the family history may be negative in recessive disorders, there is a 25% risk of affected siblings in subsequent pregnancies. In contrast, adult polycystic kidney disease *(question 13)* is inherited in an autosomal dominant pattern, and there is considerable variability in its severity, ranging from mild microscopic hematuria to severe hypertension and renal failure. Adult polycystic kidney disease may also be associated with cerebral aneurysms and early death. Alport syndrome *(question 14)* is inherited in multiple patterns, but the X-linked form is by far the most common. Alport syndrome is characterized by renal manifestations, including hypertension and hematuria, as well as renal failure more consistently in the males; hearing loss; and ocular abnormalities of the lens and retina.

CHAPTER 12

Neurology

Rujuta B. Wilson, Jason T. Lerner

I. The Hypotonic Infant

A. **Definition.** *Hypotonia is a reduction in muscle tone in which there is decreased resistance of movement during passive stretching of muscles* and a decrease in spontaneous activity. In contrast, **weakness** is the decreased or less than normal force generated by **active contraction** of muscles. Weakness is often manifested as an inability to move the limbs against gravity.

B. **Classification of hypotonia**
   1. **Central hypotonia** is dysfunction of **upper motor neurons** (i.e., cortical pyramidal neurons and their descending corticospinal pathways).
   2. **Peripheral hypotonia** is dysfunction of **lower motor neurons** (i.e., spinal motor neurons, peripheral nerves, and the neuromuscular junction).

C. **Clinical features**
   1. **History** may reveal antenatal problems, such as **decreased fetal movements in utero.**
   2. **Physical examination** findings in both central and peripheral hypotonia may include weak cry, poor suck, drooling, decreased spontaneous movements, delay of motor milestones, frog-leg positioning (hips are externally rotated and flexed), poor posture on horizontal and vertical suspension (infant slips through examiner's hands when lifted up under the axillae), and head lag when pulled to the sitting position. Other findings may include flattened occiput, occipital hair loss, arthrogryposis (muscle contractures), congenital hip dislocation, and pectus excavatum.
      a. **Central nervous system (CNS) involvement** is suggested by seizures, axial hypotonia, scissoring of the legs on vertical suspension, dysmorphic features, cortical thumbing/fisting (persistent adduction and infolding of the thumbs), and global developmental delay.
      b. **Peripheral nervous system involvement** is suggested by atrophy, muscle fasciculation, and loss of deep tendon reflexes.
      c. In addition to hypotonia, patients with **congenital neuromuscular disorders** may have additional findings such as bilateral ptosis, ophthalmoplegia, flat midface, high-arched palate, chest wall abnormalities (e.g., bell-shaped chest, pectus excavatum or carinatum), and bilateral cryptorchidism.

D. **Differential diagnosis of hypotonia** (**Figure 12-1**)
   1. **Systemic pathology**: sepsis, meningitis, and both renal and hepatic encephalopathy
   2. **Nonprogressive encephalopathies**: cerebral malformations, hypoxic–ischemic encephalopathy, intracranial hemorrhage, and trauma (e.g., spinal cord injury)
   3. **Chromosomal disorders**: Prader–Willi and Down syndromes
   4. **Metabolic disorders**: neonatal adrenoleukodystrophy, primary carnitine deficiency, acid maltase deficiency, urea cycle defects, and Zellweger syndrome
   5. **Muscle disorders**: congenital myotonic dystrophy, congenital myopathy, and congenital muscular dystrophies
   6. **Neuromuscular junction disorders**: congenital and neonatal myasthenia gravis

E. **Evaluation**
   1. It is **important to rule out acute life-threatening causes,** such as sepsis, meningitis, or an acute metabolic disorder. Serum electrolytes, including calcium and magnesium, ammonia, lactate, and pyruvate levels should be drawn to evaluate for a metabolic disorder.
   2. **When central hypotonia is suspected,** it is necessary to consider:
      a. **Head computed tomography (CT) scan** to evaluate for acute CNS injury, such as hemorrhage or trauma. Magnetic resonance imaging (MRI) may be indicated to evaluate for structural abnormalities, neuronal migrational abnormalities (i.e.,

polymicrogyria, lissencephaly), basal ganglia signal abnormalities (seen in metabolic conditions), and deep white matter changes.

b. **High-resolution chromosomal studies** to evaluate for a suspected genetic disorder, which include chromosomal microarray and fluorescent in situ hybridization (FISH).

3. **When peripheral hypotonia is suspected,** it is necessary to consider the following:
   a. **Serum creatine kinase (CK)** levels to screen for myopathy.
   b. **Electromyography (EMG)**. **Nerve conduction studies** are performed to identify myopathies (especially congenital) neuromuscular junction disorders and some neuropathies.
   c. **Muscle and nerve biopsy**
   d. **Genetic testing for spinal muscular atrophy (SMA) or myotonic dystrophy**

F. **Specific peripheral hypotonic disorders** are described in more detail in the following discussion.

1. **Spinal muscular atrophy (SMA)**
   a. **Definition.** Degeneration of anterior horn cells in the spinal cord and motor nuclei in the lower brainstem. Lower motor neurons control movement in the arms, legs, chest, face, throat and tongue. SMA therefore presents with *hypotonia, difficulty feeding, and tongue fasciculations.*
   b. **Epidemiology.** Incidence is 4–10 in 100,000 live births. SMA is the **second most common hereditary neuromuscular disorder,** after Duchenne muscular dystrophy.
   c. **Classification**
      1. **SMA type 1** is also called infantile-onset SMA or *Werdnig–Hoffman disease.* Onset <6 months of age. These children never attain sitting or walking milestones.
      2. **Type 2** or **intermediate form.** Onset at 6–18 months of age. These children sit but never walk.
      3. **Type 3.** Onset >18 months of age. These children are able to sit and walk.
      4. **Type 4 adult onset**
   d. **Etiology**
      1. **Autosomal recessive inheritance**
      2. All four forms of SMA are caused by mutations in the **survival motor neuron gene (*SMN1*)** on **chromosome 5.** Loss of SMN1 protein is partially compensated by SMN2 protein synthesis. Presence of more copies of SMN2 usually presents with a milder phenotype.
      3. **Pathology** of the spinal cord shows **degeneration and loss of anterior horn motor neurons** and infiltration of microglia and astrocytes.
   e. **Clinical features**
      1. **Weak cry, tongue fasciculations,** and difficulty sucking and swallowing
      2. **Bell-shaped chest**
      3. **Frog-leg posture** when in the supine position, with generalized hypotonia, weakness, and areflexia
      4. **Normal extraocular movements** and **normal sensory** examination
   f. **Diagnosis**
      1. **DNA testing** for the abnormal gene is **diagnostic in >90% of cases.**
      2. **Muscle biopsy** shows a characteristic atrophy of groups of muscle fibers innervated by the damaged axons.
   g. **Management. Treatment is supportive.** The mainstay of treatment is supportive care, including **gastrostomy tube feeding** to ensure adequate nutrition, overnight noninvasive ventilation to prevent sleep apnea, **diligent surveillance** and treatment

of respiratory infections, and **physical therapy** to maintain range of motion and prevent contractures. In December 2016, the Food and Drug Administration (FDA) approved a new treatment (Nusinersen) to improve motor function in children with SMA. The drug is designed to increase the amount of functional survival motor neuron protein that is deficient in patients with SMA.

h. **Prognosis. For SMA type 1,** survival beyond the first year of life is unusual. Death occurs as a result of respiratory insufficiency or pneumonia. **For SMA types 2 and 3,** survival until adolescent and adult years, respectively, is common.

2. **Infantile botulism**
   a. **Definition.** Infantile botulism is **bulbar weakness and paralysis** that develops in infants during the first year of life **secondary to ingestion of *Clostridium botulinum* spores and absorption of botulinum toxin.**
   b. **Etiology.** The source of the botulinum toxin is infected foods, such as contaminated **honey,** or spores unearthed from the ground. **The toxin prevents the presynaptic release of acetylcholine.**
   c. **Clinical features**
      1. **Onset of symptoms** occurs **12–48 hours** after ingestion of spores.
      2. **Constipation is the classic first symptom of botulism.**
      3. **Neurologic symptoms follow, including weak cry and suck, loss of previously obtained motor milestones, ophthalmoplegia, and hyporeflexia.**
      4. **Paralysis is symmetric and descending,** and at times, diaphragmatic paralysis may also occur.
   d. **Diagnosis.** Diagnosis is based on suggestive history, neurologic examination, and *identification of the toxin or bacteria in the stool.* **EMG** is sometimes performed and demonstrates brief, small-amplitude muscle potentials with **an incremental response during high-frequency stimulation.**
   e. **Management. Treatment is supportive,** with nasogastric feeding and assisted ventilation as needed.
      1. **Botulism immune globulin** improves the clinical course.
      2. **Antibiotics are contraindicated** and may worsen the clinical course.
   f. **Prognosis.** The outlook is **excellent,** and complete recovery is expected. However, recovery may take weeks or even months.

3. **Congenital myotonic dystrophy**
   a. **Definitions**
      1. **Myotonia is the inability to relax contracted muscles.**
      2. **Congenital myotonic dystrophy** is an **autosomal dominant** muscle disorder that presents in the newborn period with weakness and hypotonia.
   b. **Epidemiology.** Incidence is 1 in 30,000 live births.
   c. **Etiology.** Myotonic dystrophy is a *CTG trinucleotide repeat disorder with autosomal dominant inheritance,* with symptoms becoming more severe with each successive generation (genetic anticipation). The gene has been identified on chromosome 19. Transmission to affected infants is **through their affected mothers** in more than 90% of cases. The earlier the onset of the disease in the mother, the more likely she will have affected offspring.
   d. **Clinical features**
      1. **Antenatal history** may reveal decreased fetal movements and polyhydramnios caused by poor swallowing in utero.
      2. **Neonatal history** is often significant for **feeding and respiratory problems.**
      3. **Physical examination** of the neonate is notable for facial diplegia (bilateral weakness), which results in characteristic "V" shape of the upper lip,

hypotonia, areflexia, and arthrogryposis (multiple joint contractures).

4. **Myotonia is not present in the newborn** but develops later, almost always by 5 years of age.
5. **In adulthood,** typical myotonic features include **myotonic facies** (atrophy of masseter and temporalis muscles), ptosis, a stiff, straight smile, and an **inability to release the grip after handshaking (myotonia).**
6. **Additional problems** include intellectual disability, cataracts, cardiac arrhythmias, and infertility.

e. **Diagnosis**

1. **This disorder should be suspected in all infants with hypotonia.** The child's **mother should also be examined,** as she will often have intellectual disability, as well as the typical physical exam features of myotonic dystrophy.
2. **DNA testing** to identify the gene can be performed to confirm the diagnosis**.** Because of the availability of DNA testing, EMG and muscle biopsy are no longer indicated.

f. **Management. Treatment is supportive.** Infants may require assisted ventilation and gastrostomy tube feedings.

g. **Prognosis. The outlook is guarded.** Infant mortality can be as high as 40% because of respiratory problems.

1. All survivors have **intellectual disability (average intelligence quotient [IQ] of 50–65).**
2. Feeding problems tend to subside with time.

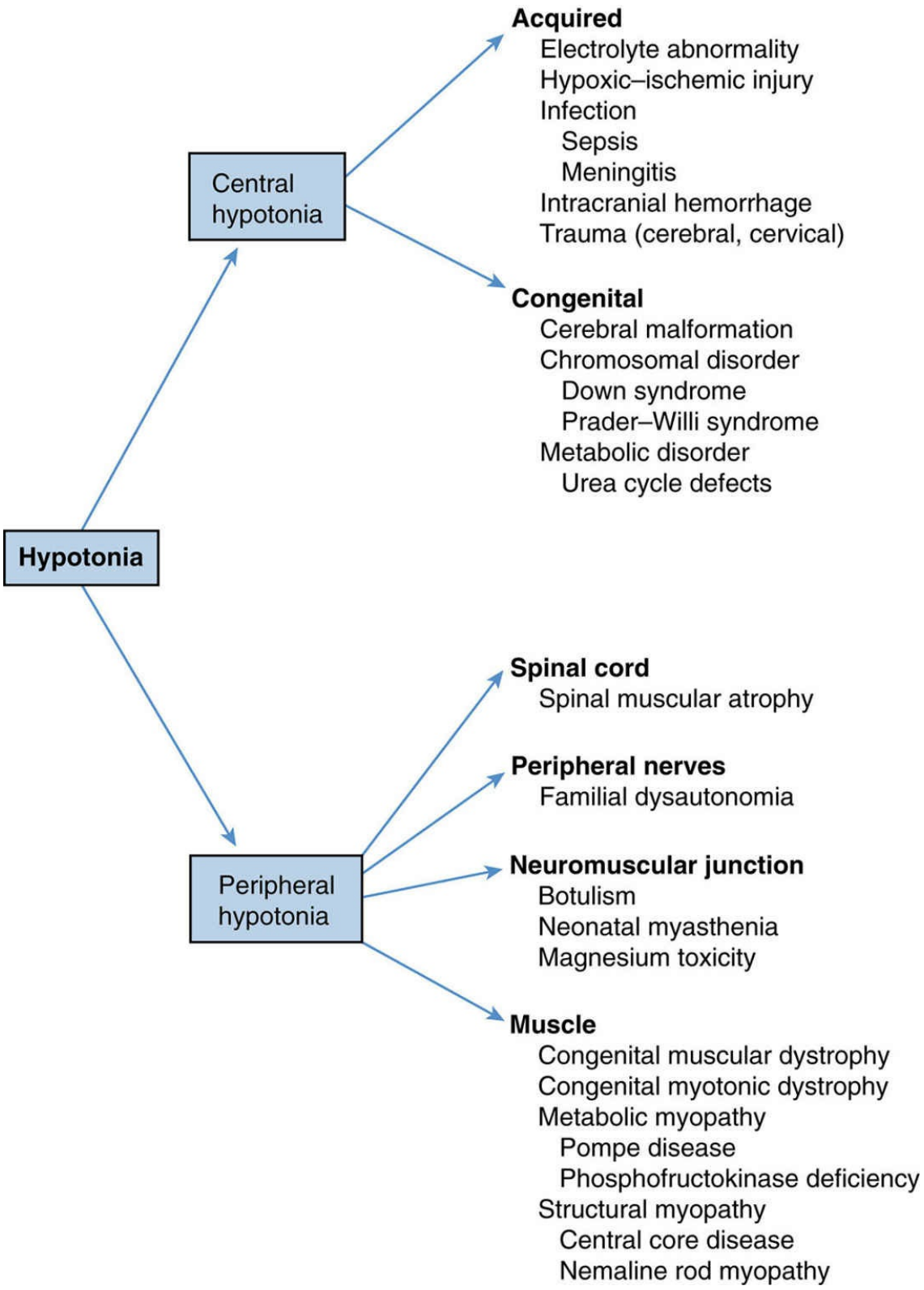

FIGURE 12.1 Differential diagnosis of hypotonia.

II. Hydrocephalus

A. **Definition.** Hydrocephalus is an elevation in intracranial pressure (ICP) due to a disturbance in the flow of cerebral spinal fluid (CSF). This can be caused by increased production, blockage of flow, or decreased absorption of CSF. The normal production of CSF is between 400 and 500 mL daily.

B. **Types of hydrocephalus**
   1. **Noncommunicating (obstructive) hydrocephalus** is due to an obstruction of CSF flow. As a result of this obstruction, the pathways of the ventricular system do not communicate correctly, and there is a buildup of CSF proximal to the blockage.
   2. **Communicating (nonobstructive) hydrocephalus** is due to either an increase in production or a decrease in absorption of CSF. Therefore, all of the pathways of the ventricular system communicate normally, and the problem occurs at the beginning or end of the pathway.
   3. **Hydrocephalus ex vacuo** is not true hydrocephalus, but rather a term used to describe ventricular enlargement caused by brain atrophy.

C. **Etiology**
   1. **Congenital causes of hydrocephalus**
      a. **Chiari type II malformation** is characterized by downward displacement of the cerebellum and medulla through the foramen magnum, blocking CSF flow. This malformation is often associated with a lumbosacral myelomeningocele.
      b. **Dandy–Walker malformation** is a combination of an absent or hypoplastic cerebellar vermis and cystic enlargement of the fourth ventricle, which blocks the flow of CSF.
      c. **Congenital aqueductal stenosis** is the **most common cause of noncommunicating hydrocephalus.** Some cases of aqueductal stenosis are inherited as an **X-linked trait,** and these patients may have thumb abnormalities and other CNS anomalies such as spina bifida (SB).
   2. *Acquired causes of hydrocephalus* include **intraventricular hemorrhage** (most common in preterm infants), **bacterial meningitis,** and **CSF-producing brain tumors.**

D. **Clinical features**
   1. **Increasing head circumference** that crosses percentile lines, or *head circumference >97%* for age
   2. **Infants** with open cranial sutures have the following clinical signs:
      a. **Large anterior and posterior fontanelles and split sutures**
      b. **Setting-sun eyes,** a tonic downward deviation of both eyes caused by pressure from the enlarged third ventricles on the upward gaze center in the midbrain
   3. **Older children** with closed cranial sutures have the following symptoms and signs of **increased ICP:**
      a. Headache
      b. Nausea and vomiting
      c. Unilateral sixth nerve palsy
      d. Papilledema
      e. Brisk deep tendon refluxes (DTRs), but usually with a downward plantar response

E. **Evaluation.** Increasing head circumference and signs or symptoms of increased ICP mandate an **urgent head ultrasound in infants or head CT scan in older children.**

F. **Management.** Hydrocephalus requires the surgical placement of a **ventriculoperitoneal shunt** to divert the flow of CSF. Complications of ventriculoperitoneal shunts include **shunt infection** and **shunt obstruction.** In older children, **acetazolamide** may be used to decrease

ICP as well.

G. **Prognosis.** Outcome varies depending on the cause of the hydrocephalus and the success of the intervention.
   1. **Patients with aqueductal stenosis** have the best cognitive outcome.
   2. **Patients with Chiari type II malformation** may have low normal intelligence and language disorders.
   3. **Patients with X-linked hydrocephalus** frequently have cognitive delays.

III. Spina Bifida

A. **Definitions**
   1. **Spina bifida (SB)** is a general term that refers to **any failure of bone fusion** in the posterior midline of the vertebral column.
   2. **Neural tube defect** is a broad term that includes all forms of failure of neural tube closure, from anencephaly to sacral meningocele.

B. **Types of SB**
   1. **SB occulta** is an incomplete closure of vertebrae *without herniation of tissue* through the cleft.
   2. **Meningocele** is the herniation of the **meninges only** through a bony cleft, most commonly in the lumbosacral region.
   3. **Myelomeningocele** is the **herniation of the meninges and spinal cord tissue** through the bony cleft, most commonly in the lumbosacral region. Myelomeningocele is more common than meningocele.

C. **Epidemiology.** The incidence of neural tube defects varies with geographic location. In the United States, the prevalence is approximately 0.5 in 1000; however, in China and India, it is as high as 10 per 1000.

D. **Etiology.** The **multifactorial etiology includes environmental, genetic, nutritional, and teratogenic factors.**
   1. Taking a prenatal multivitamin preparation that includes **folic acid** has decreased the incidence of SB in the newborn. The mechanism of action of folic acid is uncertain.
   2. **Risk factors** include a history of previous affected pregnancy, inadequate folic acid intake, and maternal diabetes.
   3. **Teratogens** causing SB include valproic acid, carbamazepine, phenytoin, colchicine, vincristine, azathioprine, and methotrexate.

E. **Clinical features**
   1. **SB occulta.** The skin on the back (usually lumbosacral region) is epithelialized, and a hairy patch or dimple often covers the area. No neurologic deficits are present.
   2. **Meningocele.** A fluctuant midline mass is present overlying the spine. The mass is filled with CSF but does not contain spinal cord tissue and can be transilluminated. **Neurologic deficits are usually not present** or are only very mild.
   3. **Myelomeningocele**
      a. A **fluctuant midline** mass is present anywhere along the spine, but most commonly in the lumbosacral region.
      b. **Neurologic defects are present and depend on the level of the lesion,** varying from complete paraplegia (above L3) to preserved ambulation and variable bladder or bowel incontinence (S3 and below).
      c. **Associated anomalies and complications**
         1. **Hydrocephalus. Ninety percent of lumbosacral myelomeningoceles are associated with Chiari type II malformation and hydrocephalus.** Cervical and thoracic myelomeningoceles are not associated with hydrocephalus.
         2. **Cervical hydrosyringomyelia** (accumulation of fluid within the central spinal cord canal and the cord itself)
         3. **Defects in neuronal migration** (e.g., gyral anomalies, agenesis of the corpus callosum)
         4. **Orthopedic problems (e.g., rib anomalies, deformities of the lower extremities, and lower extremity fractures from loss of sensation)**
         5. **Genitourinary neurologic deficits**

F. **Diagnosis**
   1. **Prenatal diagnosis is common.**
      a. ***α*-Fetoprotein (AFP),** the main serum protein in fetal life, is elevated in amniotic fluid and maternal serum in open neural tube defects, and when measured in maternal serum at 16–18 weeks' gestation, **detects 80% of spinal defects.**
      b. **Fetal sonography** is highly sensitive in detecting spinal defects.
   2. **Diagnosis after birth**
      a. **SB occulta** is suggested by finding any skin abnormality overlying the spine and may be confirmed by spinal radiographs.
      b. **Meningocele** is suggested by physical examination findings and is confirmed by MRI of the spinal cord and spine.
      c. **Myelomeningocele** is a clinical diagnosis based on physical examination at birth.

G. **Management**
   1. **SB occulta** does not require treatment.
   2. **Meningocele** requires surgical repair.
   3. **Myelomeningocele** requires urgent surgical repair within 24 hours of birth, or in some cases in utero, to reduce the morbidity and mortality from infection and to prevent further trauma to the exposed neural tissue.

H. **Prognosis**
   1. **SB occulta and meningocele have excellent prognoses** as a result of the absence of neurologic deficits.
   2. **Myelomeningocele.** Without treatment, around 85% die within the first year of life. With treatment, 90% of patients survive to adolescence, but many have functional disabilities. Associated problems include **wheelchair dependency, bladder or bowel incontinence, seizures, precocious puberty, pressure sores, and fractures.**

IV. Approach to the Comatose Patient

A. **Definition.** Coma is a state of unawareness of self and environment in which the patient lies with the eyes closed, without purposeful movement or sleep–wake cycles, and is unarousable by external stimuli.

B. **Etiology** *(*Table 12-1**).** In addition to *traumatic brain injury*, the most common non-traumatic cause of coma in children is *infection.*

C. **Assessment.** The **goal** of assessment of the comatose patient is to determine the depth of coma, to identify the neurologic signs that indicate the site and cause of the coma, and to monitor the patient's recovery.

1. **Glasgow Coma Scale** provides a standard measure to monitor the level of consciousness (see **Chapter 20, Table 20-1**).
2. **Head and neck exam.** The patient should be assessed for **scalp injuries**, **breath odors** (for alcohol intoxication or ketosis caused by diabetic ketoacidosis), and **nuchal rigidity** (caused by meningitis). **CSF or blood draining** from the nose or external auditory canal may indicate a basilar skull fracture.
3. **Abnormal motor responses** to stimuli can indicate the location of brain damage.
   a. **Flaccidity or no movement** may suggest severe spinal or brainstem injury.
   b. **Decerebrate posturing (extension of arms and legs)** is seen in diffuse toxic/metabolic disorders or midbrain compression.
   c. **Decorticate posturing (flexion of arms and extension of legs)** is seen in cortical and/or subcortical abnormalities with preservation of brainstem function.
   d. **Asymmetric responses** suggest hemispheric injury.
4. **Abnormal respiratory responses** may indicate the location of brain injury or its cause.
   a. **Hypoventilation** suggests opiate or sedative overdose.
   b. **Hyperventilation** suggests metabolic acidosis (Kussmaul respirations or rapid, deep breathing may occur), neurogenic pulmonary edema, or midbrain injury.
   c. **Cheyne–Stokes breathing** (alternating apnea and hyperpnea) suggests bilateral cortical injury and is associated with herniation, specifically displacement of the diencephalon (thalamus and hypothalamus).
   d. **Apneustic breathing** (pausing at full inspiration) indicates pons or upper medulla damage.
   e. **Ataxic or agonal breathing** (irregular respirations with no particular pattern) indicates medullary injury and impending brain death.
5. **Pupillary size and reactivity** may provide clues.
   a. Unilateral dilated nonreactive pupil suggests **uncal herniation.**
   b. Bilateral dilated nonreactive pupils suggest topical application of a dilating agent, a postictal state, or irreversible brainstem injury.
   c. Bilateral constricted reactive pupils suggest opiate ingestion or pontine injury.
6. **Other brainstem reflexes** should be assessed to determine the extent of injury to the brainstem.
   a. **Oculocephalic maneuver (doll's eyes).** When turning the head of an unconscious patient, the eyes normally look straight ahead and then slowly drift back to midline position, because the intact vestibular apparatus senses a change in position. In an **injured brainstem**, movement of the head does not evoke any eye movement. This is termed a **negative oculocephalic maneuver** or negative doll's eyes.
   b. **Caloric irrigation.** When the oculocephalic response is negative or cannot be performed because of possible cervical cord injury, caloric testing should be performed. This involves angling the head at 30° and irrigating each auditory canal

with 10–30 mL of ice water. An intact (normal) cold caloric response is reflected by eye deviation to the ipsilateral side, with nystagmus to the contralateral ear. An abnormal response suggests pontine injury.

c. **Abnormal corneal and gag reflexes** indicate significant brainstem injury.

D. **Evaluation.** Once the airway, breathing, and circulation are stable, further diagnostic workup may begin.

1. **Glucose should be checked immediately** in any comatose patient.
2. **Urine toxicology screen, serum electrolytes, and metabolic panel** should also be evaluated.
3. **Head CT scan** should be performed to identify mass lesions or trauma.
4. **Lumbar puncture (LP) to rule out meningoencephalitis should be considered** if the CT scan is negative.
5. **Urgent electroencephalography (EEG) should be considered,** even in patients without a history of clinical seizures.

Table 12-1
Causes of Impaired Consciousness and Coma in Childhood and Adolescence

Infectious Meningitis Encephalitis Focal infection (abscess, cerebritis)
Inflammatory Vasculitis Demyelinating disorders (acute disseminated encephalomyelitis)
Traumatic Concussion Abusive head trauma Diffuse axonal injury Cerebral hematoma or contusion
Vascular disease Cerebral infarction Cerebral hemorrhage
Neoplasm
Hypoxia Shock Cardiac failure Nonfatal drowning Carbon monoxide poisoning
Metabolic disorders Fluid or electrolyte imbalance Hypoglycemia/hyperglycemia Hyponatremia Diabetic ketoacidosis Organic acidemias Amino acidemias Hepatic encephalopathy Urea cycle disorders Disorders of fatty acid metabolism Reye syndrome

Hyperammonemia
Hypothyroidism or hyperthyroidism

Nutritional
Thiamine deficiency
Pyridoxine deficiency
Folate and vitamin B_{12} deficiency

Toxins/poisons
Alcohol
Prescription medications
Atropine, scopolamine, benzodiazepines, barbiturates, lithium, opiates, tricyclic antidepressants
Over-the-counter medications
Heavy metal poisoning
Lead, mercury, arsenic
Illicit drugs*

*Amphetamine, cocaine, and hallucinogens (lysergic acid diethylamide [LSD], mescaline, phencyclidine hydrochloride [PCP]) cause agitation, confusion, delirium, and hallucinations but *not* coma.

V. Seizure Disorders of Childhood

A. **Definitions**
   1. A **seizure** is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.
   2. **Epilepsy** is diagnosed if any of the following three scenarios occur:
      a. The patient has at least two unprovoked seizures >24 hours apart
      b. The patient has one unprovoked seizure and the probability of further seizures occurring over the next 10 years (i.e., the patient has another diagnosis that predisposes to an increased risk of seizures, such as a brain tumor)
      c. The patient is diagnosed with an epilepsy syndrome (e.g., childhood absence epilepsy)
   3. **Status epilepticus** is defined as 5 or more minutes of continuous seizure activity, or repetitive seizures without recovery of consciousness.

B. **Epidemiology**
   1. One percent of children have a single unprovoked seizure before 16 years of age.
   2. After a single unprovoked seizure, approximately 40% of children will have a second seizure.
   3. Prevalence of epilepsy in children is 0.5–0.8%.

C. **Etiology**
   1. The seizure discharge is caused by an imbalance between excitatory and inhibitory input within the brain, or abnormalities in the membrane properties of individual neurons.
   2. In some children, the cause of seizures is known *(***Table 12-2***)*; however, in many, the cause remains unknown.

D. **Classification of seizures.** Criteria for the classification of seizures include the presence or absence of fever, the extent of brain involvement, whether consciousness is impaired, and the nature of the movements *(***Figure 12-2***)*.
   1. **Febrile seizures** are a common but benign type of seizure associated with fever [see section V.K].
   2. **Afebrile seizures** are either generalized (starting throughout the entire brain) or partial (starting from a single part or "focus" in the brain).
      a. **Generalized seizures** are caused by the discharge from a group of neurons in **both cerebral hemispheres** and are *associated with an alteration of consciousness.* Two common types are tonic–clonic and absence seizures.
         1. **Tonic–clonic seizures** are the **most common type of generalized seizure.** These seizures are characterized by increased thoracic and abdominal muscle tone, followed by clonic movements of the arms and legs, eyes rolling upward, incontinence, decreased consciousness, and a **postictal state** of variable duration.
         2. **Absence seizures** are brief staring spells that occur without loss of posture and with only minor motor manifestations (e.g., eye blinking or mouthing movements). The seizure lasts <15 seconds, and there is **no postictal state.**
         3. **Other generalized seizures** include tonic, clonic, myoclonic, and atonic.
      b. **Focal (partial) seizures** are caused by the discharge from a group of neurons in **one hemisphere.** Seizure symptoms may have predominately **motor, sensory, or psychomotor features.** There are two types:
         1. In **focal seizures** (prior term: simple partial seizure)**,** consciousness is **not** impaired.
         2. In **focal dyscognitive seizures** (prior term: complex partial seizure),

consciousness is altered.

E. **Classification of epilepsy.** Classification may be based on either the **predominant seizure type**, **the site of origin of the epileptic discharge or the genetic mutation.**

F. **Differential diagnosis** of seizure-like events *(**Table 12-3**)*

G. **Diagnosis.** Epilepsy is diagnosed on the basis of **history** and **physical examination,** as well as testing for **genetic mutations.** Other studies (EEG, MRI) may be useful.
   1. **EEG** is useful to evaluate the background rhythms as well as seizures, particularly in determining the location of onset of focal seizures. **However, an abnormal EEG is not required for the diagnosis of epilepsy** (in particular, focal seizures may have a normal EEG during the interictal period between seizures).
   2. **Video-EEG monitoring** is a useful tool when clinical information is inadequate or incomplete (e.g., when patients are <3 years of age, when events concerning for seizures occur during sleep, or when the history is unclear). Video-EEG monitoring is also useful to capture and characterize focal seizures for possible surgical intervention.
   3. **Neuroimaging studies** (primarily MRI) may be useful in children with epilepsy. Children diagnosed with absence seizures or benign rolandic epilepsy [see sections V.L.4 and V.L.5] do not require imaging.

H. **Evaluation of an acute seizure**
   1. Initial treatment starts with assessment of the patient's airway, breathing, and circulation.
   2. For a first nonfebrile seizure, routine EEG is recommended; however, laboratory studies, LP, and neuroimaging are based on clinical circumstances and typically are unnecessary in a child with a normal neurologic exam.
   3. For a simple febrile seizure evaluation should be focused on determining the cause of the child's fever [see section V.K]. Meningitis should be considered, and LP should be performed if there are concerns for a CNS infection. Further evaluation, including lab studies, EEG, or neuroimaging, is usually not required.

I. **Management**
   1. **Treatment of status epilepticus requires intravenous anticonvulsants,** such as a **short-acting benzodiazepine (e.g., lorazepam or diazepam)** followed by a loading dose of either **phenobarbital or phenytoin.**
   2. **Treatment of epilepsy**
      a. **Pharmacotherapy.** Once the type of seizure has been determined, **single-drug therapy** is started with the antiepileptic drug that has the best combination of high efficacy and low toxicity. **Examples of commonly recommended drugs** for the following seizure types:
         1. **Generalized epilepsy:** valproic acid, lamotrigine, levetiracetam
         2. **Absence epilepsy:** ethosuximide, valproic acid, lamotrigine
         3. **Focal epilepsy:** carbamazepine, lamotrigine, levetiracetam
         4. **Lennox–Gastaut:** felbamate, rufinamide, lamotrigine, topiramate
      b. **Surgery**
         1. **For medically intractable epilepsy,** surgery to remove epileptic tissue may be an option.
         2. The best prognosis is for patients with temporal lobe lesions, >75% of whom have complete seizure control or remission after surgery.
      c. **Vagal nerve stimulator** is a pacemaker-sized device that sends an electrical impulse to the vagus nerve. A common side effect is hoarseness.
      d. **Ketogenic diet (a high-fat, low-carbohydrate diet)** is thought to suppress seizure activity by producing a **state of ketosis.**

J. **Prognosis.** Epilepsy is not necessarily a lifelong disorder. About 70% of epileptic children can

be weaned off their medications after a 2-year seizure-free period and normalization of the EEG.

K. **Febrile seizures**
   1. **Definition.** Seizures that occur in children between **6 months and 6 years of age** accompanied by a fever (temperature > 38°C), in whom CNS infection, metabolic imbalance, and history of afebrile seizure are excluded.
   2. **Epidemiology.** Febrile seizures are the **most common childhood seizure type, occurring in 2–4%** of all children.
   3. **Etiology**
      a. The **pathophysiologic mechanism is unknown.**
      b. Febrile seizures can be inherited, and several gene mutations have been found.
   4. **Classification**
      a. **A simple febrile seizure** lasts less than 15 minutes and is generalized.
      b. **A complex febrile seizure** lasts more than 15 minutes, has focal features, or recurs within 24 hours.
   5. **Risk factors for first febrile seizure** include having a first- or second-degree relative with a history of febrile seizures, neonatal hospital stays >30 days, developmental delay, attendance at daycare, high frequency of febrile episodes, peak body temperature and recent vaccination.
   6. **Diagnosis**
      a. **The diagnosis of a febrile seizure is based on history, a normal neurologic examination, and the exclusion of CNS infection.**
      b. An LP is necessary if meningitis is suspected at any age. For a child 6–12 months of age, an LP should be seriously considered if the child is deficient in vaccination for *Haemophilus influenzae* type b (HIB) or *Streptococcus pneumoniae* or when immunization status cannot be determined.
      c. **Neither neuroimaging nor EEG is needed** unless the neurologic examination is abnormal.
   7. **Management**
      a. **First-time or occasional febrile seizures** are not treated with anticonvulsants.
      b. **Antipyretic treatment during subsequent febrile illnesses is unlikely to prevent febrile seizures.**
      c. **Frequent, recurrent, or prolonged febrile seizures** do pose a risk and may require additional treatment with daily anticonvulsant prophylaxis or the use of rescue medications (e.g., rectal diazepam).
   8. **Prognosis. Approximately 30% of patients will have a recurrence.** Recurrence risk decreases with increasing patient age. The risk of epilepsy is low (2–10%).

L. **Epileptic syndromes**
   1. **Definition.** Epileptic syndromes are epileptic conditions characterized by a specific age of onset, seizure characteristic, and EEG abnormality.
   2. **Classification.** There are many types of epilepsy syndromes recognized. Each has its own seizure type, severity, and prognosis. Three common types are **infantile spasms, absence epilepsy of childhood,** and **benign rolandic epilepsy.**
   3. **Infantile spasms**
      a. **Epidemiology. Age of onset** is typically 4–7 months. Infantile spasms are rare in children older than 2 years of age.
      b. **Etiology.** Although infantile spasms are frequently cryptogenic (unknown etiology), there are a number of associations, including hypoxic–ischemic injury, tuberous sclerosis, malformations of cortical development, Down syndrome, neonatal hypoglycemia, meningitis, trauma, phenylketonuria, intraventricular

hemorrhage, pyridoxine deficiency, and infection. *Tuberous sclerosis is the most commonly identified cause of this disorder.*

c. **Clinical features**
    1. Brief tonic extension of the extremities and flexion of the trunk (jackknife or salaam seizures) lasting 1–2 seconds each, occurring in clusters of 5–10 seizures spread over 3–5 minutes
    2. **Hypsarrhythmia** is a characteristic EEG pattern consisting of a high amplitude, disorganized background with multifocal spike-wave discharges.
    3. **West syndrome** is a triad of infantile spasms, hypsarrhythmia, and developmental delay or regression.

d. **Management**
    1. **Adrenocorticotropic hormone (ACTH)** intramuscular injections for a 4- to 6-week period are effective in 50-70% of affected patients.
    2. **Vigabatrin** is frequently effective for patients with infantile spasms associated with tuberous sclerosis and is often used in combination with ACTH.
    3. **Other treatments include** valproic acid, topiramate zonisamide, ketogenic diet, pyridoxine, and surgery.

e. **Prognosis. Outlook is poor.** Despite the success of these different medications in suppressing seizures, children often develop moderate to severe intellectual disability.

4. **Absence epilepsy of childhood**
    a. **Epidemiology. Age of onset** is between 4 and 8 years of age and is more common in girls.
    b. **Etiology.** There is a presumed genetic cause, and some cases may have an autosomal dominant inheritance pattern.
    c. **Clinical features of absence seizures**
        1. **Brief,** lasting 5–10 seconds
        2. **Frequent,** tens to hundreds per day
        3. May be accompanied by **automatisms**, such as eye blinking, chewing, and incomprehensible utterances.
        4. **Loss of posture, urinary incontinence, and a postictal state do not occur.**
    d. **Diagnosis.** The **EEG** shows the characteristic **generalized 3-Hz spike-and-wave discharges. Hyperventilation** for 2–3 minutes frequently provokes absence seizures.
    e. *Management.* Treatment includes ethosuximide, valproic acid, or lamotrigine.
    f. **Prognosis. Outlook is very good;** the seizures usually resolve by adolescence without cognitive impairment.

5. **Benign epilepsy with centrotemporal spikes (BECTS), which is also known as benign rolandic epilepsy**
    a. **Definition.** BECTS involves nocturnal focal seizures occasionally with secondary generalization. Focal spike discharges in the centrotemporal region is seen on EEG.
    b. **Epidemiology**
        1. Benign rolandic epilepsy is the **most common partial epilepsy during childhood,** accounting for 15% of epilepsy.
        2. It commonly presents at 3–13 years of age. Peak incidence is at 6–7 years of age. Boys are more likely to be affected.
    c. **Etiology.** Inheritance is **autosomal dominant** with age-dependent penetrance.
    d. **Clinical features**
        1. Seizures typically occur in the **early morning hours** when patients are asleep with **oral–buccal manifestations** (i.e., moaning, grunting, pooling of saliva).

2. Seizures may spread to the face and arm and then secondarily generalize into **tonic–clonic seizures.**

e. **Diagnosis. The EEG** shows *biphasic spike and sharp-wave discharges in the mid-temporal and central regions.*

f. **Management.** Treatment includes valproic acid or carbamazepine.

g. **Prognosis. Outcome is excellent.** Seizures typically remit spontaneously during adolescence. There are reports of associated learning disabilities associated with BECTS.

Table 12-2
Causes of Acute Seizures During Childhood

Head trauma	Cerebral contusion, subdural hematoma
Brain tumor	Astrocytoma
Toxins	Amphetamines, cocaine
Infections	Meningitis, encephalitis, brain abscess, neurocysticercosis
Vascular	Cerebral infarction, intracranial hemorrhage
Metabolic disturbances	Hypocalcemia, hypoglycemia, hypomagnesemia, hypo- or hypernatremia, pyridoxine deficiency
Systemic diseases	Hypertension, hypoxic–ischemic injury, inherited metabolic disorder, liver disease, renal failure, neurocutaneous disorders (e.g., tuberous sclerosis, neurofibromatosis and Sturge-Weber syndrome)

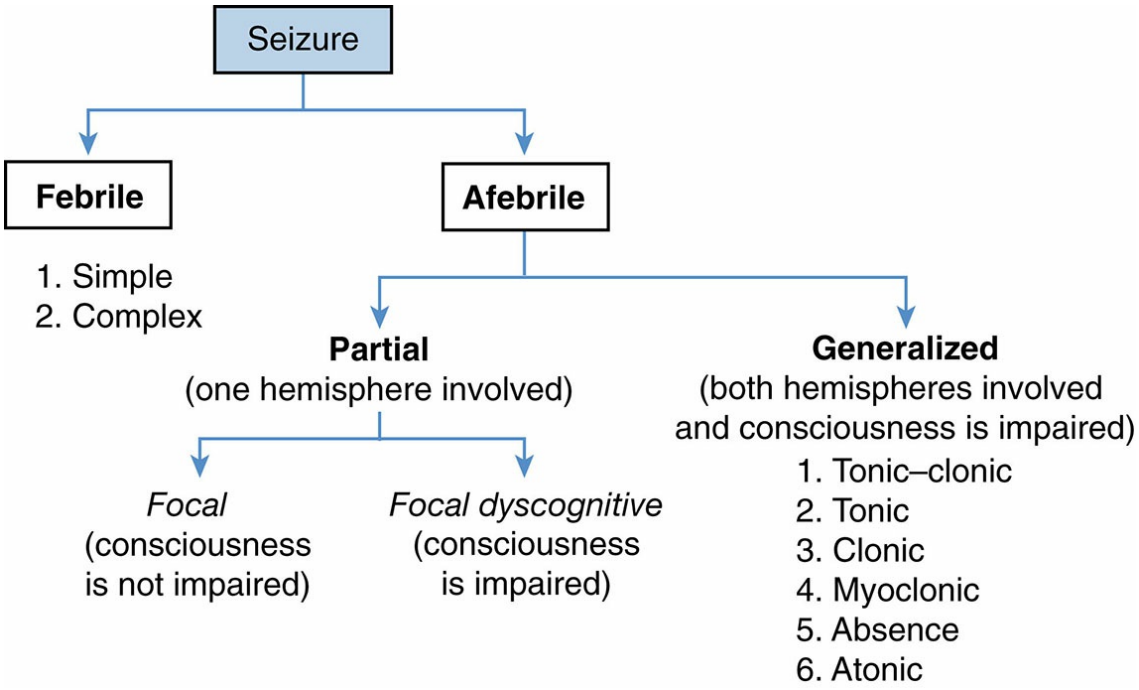

FIGURE 12.2 Classification of seizures.

Table 12-3
Differential Diagnosis of Seizure-like Events

Breath-holding spells (in infants)
Gastroesophageal reflux disease (Sandifer syndrome)
Syncope

Migraine
Vertigo
Movement disorder (e.g., tics, chorea)
Sleep disturbances (e.g., night terrors, somnambulism)
Transient ischemic attack
Rage attacks
Psychogenic nonepileptic events (pseudoseizures)

VI. Headaches in Childhood

A. **Etiology.** Headaches may have intracranial or extracranial causes (**Figure 12-3**).
   1. **Intracranial causes**
      a. **Primary headaches** are more common and are idiopathic, not occurring for a specific reason, or the result of an underlying disease. These are likely due to a combination of genetic, developmental, and environmental risk factors. Migraine, tension-type, and cluster are common primary headaches.
      b. **Secondary headaches** are caused by an underlying disease process such as increased intracranial pressure (e.g., hydrocephalus), meningeal irritation (e.g., meningitis, subarachnoid hemorrhage), or inflammatory processes.
   2. **Extracranial causes**
      a. **Local causes** include sinusitis, perioral abscess, toothache, chronic otitis media, or refractive errors.
      b. **Systemic causes** include anemia, hypoglycemia, depression, and hypertension.

B. **Important clinical information** about a patient's headache helps to determine the cause.
   1. **Quality of pain.** Throbbing or pounding pain suggests migraine headaches, whereas a sensation of squeezing or pressure is more common in tension-type headaches.
   2. **Location and radiation.** Migraine headaches are frequently unilateral (although commonly bilateral in children) and may begin in the periorbital area and spread to the forehead and occiput, whereas tension-type headaches are often generalized or bitemporal.
   3. **Time of onset.** Tension headaches occur toward the end of the day, whereas headaches from increased ICP occur in the morning.
   4. **Duration.** The shorter the headache duration, the less likely a serious disorder is responsible.
   5. **Red flags** indicating more serious pathology may include an abnormal neurologic examination, a new and unusual headache (especially when described as "a sudden worst headache of one's life"), a patient with an immunocompromised state, fever, or stiff neck, and blurring of optic disc margins on examination.

C. **Migraine headaches**
   1. **Definition.** Migraine headaches are prolonged (often 30–60 minutes, but may last up to 72 hours), unilateral (may be bilateral in children) headaches that are associated with nausea, vomiting, or visual changes and are caused by changes in cerebral blood flow.
   2. **Epidemiology**
      a. Migraines are the **most common cause of headaches in children and adolescents.** The prevalence increases from 3% in 7-year-olds, to 11% in 11-year-olds, and up to 20% in adolescents.
      b. Before puberty, incidence is higher in males; after puberty, incidence is higher in females.
   3. **Etiology**
      a. Seventy to eighty percent of children with migraines have at least one affected parent.
      b. The pathophysiology of migraines is complicated and evolving. Serotonin (5-HT), calcitonin gene related peptide (CGRP), inflammatory markers (substance P, vasoactive intestinal peptide), the trigeminal nerve and changes in cerebral blood flow all appear to play a role.
   4. **Classification**
      a. **Migraine without aura is the most common form of migraine in children.**

Headaches occur in the absence of any warning symptoms.

b. **Migraine with aura.** The onset of the headache is preceded by transient visual changes or unilateral paresthesias or weakness. The visual changes may include blurred vision, small areas of decreased vision (scotomata), streaks of light, or hemianopsia.
c. **Migraine equivalent.** In young children, the headache itself may be absent, but there is a prolonged, albeit transient, alteration of behavior that manifests as cyclic vomiting, cyclic abdominal pain, or paroxysmal vertigo.
d. Migraines associated with focal neurologic signs
    1. **Ophthalmoplegic migraine.** Unilateral ptosis or cranial nerve III palsy accompanies this headache.
    2. **Basilar artery migraine.** Vertigo, tinnitus, ataxia, or dysarthria may precede the onset of this headache.

5. **Precipitating factors.** There is **no obvious precipitating cause,** although many migraine sufferers have triggers such as red wine, cheese, preserved meats, and chocolate. Some patients note that stress, fatigue, menstruation, dehydration, skipping meals, or exercise induces the headache.
6. **Clinical features**
    a. **A prolonged, throbbing, unilateral headache** starts in the supraorbital area and radiates to the occiput. In young children, the headache is often bifrontal.
    b. **Nausea and vomiting** may occur. A history of motion sickness is common.
    c. **Visual disturbances** include blurred vision, scotomata, and jagged streaks of light that take on the outline of old forts (**fortifications**).
    d. **Photophobia or phonophobia** occurs. Many patients treat themselves by lying in a dark, quiet room.
    e. **Symptoms are improved by sleep.**
    f. **Neurologic examination is normal.**
7. **Diagnosis.** Diagnosis is made by history and the presence of a normal neurologic examination.
8. **Management.** Treatment includes rest and elimination of known triggers. Medications may be very helpful.
    a. **Abortive treatment** includes **nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans, selective 5-HT agonists,** available in injectable, intranasal, and oral forms.
    b. **Preventive treatment** options include **propranolol, amitriptyline**, **topiramate, valproic acid and cyproheptadine.**
9. **Prognosis.** Migraines can be a lifelong disorder with a waxing and waning course.

D. **Tension headaches**
1. **Definition.** Tension headaches are bifrontal or diffuse, dull, aching headaches that are often associated with muscle contraction.
2. **Epidemiology.** Tension headaches are more commonly seen in children older than 7 years with a prevalence as high as 25%.
3. **Clinical features**
    a. Pain is described as **dull, aching, and rarely throbbing,** and it increases in intensity during the day.
    b. The pain is usually bifrontal but may be diffuse.
    c. **Isometric contraction** of the temporalis, masseter, or trapezius muscle often accompanies the headache.
    d. **No vomiting, visual changes, or paresthesias occur.**
4. **Diagnosis.** Clinical presentation provides a clue to the diagnosis, and no laboratory or imaging study is diagnostic. **Tension headaches are rare in young children, and**

therefore, other diagnoses (e.g., migraines) should be preferentially considered.

5. **Management.** Treatment includes reassurance and pain control (e.g., acetaminophen, ibuprofen). Stress and anxiety reduction may provide long-term relief.

E. **Cluster headaches.** These headaches are extremely *rare* during childhood.

1. Diagnostic criteria includes the following:
   a. **Attacks of severe unilateral facial/orbital pain**
   b. **At least five attacks that last between 15 minutes and 3 hours**
   c. **Sense of restless agitation**
   d. **Ipsilateral conjunctival injection, eyelid edema, lacrimation, nasal congestion, rhinorrhea, and forehead sweating.**
2. Treatment includes abortive therapy with oxygen or triptans. Prophylactic treatments include calcium-channel blockers and valproic acid.

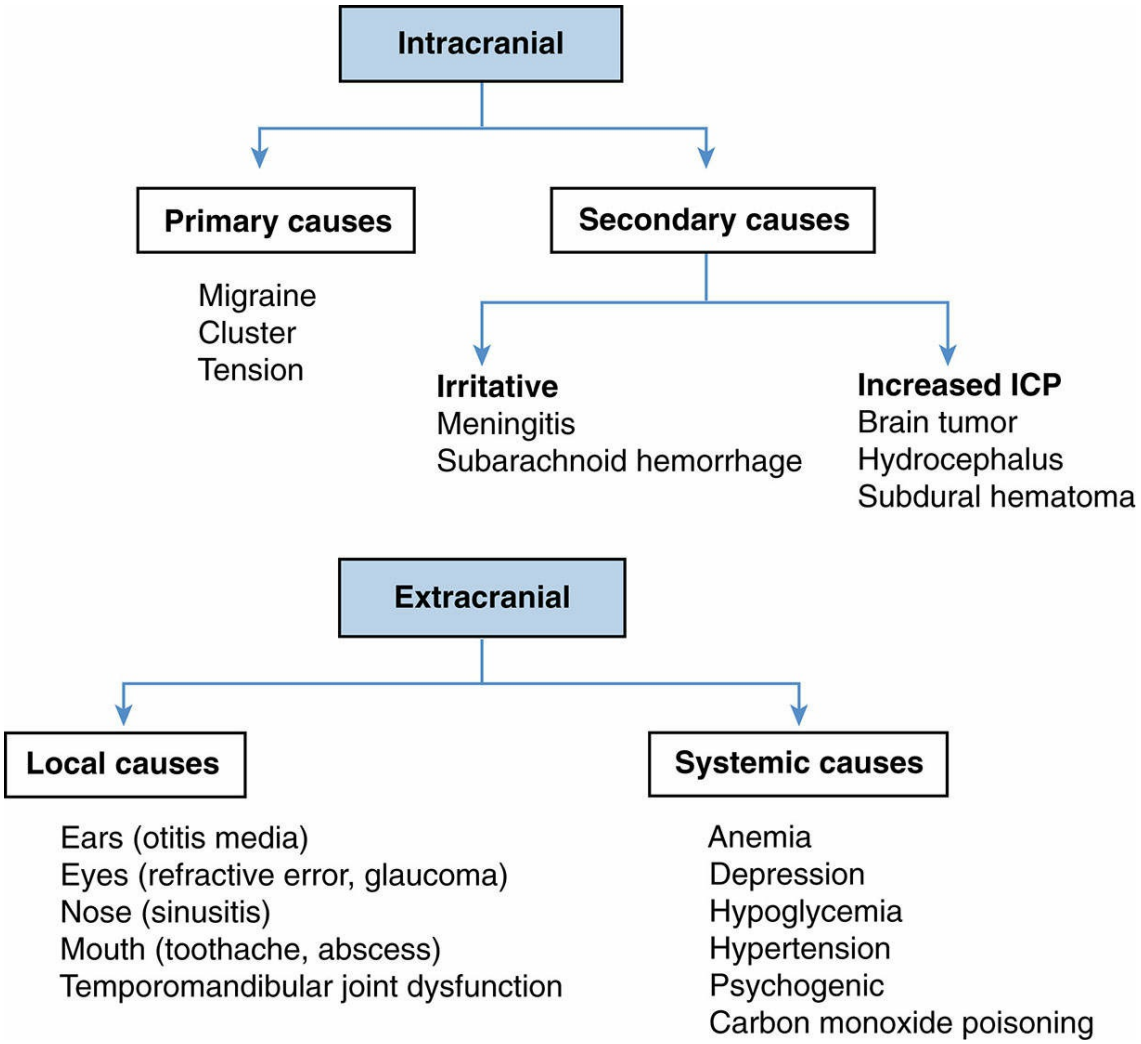

FIGURE 12.3 Causes of headache. *ICP* = intracranial pressure.

VII. Approach to Unsteady Gait

A. **Definition.** *Ataxia* is a disturbance in smooth coordination of movements and often manifests as unsteady gait. Ataxia can be the result of cerebellar or proprioceptive dysfunction (sensory loss ataxia).

B. **Differential diagnosis.** A variety of neurologic problems can give the appearance of an unsteady gait.

1. **Cerebellar dysfunction.** Children with a **cerebellar gait** have **an unsteady, wide-based stance with irregular steps, also known as a "drunken gait."** See **Table 12-4** for the causes of cerebellar ataxia.
2. **Weakness.** Any cause of muscle weakness or sensory loss, such as spinal cord lesions or acute disorders of the motor unit [e.g., **Guillain–Barré syndrome**, see section VII.D], can lead to an unsteady gait.
3. **Encephalopathy as a result of infection, drug overdose, or recent head trauma** may cause decreased levels of consciousness, which may affect gait.
4. **Seizures.** During a **seizure, or while in the postictal period,** the patient's gait may be irregular and unsteady.
5. **Vision problems** can mimic the appearance of an unsteady gait.
6. **Vertigo** from migraines, acute labyrinthitis, and brainstem tumors may lead to unsteady walking.

C. **Acute cerebellar ataxia of childhood**

1. **Definition.** Acute cerebellar ataxia is an unsteady gait secondary to a presumed autoimmune or postinfectious cause.
2. **Epidemiology**
   a. Acute cerebellar ataxia is the **most common cause of ataxia in children.**
   b. **Age of onset** is between 18 months and 7 years. Acute cerebellar ataxia rarely occurs in children older than 10 years.
3. **Etiology**
   a. **Common preceding infections** include **varicella, coxsackievirus, Epstein–Barr virus (EBV), and mycoplasma.** The ataxia usually follows a viral illness by 2–3 weeks.
   b. The postulated cause is thought to be molecular mimicry, where molecular similarity between antigens from the infectious entity and the patient (e.g., cerebellar structures) triggers an autoimmune response.
4. **Clinical features**
   a. **Truncal ataxia** with deterioration of gait is characteristic. Young children may refuse to walk for fear of falling.
   b. **Slurred speech and nystagmus** are often present, and hypotonia and tremors are less common.
   c. **Fever is absent.**
5. **Diagnosis. Diagnosis is by history and physical examination and by exclusion** of other causes of ataxia. For patients with clear acute cerebellar ataxia, neuroimaging is generally not necessary. If there are atypical features or concern for other causes of ataxia, however, neuroimaging is necessary (e.g., to rule out acute life-threatening causes such as tumors or hemorrhage in the posterior fossa). If head CT is obtained to rule out acute life-threatening causes, it is normal in acute cerebellar ataxia. MRI provides better detail to visualize the posterior fossa for evaluation of other causes of ataxia.
6. **Management. Treatment is supportive.** Complete resolution of symptoms generally occurs in 2–3 weeks. Physical therapy is often needed.

D. **Guillain–Barré Syndrome (acute inflammatory demyelinating polyneuropathy)**

1. **Definition.** Guillain–Barré syndrome is a demyelinating polyneuritis characterized by ascending weakness, areflexia, and paresthesias.
2. **Etiology.** The **most commonly associated infectious agent is *Campylobacter jejuni,*** which causes a prodromal gastroenteritis. Many other infectious agents have been associated with Guillain–Barré syndrome, such as *Mycoplasma pneumoniae,* cytomegalovirus, EBV, herpes zoster virus, influenza, varicella, and coxsackievirus.
3. **Pathophysiology**
   a. The **principal sites of demyelination** are the ventral spinal roots and peripheral myelinated nerves.
   b. Injury is triggered by a **cell-mediated immune response** to an infectious agent that cross-reacts to antigens on the Schwann cell membrane.
4. **Clinical features**
   a. **Ascending, symmetric paralysis** may progress to respiratory arrest.
   b. **No sensory loss occurs,** although **low-back or leg pain may be present in 50% of patients.**
   c. **Cranial nerve involvement.** Facial weakness occurs in 40–50% of patients and is often bilateral.
   d. Dysautonomia, arrhythmia, orthostatic hypotension, and urinary retention may occur.
   e. **Miller Fisher syndrome,** a *variant of Guillain–Barré syndrome,* is characterized by ophthalmoplegia, ataxia, and areflexia.
5. **Diagnosis**
   a. **LP** shows **albuminocytologic dissociation** (i.e., increased CSF protein in the absence of an elevated cell count), which is usually evident 1 week after symptom onset.
   b. **EMG** demonstrates decreased nerve conduction velocity or conduction block.
   c. **Spinal MRI** may be necessary in children younger than 3 years to rule out compressive lesions of the spinal cord, because the sensory examination in children of this age is often difficult to evaluate.
6. **Management.** Treatment should be initiated as soon as the diagnosis is established because of the risk of respiratory muscle paralysis.
   a. **Intravenous immune globulin (IVIG),** given for 2–4 days, is the **preferred treatment for children** because of its relative safety and ease of use.
   b. **Plasmapheresis** removes the patient's plasma along with the presumed antimyelin antibodies and is performed over a 4- to 5-day period.
7. **Prognosis. Complete recovery is the rule in children** but depends on the severity and extent of the weakness. Physical therapy may be necessary for several weeks or longer to aid recovery.

Table 12-4
Differential Diagnosis of Cerebellar Ataxia

Brain tumors	Pilocytic astrocytoma (occurring in the cerebellum)
	Medulloblastoma (occurring in posterior fossa)
	Neuroblastoma (opsoclonus myoclonus ataxia syndrome)
Trauma	Cerebellar contusion
	Subdural hematoma
Toxins	Ethanol
	Antiepileptic medications
Vascular	Cerebellar infarction or hemorrhage
Infections	Meningitis

	Encephalitis
Inflammatory	Acute cerebellar ataxia of childhood
Demyelination	Acute disseminated encephalomyelitis (ADEM)
	Multiple sclerosis
Migraine syndromes	Basilar migraines and familial hemiplegic migraines
	Benign paroxysmal vertigo (may have history of migraine)

VIII. Movement Disorders

A. **Sydenham chorea (St. Vitus dance)**
   1. **Definition.** Sydenham chorea is a self-limited **autoimmune disorder** and is one of the major Jones criteria for diagnosis of **rheumatic fever (see Chapter 16, section VI).** It presents with chorea (involuntary, brief, purposeless movements of the limbs and upper body) and emotional lability.
   2. **Epidemiology**
      a. Sydenham chorea occurs in approximately **25% of patients with rheumatic fever.**
      b. **Onset is most common between 5 and 13 years of age.**
   3. **Pathophysiology.** Sydenham chorea occurs secondary to **antibodies that cross-react with membrane antigens on both group A β-hemolytic streptococcus and basal ganglia cells.**
   4. **Clinical features**
      a. **Immunologic response** usually follows streptococcal pharyngitis by **2–7 months.**
      b. **Children appear restless.** The face, hands, and arms are mainly affected, and the movements appear continuous, quick, and random. The chorea may begin as clumsiness of the hands.
      c. **Speech is also affected** and can be jerky or indistinct.
      d. Patients are unable to sustain protrusion of the tongue (**chameleon tongue**).
      e. The wrist is held flexed and hyperextended at the metacarpal joints (**choreic hand**). On gripping the examiner's fingers, patients are unable to maintain the grip (**milkmaid's grip**).
      f. **Emotional lability** (impulsivity, obsessive compulsive symptoms, aggression) is common and may precede signs of chorea.
      g. **Gait and cognition are not affected.**
   5. **Differential diagnosis. Other conditions that may cause chorea** include many acquired and congenital conditions, including N-methyl-d-aspartate (NMDA) receptor encephalitis, kernicterus, systemic lupus erythematosus, Huntington disease, and Wilson disease.
   6. **Diagnosis.** There is **no single confirmatory test for Sydenham chorea.** The diagnosis is made clinically based on presumptive evidence of rheumatic fever and the exclusion of other likely causes of chorea.
      a. **Elevated antistreptolysin O (ASO) or anti-DNase B (ADB) titer** may indicate a recent streptococcal infection.
      b. **Neuroimaging**
         1. **Head MRI** may show **increased signal intensity in the caudate and putamen** on T_2-weighted sequences.
         2. **Single-photon emission computed tomography (SPECT)** may demonstrate **increased perfusion** to the thalamus and striatum.
   7. **Management.** Treatment should be initiated when chorea is leading to significant impairment of motor function. Treatment options include **corticosteroids, haloperidol, valproic acid, or phenobarbital.**
   8. **Prognosis.** Symptoms **may last from several months to 2 years.** Generally, all patients recover.

B. **Tourette syndrome**
   1. **Definitions**
      a. **Tics are brief, stereotypical behaviors** that are initiated by an unconscious (premonitory) urge that can be temporarily suppressed.

   b. **Tourette syndrome is defined as having two or more motor tics and at least one vocal tic (do not have to occur at the same time), for at least 1-year duration and beginning before 18 years of age.** In addition, symptoms cannot be secondary to other illnesses or medications.
2. **Epidemiology.** The prevalence of Tourette syndrome is 1 in 1000 live births. However, tics occur in 3% of children.
3. **Etiology.** The cause of Tourette syndrome is unknown. In some patients, there is a genetic predisposition.
4. **Clinical features**
   a. **Motor tics** can be simple (e.g., eye blinking, head or shoulder shaking) or complex (e.g., bouncing, jumping, kicking).
   b. **Vocal tics** can be simple (e.g., coughing, grunting, humming, clearing the throat) or complex (e.g., echolalia, which is the repetition of heard words or phrases).
   c. **Tics must be present ≥1 year,** although their severity and frequency waxes and wanes.
   d. **Absence** of any signs of a neurodegenerative disorder
   e. **Coprolalia, the utterance of obscene words,** is a dramatic symptom that occurs in <10% of patients.
   f. **Associated findings** include mood disorders, anxiety, attention deficit/hyperactivity disorder, and obsessive–compulsive traits.
5. **Differential diagnosis. Disorders that may cause tics** include Wilson disease, Sydenham chorea, partial or myoclonic seizures, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (**PANDAS or PANS** disorder is an autoimmune neuropsychiatric disorder which follows infection with wide variety of agents, including streptococcal or mycoplasma infection, and is characterized by dramatic and acute onset of obsessive compulsive behaviors and/or severe restricted food intake, with associated neuropsychiatric symptoms which may include tics, anxiety, emotional lability, deterioration in school performance or behavioral regression), or simple habits. (**Habits differ from tics** in that habits are situation-dependent and are under voluntary control.)
6. **Diagnosis**
   a. Tourette syndrome is **a clinical diagnosis based on history and neurologic findings.**
   b. No laboratory or imaging tests confirm the diagnosis.
7. **Management**
   a. For tics that are mild and nondisabling, no treatment is recommended.
   b. **Nonpharmacologic treatment** includes habit reversal therapy and comprehensive behavioral intervention for tics.
   c. **Pharmacologic treatment** includes alpha-adrenergics (clonidine, guanfacine) and both typical and atypical neuroleptics (pimozide, haloperidol, risperidone). Botulinum toxin injection may be effective for some focal motor tics.
8. **Prognosis**
   a. Tics wax and wane over a lifetime and tend to decrease in adulthood.
   b. Pharmacotherapy is generally successful, but side effects from the medications may be limiting.

IX. Duchenne and Becker Muscular Dystrophies (DMD, BMD)

A. **Definition.** DMD and BMD are progressive, **X-linked myopathies** characterized by myofiber degeneration. **DMD is more severe than BMD.**

B. **Epidemiology**
   1. These worldwide disorders occur in all ethnic groups.
   2. Prevalence is 1 in 10,000 live births.
   3. **Onset** of symptoms is between *2 and 5 years of age.*

C. **Etiology.** These X-linked disorders are caused by a **deletion in the dystrophin gene.**

D. **Pathophysiology**
   1. **Dystrophin** is located on the plasma membrane of muscle fibers and provides mechanical reinforcement and stabilization. It is a high–molecular weight cytoskeletal protein that associates with actin and other structural membrane elements.
   2. The **absence of dystrophin** causes weakness and eventually rupture of the plasma membrane, leading to injury and degeneration of muscle fibers.

E. **Pathology.** Both DMD and BMD have the same appearance on light microscopy.
   1. **Degeneration and regeneration** of muscle fibers
   2. **Infiltration of lymphocytes** into the injured area and **replacement** of damaged muscle fibers **with fibroblasts and lipid deposits**

F. **Clinical features**
   1. **Slow, progressive weakness affecting the legs first**
   2. **In DMD, children lose the ability to walk by around 12 years of age. In BMD, patients lose the ability to walk by 20 or more years of age.**
   3. **Pseudohypertrophy of calves** is present because of the excess accumulation of lipids, which replace the degenerating muscle fibers. This is more common in DMD than in BMD.
   4. **Gowers sign is present.** Because of the weakness of pelvic muscles, patients arise from the floor in a characteristic manner by extending each leg and then "climbing up" each thigh until they reach an upright position.
   5. **Cardiac involvement** (e.g., cardiomegaly, tachycardia, or cardiac failure) occurs in 50% of patients.
   6. Mild cognitive impairment may occur in DMD, but normal intelligence is present in BMD.

G. **Diagnosis**
   1. **The presence of enlarged calf muscles in a young boy with muscle weakness suggests the diagnosis.**
   2. **CK levels are VERY high, even before muscle weakness.**
   3. **EMG** shows small, polyphasic muscle potentials with normal nerve conductions.
   4. **Muscle biopsy** shows the typical dystrophic pattern.
   5. **Absent or decreased dystrophin levels** are present on immunocytochemistry or Western blot assay of muscle.
   6. **DNA testing** may reveal the gene deletion in >90% of patients.

H. **Management.** There is no cure, but oral steroids can improve strength transiently and prolong duration of ambulation when the disease is in the early stages. Current research is evaluating gene replacement therapy to convert DMD to the more favorable BMD.

I. **Prognosis**
   1. **In DMD,** patients are wheelchair dependent by 12 years of age and often die in their late teens from respiratory failure or cardiomyopathy. Assisted ventilation may help individuals to live longer.

2. **In BMD,** patients become wheelchair dependent in their twenties. Life expectancy is beyond the age of 30 years.

X. Myasthenia Gravis

A. **Definition.** Myasthenia gravis is an **autoimmune disorder** that presents with generalized weakness, fatigability of muscles, ptosis, and diplopia.
B. **Etiology.** Myasthenia gravis is caused by **antibodies against the acetylcholine receptor (AChR) in the postsynaptic membrane of the neuromuscular junctions.**
C. **Classification**
    1. **Neonatal myasthenia** is a **transient weakness** in the newborn period secondary to transplacental transfer of maternal AChR antibodies from a mother affected with myasthenia gravis.
    2. **Congenital myasthenia** *is familial and is not transferred by the mother.* There are no maternal antibodies, and this disorder consists of multiple subtypes.
    3. **Juvenile** myasthenia gravis presents in childhood secondary to AChR antibody formation.
D. **Epidemiology.** Juvenile myasthenia gravis affects **girls** two to six times more frequently than boys.
E. **Clinical features**
    1. **In neonatal myasthenia, hypotonia, weakness, feeding problems, and weak cry** are the most common findings.
    2. **In juvenile myasthenia gravis,** several findings are characteristic.
        a. **Bilateral ptosis is the most common presenting sign.**
        b. **Characteristic increasing weakness** *occurs later in the day* and with repetitive or sustained muscle activity.
        c. **Diplopia** secondary to decreased extraocular movements may be the only manifestation.
        d. **DTRs are preserved.**
        e. **Other autoimmune disorders,** including juvenile rheumatoid arthritis, diabetes mellitus, and thyroid disease, may coexist.
F. **Diagnosis.** Diagnosis is made by the following:
    1. **Tensilon test. Intravenous injection of edrophonium chloride,** a rapidly acting cholinesterase inhibitor, produces transient improvement of ptosis.
    2. **Decremental response** *to low-frequency (3–10 Hz) repetitive nerve stimulation*
    3. **Presence of AChR antibody titers**
G. **Management**
    1. **In neonatal myasthenia, treatment is supportive** because the disorder is self-limited. Small feedings by nasogastric tubes and assisted ventilation are provided if needed. Cholinesterase inhibitors can be used to aid with feeding and respiratory support.
    2. **In juvenile myasthenia gravis,** treatment involves the following:
        a. **Cholinesterase inhibitors** are the mainstay of treatment. **Pyridostigmine bromide** is the drug of choice.
        b. **Immunotherapy**
            1. **Corticosteroids** are used when cholinesterase inhibitors fail.
            2. **Plasmapheresis lowers the level of AChR antibodies.** It is useful when symptoms worsen, when respiratory effort is compromised, or when the patient is unresponsive to other therapies.
            3. **IVIG** may also be effective.
        c. **Thymectomy** is performed if there is evidence of thymoma (there is also some evidence for thymectomy even in the absence of thymoma)
H. **Prognosis**

1. **In neonatal myasthenia, symptoms are mild and generally resolve within 1–3 weeks.**
2. **In juvenile myasthenia gravis,** remission of symptoms can be as high as 60% after thymectomy.

Review Test

1. You are called to the nursery to examine a "floppy" female infant born within the past 24 hours. The neonate is hypotonic with diminished deep tendon reflexes. There are no tongue fasciculations. When you greet the baby's mother, she is anxious and has difficulty releasing her grip after shaking your hand. Which of the following is the most likely diagnosis?
   A. Muscular dystrophy
   B. Congenital myotonic dystrophy
   C. Neonatal myasthenia gravis
   D. Spinal muscular atrophy, type 1
   E. Infantile botulism
2. A 10-year-old girl is being evaluated for "weakness" of 3 days' duration. Medical history is significant for a 4-day episode of diarrhea 2 weeks before her current presentation. She is otherwise well with no chronic medical conditions and is taking no medications. Physical examination reveals symmetric weakness at the ankles and knees, with normal strength at the hip joints. Deep tendon reflexes are absent in the distal lower extremities. Sensory examination is normal. Which of the following statements is most consistent with the most likely diagnosis?
   A. This patient is most likely to have had a prodromal gastroenteritis with *Salmonella typhi.*
   B. Electromyography would be expected to show normal nerve conduction.
   C. Management should include intravenous immune globulin.
   D. This patient is likely to have elevated antistreptolysin O or anti-DNase B titers.
   E. The prognosis for complete recovery is poor.
3. A 6-month-old male infant is evaluated for lethargy and poor feeding. Recent dietary changes include the introduction of cereals, fruits, and herbal tea with honey. Physical examination reveals an afebrile infant with normal vital signs. Neurologic examination is notable for decreased muscle tone and a weak suck. Which of the following statements regarding this infant's most likely diagnosis is most accurate?
   A. Infants typically present with ascending paralysis.
   B. Antibiotics should be administered immediately.
   C. Infants present with brisk deep tendon reflexes.
   D. Electromyography is not helpful in making the diagnosis.
   E. Constipation is often the initial symptom in infants.
4. An 8-year-old girl is noted by her teacher to have brief staring spells throughout the day. She is referred to you for further evaluation. Neurologic examination is normal. You order an electroencephalogram, which shows a generalized 3-Hz spike-and-wave discharge pattern arising from both hemispheres. Which of the following statements regarding the most likely diagnosis is most accurate?
   A. Further questioning would probably reveal that this patient loses control of her bladder during the event.
   B. This patient's condition is inherited in an autosomal recessive pattern.
   C. This patient's staring spells would be expected to last less than 10 seconds each.
   D. This patient is likely to have prolonged postictal periods.
   E. Phenobarbital is the drug of choice for this patient's condition.
5. A 4-month-old female infant is brought to your office by her parents, who are concerned about some behaviors they have witnessed. They note that during the past week, she has had brief jerking episodes, lasting 1–2 seconds each, with sudden arm extension followed by flexion of the head. You order an electroencephalogram, which reveals a highly disorganized pattern of high-amplitude spike and waves in both cerebral hemispheres, consistent with a hypsarrhythmia pattern. Which of the following is the most commonly identified cause of the

patient's disorder?

A. Prior episode of bacterial meningitis
B. Perinatal asphyxia
C. Shaken baby syndrome
D. Tuberous sclerosis
E. Neurofibromatosis type 1

6. A 6-year-old boy complains of a 4-day history of low-back pain and difficulty walking. On examination, you note weakness in his lower extremities and absent lower extremity deep tendon reflexes. Sensation in the lower extremities is intact. A magnetic resonance imaging scan of the spine is normal. Which of the following is the most likely diagnosis?
   A. Duchenne muscular dystrophy
   B. Myasthenia gravis
   C. Acute cerebellar ataxia of childhood
   D. Guillain–Barré syndrome
   E. Becker muscular dystrophy
7. A 2-year-old boy is brought to the office by his parents, who note that their son has had weakness in his legs for the past several months that appears to be getting worse. On examination, you note that the calf muscles are enlarged. Which of the following statements regarding this patient's condition is correct?
   A. DNA testing is normal.
   B. Dystrophin levels are normal.
   C. Progressive weakness leads to loss of ambulation before 12 years of age.
   D. Electromyography reveals delayed nerve conduction.
   E. Treatment with intravenous immune globulin can transiently improve symptoms.
8. Two hours ago a 2-year-old boy had a 5-minute episode of whole body shaking associated with a temperature of 39.4°C (103°F). The boy's parents state that their son has had runny nose and cough for the past 24 hours. He now acts normal except for his cold symptoms, according to his parents. The parents remind you that this is his second febrile seizure. Physical examination is normal, revealing no focal neurologic signs. Which of the following would be the most appropriate recommendation at this time?
   A. Order a stat head computed tomography scan.
   B. Order an electroencephalogram.
   C. Begin treatment with phenobarbital.
   D. Reassure the parents that no workup or medications are necessary at this point.
   E. Admit the patient to the hospital for overnight observation.
9. A 12-year-old girl is brought to see you for evaluation of frequent headaches. She has had headaches three times per week for the past several months, and her parents are concerned that she may be having migraines. Which of the following statements would support this diagnosis?
   A. The headaches are bilateral, dull, and achy, but mild.
   B. The neurologic examination is abnormal during the headache.
   C. The headaches awaken the patient in the early morning hours.
   D. The duration of the headache is >1 hour.
   E. This patient is likely to have an aura with her headache.
10. Examination of a comatose 13-year-old boy in the emergency department is significant for bilaterally nonreactive and dilated pupils. An oculocephalic maneuver is negative. Which of the following is the most likely diagnosis?
    A. Postictal state from status epilepticus
    B. Brainstem injury
    C. Subdural hematoma with herniation

D. Opiate overdose
E. Alcohol intoxication

11. A 2-month-old boy is brought to your office for evaluation with a 2-day history of poor feeding and vomiting. Parents deny fever, cold symptoms, or diarrhea. On physical examination, the child is well hydrated but has a large anterior and posterior fontanelle and a persistent downward deviation of both eyes. This patient's presentation is most consistent with which of the following diagnoses?
    A. Cerebral infarct
    B. Congenital myotonic dystrophy
    C. Myasthenia gravis
    D. Becker muscular dystrophy
    E. Infantile hydrocephalus

The response items for statements 12–14 are the same. You will be required to select one answer for each statement in the following set.

A. Dandy–Walker malformation
B. X-linked hydrocephalus
C. Infantile botulism
D. Spinal muscular atrophy type 1 (Werdnig–Hoffman disease)
E. Juvenile myasthenia gravis
F. Congenital myotonic dystrophy

For each patient, select the most likely diagnosis.

1. A 4-month-old male infant has generalized weakness, hypotonia, areflexia, and tongue fasciculations.
2. An 8-month-old female infant with a 5-day history of constipation presents with a weak cry, hyporeflexia, ophthalmoplegia, and loss of the ability to sit without support.
3. A 6-month-old male has had hypotonia, facial weakness, areflexia, and a history of feeding problems since birth.

Answers and Explanations

1. **The answer is B** [I.F.3]. This patient most likely has congenital myotonic dystrophy. Patients present with hypotonia and often have feeding and respiratory problems. Facial weakness and hyporeflexia are common. Infants acquire the disorder through autosomal dominant inheritance, most commonly from an affected mother. Mothers of infants with congenital myotonic dystrophy have myotonia, an inability to relax contracted muscles, which manifests as difficulty releasing a hand grip during a firm handshake. Muscular dystrophy rarely presents during infancy. Infants with botulism have constipation, hypotonia, problems with suck and swallow, and progressive weakness that may lead to paralysis. Neonatal myasthenia is a transient muscle disorder caused by the transplacental passage of acetylcholine receptor antibodies. Weakness and hypotonia may be present, but deep tendon reflexes are preserved. Infants with spinal muscular atrophy have hypotonia but also have characteristic tongue fasciculations.
2. **The answer is C** [VII.D]. This patient's presentation is most consistent with Guillain–Barré syndrome. The diagnosis of Guillain–Barré syndrome should be considered in any child with ascending symmetric weakness or paralysis, absence of deep tendon reflexes, and a normal sensory examination. Management should be initiated as soon as the diagnosis is established because of the risk of respiratory muscle paralysis. Intravenous immune globulin is the preferred treatment in children. Many infectious agents have been associated with Guillain–Barré syndrome, but the most common infectious agent is *Campylobacter jejuni*, which causes a prodromal gastroenteritis. Electromyography would be expected to demonstrate decreased nerve conduction velocity or conduction block. There is no known association between Guillain–Barré syndrome and prior group A β-hemolytic streptococcal infection. The prognosis for children with Guillain–Barré syndrome is excellent, and complete recovery is likely.
3. **The answer is E** [I.F.2]. Infantile botulism is caused by the ingestion of *Clostridium botulinum* spores and the release of botulinum toxin within the intestine. The toxin prevents the release of acetylcholine at peripheral cholinergic synapses, initially causing constipation, which is followed by a weak suck and swallow, cranial nerve palsies, and weakness. Patients with infantile botulism have a symmetric descending paralysis. Contaminated honey is a common source of the toxin. Physical examination is notable for diffuse weakness, hypotonia, and hyporeflexia (i.e., diminished deep tendon reflexes). The diagnosis is suggested by the history and physical examination findings and confirmed by the identification of the toxin or bacteria within the stool. Electromyography may also be helpful in diagnosis and may show brief, small-amplitude muscle potentials with an incremental response during high-frequency stimulation. Treatment includes supportive care and botulism immune globulin. Antibiotics are not helpful.
4. **The answer is C** [V.L.4]. This patient's clinical presentation and electroencephalogram (EEG) are consistent with absence epilepsy of childhood. Patients usually present with multiple absence seizures, which are brief staring spells that occur without warning and are not followed by postictal drowsiness. Urinary continence and loss of posture are also not seen in absence seizures. Absence seizures last less than 10 seconds and have a very characteristic EEG pattern, showing a generalized 3-Hz spike-and-wave abnormality. Absence epilepsy of childhood is inherited in an autosomal dominant pattern with age-dependent penetrance. The antiepileptic medications usually used include ethosuximide, valproic acid, or lamotrigine.
5. **The answer is D** [V.L.3]. This clinical presentation is consistent with infantile spasms. Patients with infantile spasms typically present with brief, myoclonic jerks, lasting 1–2 seconds each, occurring in clusters of 5–10 seizures spread out over 3–5 minutes. Patients may have sudden

extension of the arms and sudden flexion of the head (jackknife or salaam seizures). A variety of different prenatal, perinatal, and postnatal insults to the central nervous system may result in infantile spasms. Tuberous sclerosis is the most commonly identified cause of this disorder. Perinatal asphyxia, intraventricular hemorrhage, and meningitis are other causes of infantile spasms. Neurofibromatosis type 1 is not typically associated with infantile spasms.

6. **The answer is D** [VII.D]. Guillain–Barré syndrome (acute inflammatory demyelinating polyneuropathy) typically presents with ascending paralysis without sensory loss. Despite this finding, about 50% of children complain of low-back pain or discomfort in their legs. Deep tendon reflexes are absent, and spinal magnetic resonance imaging is normal. The diagnosis is based on the findings of albuminocytologic dissociation in the cerebrospinal fluid and by decreased nerve conduction velocity on electrophysiologic studies. In both Duchenne and Becker muscular dystrophy, the onset of weakness is slow and progressive. Myasthenia gravis, which is more common in girls, presents with weakness that increases during the day and normal deep tendon reflexes. Acute cerebellar ataxia of childhood presents with ataxia (unsteady gait or truncal unsteadiness) rather than weakness.
7. **The answer is C** [IX.B, IX.E, and IX.I.1]. This patient's presentation with increasing weakness in the lower extremities and calf enlargement is consistent with Duchenne muscular dystrophy, an X-linked progressive degenerative muscle disorder for which there is no cure. Children typically present between 2 and 5 years of age with gait problems and weakness, and they are often wheelchair dependent by around their 12th birthday. On examination, patients have enlarged calf muscles (pseudohypertrophy) as a result of fatty infiltration of the degenerating muscles, and laboratory studies reveal elevated creatine kinase levels. The diagnosis can be made by DNA testing of the dystrophin gene, which shows a deletion in more than 90% of patients. Electromyography shows small, polyphasic muscle potentials but normal nerve conduction velocities. Intravenous immune globulin has no role in the management of Duchenne muscular dystrophy.
8. **The answer is D** [V.K.7]. Febrile seizures are defined as any seizure that accompanies a fever owing to a non-CNS (central nervous system) cause in patients between the ages of 6 months and 6 years. Febrile seizures are benign events that are not generally associated with serious acute or long-term neurologic sequelae. A computed tomography scan is not indicated in the absence of papilledema or focal neurologic deficits. An electroencephalogram is useful when the diagnosis of epilepsy is being considered but not in recurrent febrile seizures. A complex febrile seizure is distinguished from a simple febrile seizure if it lasts more than 15 minutes, has focal features, or recurs within 24 hours. For simple febrile seizures, anticonvulsant treatment is usually not initiated until a patient has multiple febrile seizures. Febrile seizures do not require inpatient observation.
9. **The answer is D** [VI.B and VI.C]. Migraines are characterized by unilateral, or sometimes bilateral, frontal throbbing headaches that last for at least 1 hour. The neurologic examination of patients with migraines is usually normal. Headaches that occur on awakening in the morning are more characteristic of headaches resulting from increased intracranial pressure. Migraine without aura is the most common form of migraine in children.
10. **The answer is B** [IV.C.6]. The physical examination of this patient's eyes, including both the negative oculocephalic test and bilateral dilated nonreactive pupils, is most consistent with brainstem injury. The oculocephalic maneuver is also termed doll's eyes, and an abnormal response (when the head is turned, the eyes follow the head and continue to look straight ahead rather than drifting to midline) suggests a damaged vestibular system. Pupils may also be dilated during and immediately after a seizure or after topical ophthalmic application of a dilating agent, but the vestibular nerve is usually unaffected in these situations (the oculocephalic maneuver would be positive). An enlarging subdural hematoma can cause uncal herniation with a unilateral dilated, nonreactive pupil. Opiate ingestion causes

constricted pupils. Alcohol intoxication less frequently causes coma and more often leads to somnolence. Alcohol intoxication can cause pupils to be slow to react but pupils would not be nonreactive.

11. **The answer is E** [II.D]. This patient's eye findings are termed the setting-sun sign, or a tonic downward deviation of the eyes. The setting-sun sign is suggestive of hydrocephalus. Increased pressure in the third ventricle from noncommunicating hydrocephalus injures the upward gaze center in the midbrain, causing this downward deviation of the eyes. In contrast, patients with myasthenia commonly present with ptosis. There are no specific eye abnormalities in congenital myotonic dystrophy, muscular dystrophy, or cerebral infarcts.
12. **The answers are D, C, and F, respectively** [I.F.1–3]. The 4-month-old infant has spinal muscular atrophy type 1 (Werdnig–Hoffman disease), an autosomal recessive disorder that presents with hypotonia, weakness, problems with suck and swallow, and tongue fasciculations. It presents within the first 6 months of life. The 8-month-old infant has infantile botulism, an environmentally acquired disorder of the neuromuscular junction in which botulinum neurotoxin blocks release of acetylcholine at the neuromuscular junction. The toxin is released from the spores of *Clostridium botulinum,* which are found in contaminated honey or soil. Constipation is often the presenting symptom, followed by weakness, cranial nerve findings, poor abilities to feed, and paralysis. The 6-month-old infant has congenital myotonic dystrophy, an autosomal dominant disorder presenting in infancy with hypotonia, facial weakness, and feeding problems. The diagnosis may be missed if the mother of the patient is not seen or examined because the typical myotonia (i.e., inability to relax contracted muscles) is most apparent in adults.

CHAPTER 13

Hematology

Carol Diamond

I. Anemia

A. **General concepts**
   1. **Definition.** Anemia is a reduction in the red blood cell (RBC) number or in the hemoglobin (Hgb) concentration to a level more than 2 standard deviations below the mean.
   2. **Hgb and age**
      a. The Hgb is **high at birth** in most newborns and then declines, reaching the **physiologic lowest point (nadir)** between **2 and 3 months of age in the term infant** and between **1 and 2 months of age in the preterm infant.** Hgb values reach adult levels after puberty.
      b. **Fetal hemoglobin (Hgb F)** is a major constituent of Hgb during fetal and early postnatal life. It declines and gradually disappears by 6–9 months of age.
   3. **Epidemiology.** Anemia is one of the **most common laboratory abnormalities** during childhood. Approximately 20% of all children in the United States and 80% of children in developing nations have anemia at some time during childhood.

B. **Classification**
   1. Classification is made on the basis of the **mean corpuscular volume (MCV) and the morphologic appearance of the RBC** (i.e., size, color, and shape). Terms used include the suffix *-cytic,* referring to size, and the suffix *-chromic,* referring to color. Primary classifications include the following:
      a. **Microcytic, hypochromic anemia** (small, pale RBCs; low MCV)
      b. **Macrocytic anemia** (large RBCs; high MCV)
      c. **Normocytic, normochromic anemia** (normal RBCs in size, color, and shape; normal MCV)
   2. Classification based on **reticulocyte count** is also helpful. The reticulocyte count reflects the number of immature RBCs in the circulation and, therefore, the activity of the bone marrow in producing RBCs. The usual percentage of RBCs that are reticulocytes is 1% (normal absolute count = 50,000 cells/mm^3). In the steady state, when a patient has a normal Hgb level, the reticulocytes should constitute 1% of all RBCs. In most anemias, reticulocyte counts should rise. A **low reticulocyte count indicates bone marrow failure or diminished hematopoiesis.**
   3. Figure 13-1 presents the differential diagnosis of anemia on the basis of the previously discussed classification schemes. Descriptions of the more common forms of anemia in childhood follow.

C. **Clinical features of anemia** (Table 13-1)

D. **Microcytic, hypochromic anemias.** The two most common types of microcytic, hypochromic anemia during childhood are **iron-deficiency anemia** and **β-thalassemia minor.**
   1. **Iron-deficiency anemia** is the **most common blood disease during infancy and childhood.**
      a. **Etiology.** The majority of cases are caused by **inadequate iron intake.**
         1. **Nutritional iron deficiency** is most common in two age groups.
            a. **Nine to twenty-four months of age:** owing to inadequate intake and inadequate iron stores (which are typically depleted by 4–6 months of age). Blood loss during birth may contribute to the anemia. The typical toddler's diet consists of large quantities of iron-poor cow's milk. Iron-rich foods (e.g., iron-fortified cereal, meats, legumes) or iron supplementation is therefore recommended beginning at 4–6 months of age to prevent anemia.

b. **Adolescent girls:** owing to poor diet, rapid growth, and loss of iron in **menstrual blood**

2. **Occult blood loss** with resultant iron deficiency may be secondary to polyps, Meckel diverticulum, inflammatory bowel disease (IBD), peptic ulcer disease, celiac disease, and the early ingestion of whole cow's milk before 1 year of age.

b. **Clinical features.** The signs and symptoms of anemia are listed in **Table 13-1**.

c. **Laboratory findings**

1. Because iron stores disappear first, an **early finding of iron-deficiency anemia** is **low serum ferritin.** Ferritin can be a useful assessment of iron stores; however, because ferritin is also an acute-phase reactant, it may be increased in infection, disease states, and stress, therefore appearing normal.
2. As **serum iron decreases, iron-binding capacity increases**, manifested as **increased transferrin** and **decreased transferrin saturation.**
3. **Increased free erythrocyte protoporphyrin** may be noted.
4. Other findings include a normal or increased reticulocyte count.

d. **Management**

1. **Elemental iron** (4–6 mg/kg/day) is prescribed orally for mild to moderate anemia. Iron is given with vitamin C (e.g., orange juice) to enhance intestinal iron absorption.
2. **Dietary counseling** may be required to increase nutritional iron through iron-rich foods (e.g., meats, legumes, prunes, iron-fortified cereals).
3. RBC transfusion may be required for severe anemia associated with cardiovascular compromise. Not only will this improve oxygen-carrying capacity, but this will contribute to iron repletion.
4. **Further evaluation to rule out other causes of anemia is necessary in patients with anemia unresponsive to iron**.

2. **α-Thalassemia and β-thalassemia syndromes**

a. **Definition.** Thalassemia is a group of inherited anemias characterized by **defective synthesis of one of the Hgb chains.**

b. **Pathophysiology**

1. **Normally,** the major Hgb in RBCs is hemoglobin A_1, a tetramer of two α-chains and two β-chains. $HgbA_2$ and Hgb F may also be present in small amounts.
2. **α-Thalassemia** results from **defective α-globin chain synthesis,** and **β-thalassemia** results from **defective β-globin chain synthesis.**
3. Both types of thalassemia result in hemolysis that leads to increased bone marrow activity. As marrow activity increases, the marrow spaces enlarge, increasing the size of bones in the face, skull, and other bones if severe and untreated.

c. **α-Thalassemia** is the result of deletions of the **α-globin chain** and occurs predominantly in Southeast Asians. There are four states categorized on the basis of the number of α-globin genes deleted (normally there are four α-globin genes per diploid cell).

1. **Silent carrier.** One α-globin gene is deleted. Patients have **no anemia** and are **asymptomatic.**
2. **α-Thalassemia minor.** Two α-globin genes are deleted. Patients have **mild microcytic anemia**.
3. **Hgb H disease.** Three α-globin genes are deleted. Patients have **moderate to severe anemia at birth** with an elevated **Hgb Bart's** (which is a type of Hgb made up of four gamma-globins that bind oxygen very strongly and do not

release it to tissue). Anemia is lifelong.

4. **Fetal hydrops.** Four α-globin genes are deleted. Only Hgb Bart's are formed, and in utero, this causes profound anemia, congestive heart failure (CHF), and death if not identified early enough for intrauterine transfusion to occur.

d. **β-Thalassemia** is the result of mutations of the **β-globin chain.** Because there are only two β-globin genes in each cell, there are only two states:

1. **β-Thalassemia major** (Cooley anemia or homozygous β-thalassemia) may be caused by either **total absence of the β-globin chains or deficient β-globin chain production.**
    a. **Epidemiology.** β-Thalassemia major occurs predominantly among patients of Mediterranean background.
    b. **Clinical features.** Clinical findings include **profound hemolytic anemia** beginning in infancy, marked **hepatosplenomegaly,** and, if untreated, **bone marrow hyperplasia** in sites that result in a characteristic **"thalassemia facies"** appearance (frontal bossing, maxillary hyperplasia with prominent cheekbones, and skull deformities). Delayed growth and puberty may also be present.
    c. **Laboratory findings.** Studies show **severe hypochromia and microcytosis, elevated reticulocyte count,** target cells and poikilocytes (abnormally shaped red blood cells) on the blood smear, and elevated unconjugated bilirubin, serum iron, and lactate dehydrogenase (LDH). Electrophoresis demonstrates low or absent Hgb A and elevated Hgb F.
    d. **Management.** Treatment includes **lifelong transfusions, chelation therapy** to avoid iron overload and often splenectomy. *Bone marrow transplant* is curative and is the therapy of choice.
    e. **Complications. Hemochromatosis** (iron accumulation within the heart, liver, lungs, pancreas, and skin) is a major complication and is caused by increased iron absorption from the intestine and from iron in transfused RBCs. Chelation of iron with the intravenous agent deferoxamine and/or the oral agent deferasirox promotes iron excretion and may help prevent or delay hemochromatosis.
2. **β-Thalassemia minor** (heterozygous β-thalassemia or β-thalassemia *trait*) causes a **mild asymptomatic anemia** with Hgb levels 2–3 g/dL below age-appropriate norms.
    a. Laboratory findings include hypochromia and microcytosis with target cells and anisocytosis (excessive variation of size of RBCs) on smear.
    b. No treatment is required.
    c. **It is important to note that patients with β-thalassemia minor may be very easily misdiagnosed as having iron-deficiency anemia and treated inappropriately with iron. However, the iron level in β-thalassemia minor is normal or elevated. Patients with thalassemia minor have normal to elevated RBC counts as opposed to iron deficiency in which the RBC count is low to normal.**

3. **Sideroblastic anemia** is a group of anemias characterized by the presence of **ring sideroblasts** in the bone marrow. Ring sideroblasts result from the accumulation of iron in the mitochondria of RBC precursors. Sideroblastic anemia may be inherited or may be acquired as a result of drugs or toxins (e.g., isoniazid, alcohol, lead poisoning, chloramphenicol).
4. **Lead poisoning** (see Chapter 1, section IV.J) and **chronic diseases**, such as malignancy, infections, and kidney disease (termed *anemia of inflammation*), may present with a

microcytic, hypochromic anemia.

E. **Macrocytic (megaloblastic) anemias.** These anemias are characterized by **large RBCs** with **MCV > 95.** The two major causes in children are folic acid and vitamin B_{12} deficiencies. In addition, rare but important causes of macrocytic anemia include bone marrow failure syndromes [e.g., Fanconi anemia, see section II.B.1].
   1. **Folic acid deficiency**
      a. **Etiology.** Causes include **decreased folic acid intake** (i.e., from a diet lacking uncooked fresh fruits and vegetables or from **exclusive feedings with goat's milk** as the sole source of milk protein) and **decreased intestinal absorption of folic acid** (i.e., from diseases affecting the small intestine, such as celiac disease, chronic infectious enteritis, Crohn disease, or medications, such as anticonvulsants and oral contraceptives).
      b. **Clinical features.** In addition to the characteristic signs and symptoms of anemia, patients may have failure to thrive, chronic diarrhea, and irritability.
      c. **Diagnosis.** Documentation of **low serum folic acid** is diagnostic.
      d. **Management.** Treatment includes **dietary folic acid** and identification and treatment of the underlying cause.
   2. **Vitamin B_{12} deficiency**
      a. **Normal physiology.** To be absorbed, dietary vitamin B_{12} must first combine with a glycoprotein (**intrinsic factor**) secreted by the gastric parietal cells. Absorption then occurs in the terminal ileum.
      b. **Etiology.** Causes include **inadequate dietary intake** (e.g., from a strict vegetarian [vegan] diet), an inherited **inability to secrete intrinsic factor** (juvenile pernicious anemia), or an **inability to absorb vitamin B_{12}** (e.g., Crohn disease, short gut syndrome).
      c. **Clinical features.** In addition to the characteristic features of anemia, patients may also have anorexia, **a smooth red tongue,** and **neurologic manifestations** (such as ataxia, hyporeflexia, and positive Babinski responses).
      d. **Diagnosis.** Documentation of **low serum vitamin B_{12} level** is diagnostic.
      e. **Management.** Treatment is by **monthly intramuscular vitamin B_{12} injections.**

F. **Normocytic, normochromic anemias.** These anemias are characterized by normal size (normal MCV) and shape of the RBCs.
   1. **General concepts**
      a. **Common causes** include hemolytic anemias (premature destruction of RBCs), some RBC aplasias, and sickle cell (SS) anemia.
      b. **Reticulocyte count** may be used to differentiate among the disorders [see **Figure 13-1**].
         1. **Low reticulocyte count** reflects bone marrow suppression or failure and can be seen with RBC aplasias, viral suppression, medication effect, and pancytopenia associated with aplastic anemia.
         2. **High reticulocyte count** reflects high bone marrow production of RBCs as seen in hemolytic anemias, recent acute hemorrhage, or any other condition associated with shortened RBC life span.
   2. **Hemolytic anemias**
      a. **Intrinsic RBC defects** that cause hemolysis include RBC membrane disorders and RBC enzyme disorders. Examples of RBC membrane disorders include hereditary spherocytosis and hereditary elliptocytosis, and examples of RBC enzyme disorders include glucose-6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase (PK) deficiency.
         1. **Hereditary spherocytosis** is the **most common inherited abnormality of the**

RBC membrane and occurs predominantly in persons of Northern European ancestry. There is a large spectrum of phenotypes, with some patients who are largely asymptomatic and others who are transfusion-dependent starting in infancy.

a. **Etiology.** There is a deficiency or abnormality of the structural RBC membrane protein **spectrin,** causing the RBC to assume its spherical shape. Inheritance is usually **autosomal dominant.**
b. **Clinical features.** Clinical findings are related to extravascular hemolysis. Infants may present with jaundice and anemia. By 2–3 years of age, patients develop pallor, weakness, and **splenomegaly**, as spherocytes are trapped in the spleen and destroyed. Other complications include **aplastic crises,** most commonly associated with parvovirus B19 infection, and **pigmentary gallstones.**
c. **Laboratory findings.** Studies show an elevated reticulocyte count, hyperbilirubinemia, **spherocytes** on blood smear, increased MCHC (mean corpuscular hemoglobin concentration), and **abnormal RBC fragility with osmotic fragility studies.**
d. **Management.** Treatment includes transfusions. Splenectomy cures the disorder, but to decrease the incidence of invasive disease caused by encapsulated bacteria, splenectomy is generally delayed until after 5 years of age.

2. **Hereditary elliptocytosis** is another **autosomal dominant** defect in the structure of **spectrin** that may or may not result in hemolysis. Clinical features are more variable than in hereditary spherocytosis. The **majority of patients are asymptomatic,** although 10% have jaundice at birth, and later may develop splenomegaly and gallstones. **Elliptical RBCs** are found on blood smear in older children. Treatment includes splenectomy for patients with severe chronic hemolysis. No treatment is needed for patients who have well-compensated hemolysis.
3. **Glycolytic enzymatic defects** of RBCs include **glucose-6-phosphate dehydrogenase deficiency and PK deficiency.**
   a. **Glucose-6-phosphate dehydrogenase deficiency (G6PD) is the most common RBC enzymatic defect.** It may occur as an **acute** hemolytic disease, induced by infection or medications, or as a **chronic** hemolytic disease. The epidemiology, etiology, clinical findings, and treatment are described in **Table 13-2.**
   b. **PK deficiency** is an **autosomal recessive** disorder that results in decreased production of PK isoenzyme leading to ATP (adenosine triphosphate) depletion and decreased RBC survival.
      1. **Clinical features** include pallor, jaundice, and splenomegaly. Kernicterus has been reported in neonates.
      2. **Laboratory findings** include varying degrees of anemia and a blood smear showing **polychromatic RBCs.**
      3. **Diagnosis** is by finding decreased PK activity in the RBCs.
      4. **Management** includes transfusions and splenectomy for severe disease.

b. **Defects extrinsic to the RBC that cause hemolysis**
   1. **Autoimmune hemolytic anemia (AIHA)** occurs when **antibodies are misdirected against the RBCs.**
      a. **Etiology**

1. **Primary AIHA** is generally **idiopathic** in which no underlying disease is identified. Viral infections and occasionally drugs may be causal in some patients.
2. **Secondary AIHA** is associated with an **underlying disease process,** such as lymphoma, systemic lupus erythematosus (SLE), or immunodeficiency.

b. **Clinical features**
1. **Fulminant acute-type AIHA** occurs in infants and young children and is preceded by a respiratory infection. Presenting features include the acute onset of pallor, jaundice, hemoglobinuria, and splenomegaly. A **complete recovery is expected.**
2. **Prolonged-type AIHA** is characterized by a protracted course and high mortality. Underlying disease is frequently present.

c. **Laboratory findings.** Studies show severe anemia, spherocytes on blood smear, prominent reticulocytosis, and leukocytosis. A **direct Coombs test is positive** (detects coating of antibodies on the surface of RBCs or complement).

d. **Management.** Treatment may include transfusions that unfortunately may provide only transient benefit. **Corticosteroids** are often used for severe anemia and are continued until hemolysis diminishes. The acute form responds well to steroids.

2. **Alloimmune hemolytic anemia** occurs when **antibodies from someone else are directed at the patients' RBCs** and is most commonly caused by newborn Rh and ABO hemolytic diseases.
   a. **Rh hemolytic disease** occurs when the mother, who has no Rh antigen (maternal Rh negative), produces antibodies to the Rh antigen on her fetus's RBCs (fetal Rh positive). In **subsequent pregnancies,** antibodies pass from the mother to the fetus causing hemolysis that presents as severe jaundice (which can lead to kernicterus), anemia, hepatosplenomegaly, and **hydrops fetalis.** A direct Coombs test is **strongly positive.**
   b. **ABO hemolytic disease** occurs when the mother is blood group O and her fetus is blood group A, B, or AB. The mother produces antibodies to either the A or B blood group antigen that then pass to the fetus, causing hemolysis with resultant jaundice. A direct Coombs test is **weakly positive.** Of note, **ABO disease can occur in the first pregnancy, unlike Rh hemolytic disease.**
   c. **Management.** Treatment may include phototherapy for mild to moderate jaundice and exchange transfusion for severe jaundice.
3. **Microangiopathic hemolytic anemia**
   a. **Definition.** This form of anemia results from mechanical damage to RBCs caused by passage through an injured vascular endothelium.
   b. **Etiology.** Causes include severe hypertension, **hemolytic uremic syndrome** (HUS), artificial heart valves, a giant hemangioma, and disseminated intravascular coagulation (DIC).
   c. **Clinical features.** Signs and symptoms are those characteristic of anemia and thrombocytopenia.
   d. **Laboratory findings.** Studies show RBC fragmentation seen as "burr" cells, "target" cells, and irregularly shaped cells on the blood smear, along with thrombocytopenia.

e. **Management.** Therapy includes supportive care and treatment of the underlying cause.

3. **SS hemoglobinopathies**
   a. **Epidemiology.** SS disease occurs in 1 in 800 black newborns in the United States. Eight percent have S trait. Compound heterozygotic disease can occur with Hgb C or β-thalassemia, leading to Hgb SC or sickle β-thalassemia disease, respectively.
   b. **Etiology and pathophysiology**
      1. **SS disease** is caused by a **single amino acid substitution** of **valine for glutamic acid** on the **number 6 position of the β-globin chain** of Hgb.
      2. The mutation results in polymerization of Hgb within the RBC membrane when the RBC is exposed to low oxygen or acidosis.
      3. Polymerization of Hgb results in a **distorted RBC shape** (sickled) that leads to decreased RBC life span **(hemolysis)** and **occlusion of small vessels,** resulting in distal ischemia, infarction, and organ dysfunction.
      4. **SS disease** is the result of having **two genes for Hgb S** (homozygous).
      5. **S trait** is defined as having only **one gene for Hgb S** (heterozygous). Persons with S trait have Hgb A (50–60%), Hgb S (35–45%), and a small percentage of Hgb F. Patients are **asymptomatic without anemia** unless exposed to severe hypoxemia. Some patients have an inability to concentrate the urine or may present with hematuria (5%) during adolescence.
   c. **Diagnosis.** Diagnosis of SS disease is now usually made at birth through state newborn screening programs. Hgb electrophoresis is a highly sensitive and specific test that demonstrates Hgb S and Hgb F (fetal hemoglobin) in the newborn with SS disease.
   d. **Clinical features.** Clinical characteristics are not generally present until protective Hgb F declines (by 6 months of age). Clinical episodes are often termed *crises* because they occur suddenly. **Table 13-3** describes the clinical features and management of the common SS disease crises.
   e. **Laboratory findings (Table 13-4)**
   f. **Management Historically, infection was the leading cause of death due to impaired splenic function.**
      1.
         a. Patients are at risk for infection with **encapsulated bacteria (i.e., *Haemophilus influenzae* type b, *Streptococcus pneumoniae, Salmonella, Neisseria meningitidis)***.
         b. **Fever** in any patient with SS disease is managed with urgent assessment and appropriate cultures (blood and urine), chest radiograph to rule out pneumonia, and parenteral antibiotics until bacterial infection can be safely excluded.
         c. **Osteomyelitis** may occur and **may mimic a painful bone crisis.** Infection is most commonly caused by ***Salmonella*** species acquired through the gastrointestinal (GI) tract, although *Staphylococcus aureus* may also cause osteomyelitis. Clinical features include fever and pain, induration, tenderness, warmth, and erythema of the involved area. Treatment includes appropriate intravenous antibiotics.
   g. **Preventive care**
      1. **Hydroxyurea,** a chemotherapeutic agent that increases Hgb F, has been shown to decrease the incidence of vaso-occlusive crises.
      2. **Daily oral penicillin prophylaxis** is started in the first few months of life to decrease the risk of *S. pneumoniae* infection.

3. **Daily folic acid** is given to prevent folic acid deficiency.
4. **Routine immunizations** and also yearly influenza vaccination, 23-valent polysaccharide pneumococcal vaccine at 2 years of age, and meningococcal vaccine should all be given.
5. **Serial transcranial Doppler ultrasound or magnetic resonance angiography** is recommended beginning at 2 years of age to identify patients at increased risk for stroke.
6. **Bone marrow transplant is curative and is considered for children with severe manifestations.**

h. **Prognosis**

1. Median life expectancy is in the 50s.
2. **Long-term complications** include delayed growth and puberty, cardiomegaly, hemochromatosis, cor pulmonale, pulmonary hypertension, renal insufficiency, gallstones, poor wound healing, avascular necrosis of the femoral and humeral heads, osteopenia, retinopathy, and diminished cognitive and school performance.

i. **Other SS diseases** include **sickle cell–thalassemia disease** (with clinical features similar to SS disease) and **sickle cell–hemoglobin C disease** (Hgb SC disease) caused by the inheritance of both Hgb S and Hgb C genes. Clinical features of Hgb SC disease are less severe than SS disease.

4. **RBC aplasias** are a group of congenital or acquired blood disorders characterized by anemia, reticulocytopenia, and a paucity of RBC precursors in the bone marrow. The clinical features of the three most common disorders occurring in childhood, **congenital hypoplastic anemia (Diamond–Blackfan anemia), transient erythroblastopenia of childhood, and parvovirus B19–associated RBC aplasia,** are presented in **Table 13-5.**

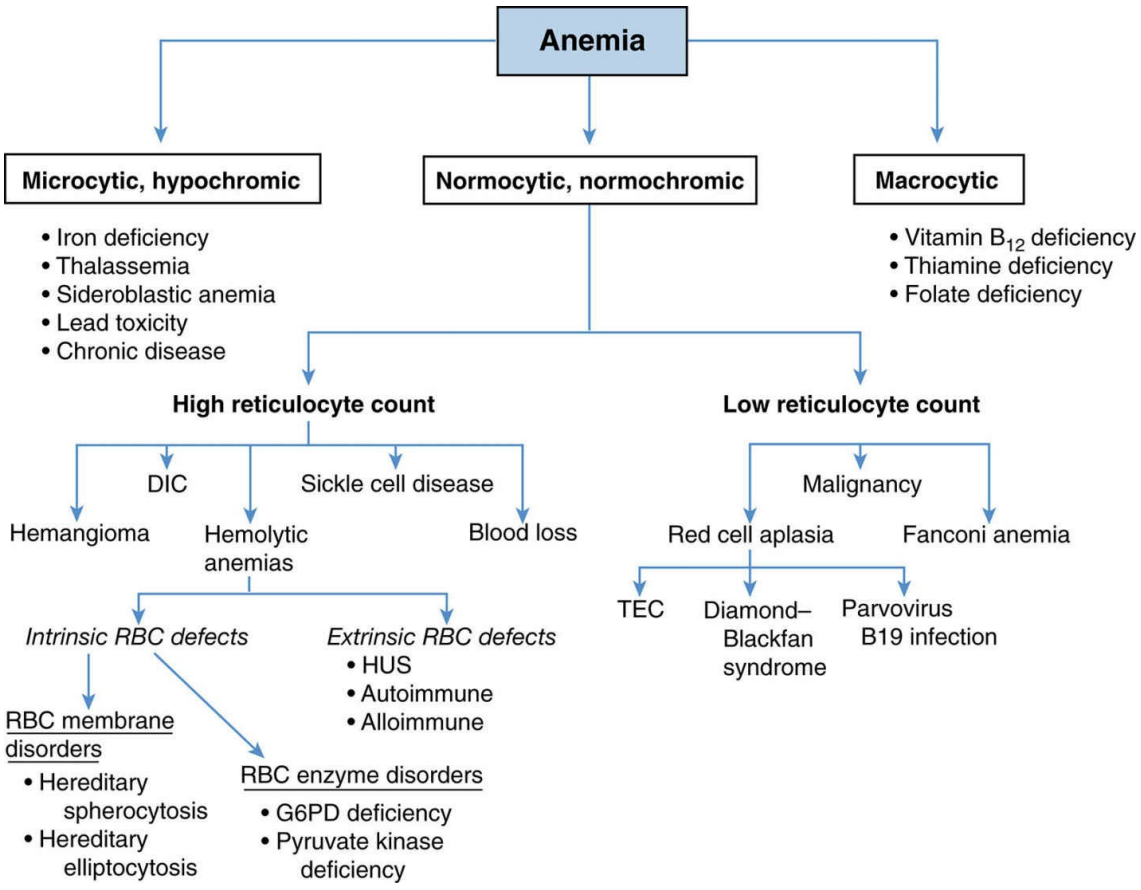

FIGURE 13.1 Classification and differential diagnosis of anemia. *DIC* = disseminated intravascular coagulation; *HUS* = hemolytic uremic syndrome; *TEC* = transient erythroblastopenia of childhood; *G6PD* = glucose-6-phosphate dehydrogenase; *RBC* = red blood cell.

Table 13-1
Clinical Features of Anemia

Mild
Pallor (noted especially on skin and on mucous membranes) Diminished attention
Moderate
Weakness and fatigue
Decreased exercise tolerance
Irritability
Tachycardia
Tachypnea
Anorexia
Systolic heart murmur
Severe
Congestive heart failure
Cardiac dilation
Shortness of breath
Hepatosplenomegaly Spoon-shaped nails

Table 13-2
Features of Glucose-6-Phospate Dehydrogenase (G6PD) Deficiency

Epidemiology	Mediterranean, Arabic, Asian, and African ethnic groups
Pathophysiology	G6PD enzyme is critical for protecting the RBC from oxidative stress; deficiency results in RBC damage when the RBC is exposed to oxidants
Triggers of hemolysis	Infection Fava beans Drugs (e.g., sulfa, salicylates, antimalarials)
Clinical features	Symptoms occur 24–48 hours after exposure to oxidant Hemolysis occurs, resulting in abdominal pain, V/D, fever, and hemoglobinuria followed by jaundice; HSM may be present
Laboratory findings	Hemoglobinuria Elevated reticulocyte count

	Smear shows "bite" cells, "hemighosts" and Heinz bodies
Diagnosis	Low levels of G6PD in RBCs
Treatment	Transfusions as needed; splenectomy is not beneficial

V/D = vomiting, diarrhea; *RBC* = red blood cell; *HSM* = hepatosplenomegaly.

Table 13-3

Clinical Features and Management of Crises Occurring in Sickle Cell Disease

Crisis	Clinical Features	Management
Vaso-occlusive crisis		
Painful bone crisis	Most common crisis Ischemia/infarction of bone or marrow Deep, gnawing, or throbbing pain lasting 3–7 days Subtype: **acute dactylitis**—painful swelling of digits of the hands and feet	Pain control Intravenous fluids at 1–1.5 × maintenance Incentive spirometry to decrease the risk of acute chest syndrome Severe, unremitting pain may respond to partial exchange transfusion. (Simple transfusion of RBCs is not indicated. It increases viscosity of blood and may worsen crisis.)
Acute abdominal crisis	Abdominal pain and distension Often caused by sickling within mesenteric artery	Low threshold for imaging the abdomen Same management as for painful bone crisis
Stroke	Dysarthria and hemiplegia, but may be asymptomatic Occurs in up to 11% of patients (subclinical stroke occurs in up to 20% of patients)	Same management as for painful bone crisis Urgent exchange transfusion Patient should be started on chronic transfusion program to prevent recurrence, which occurs in 60–90%
Priapism	Painful, sustained erection **Always consider SS disease in any patient presenting with priapism**	Same management as for painful bone crisis
Acute chest syndrome (ACS)		
	New pulmonary infiltrate associated with respiratory symptoms (e.g., cough, shortness of breath, chest pain) Hypoxemia May be severe and may cause up to 25% of deaths in patients with SS disease Causes include infection (e.g., viral, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae, Streptococcus pneumoniae*), sickling, atelectasis, fat embolism, painful bone crisis involving the ribs, and pulmonary edema from fluid overload	Careful hydration and pain management Oxygen Appropriate antibiotics (usually cefuroxime and azithromycin) Incentive spirometry Early use of partial exchange transfusion in a patient who does not improve rapidly
Sequestration crisis	Rapid accumulation of blood in spleen (or less commonly, liver) Occurs in patients <6 years of age Abdominal distension, abdominal pain, shortness of breath, tachycardia, pallor, fatigue, and shock; mortality can be high Lab findings: low Hgb; elevated reticulocytes	Supportive care Transfusion of RBCs Splenectomy recommended by some practitioners because recurrence occurs in up to 50%

Aplastic crisis	Temporary cessation of RBC production often caused by parvovirus B19 or other infectious agent Pallor, fatigue, tachycardia Lab findings: low Hgb; low reticulocytes	Supportive care Transfusion of RBCs
Hyperhemolytic crisis	Rapid hemolysis; often occurs in patients with other hemolytic diseases (e.g., G6PD deficiency) Pallor, fatigue, tachycardia, jaundice Lab findings: low Hgb; elevated reticulocytes; elevated bilirubin	Supportive care Transfusion of RBCs

RBCs = red blood cells; *SS* = sickle cell; *G6PD* = glucose-6-phosphate dehydrogenase; *Hgb* = hemoglobin.

Table 13-4

Usual Laboratory Findings in Sickle Cell Anemia

Red blood cell life span	10–50 days
Hemoglobin	6–9 g/dL
Hematocrit	18–27%
Reticulocyte count	5–15%
White blood cell count	12,000–20,000 cells/mm^3
Platelet count	Increased, often > 500,000 platelets/μL
Bilirubin	Increased
Blood smear	Sickled cells, target cells, Howell–Jolly bodies
Bone marrow	Erythroid hyperplasia

Table 13-5

Characteristics of the Red Blood Cell Aplasias

Aplasia	Etiology	Clinical Features	Laboratory Findings	Treatment
Congenital hypoplastic anemia (Diamond–Blackfan anemia)	Unknown Autosomal recessive or autosomal dominant inheritance	Anemia within the first year of life Rapid onset One-fourth to one-third have physical findings: craniofacial, renal, cardiac anomalies; short stature; triphalangeal thumbs Signs and symptoms of anemia	↓Hgb ↓Reticulocytes ↑Hgb F ↓or normal platelet count Marrow: ↓RBC precursors; other marrow elements normal	RBC transfusion Corticosteroids (up to 70% respond) Bone marrow transplant if no response to corticosteroids
TEC	Unknown Possible postviral autoimmune reaction	Anemia begins >1 year of age Slow in onset Signs and symptoms of anemia	↓Hgb ↓Reticulocytes Normal platelet count Marrow: ↓RBC precursors	Spontaneous recovery within several weeks No treatment required
Parvovirus B19–associated pure RBC aplasia*	Parvovirus B19 infection	Anemia generally not symptomatic May have associated URI symptoms and facial rash ("slapped cheeks") of fifth disease Aplastic crisis in patients with SS disease	↓Hgb ↓Reticulocytes Normal platelet count	Spontaneous recovery within 2 weeks RBC transfusions may be required for patients with aplastic crisis associated with SS disease

*Note that Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus (HIV), and drugs (e.g., chloramphenicol) may cause an acquired RBC aplasia similar to parvovirus B19.

TEC = transient erythroblastopenia of childhood; *SS* = sickle cell; *URI* = upper respiratory infection; *Hgb* = hemoglobin; *RBCs* = red blood cells.

II. Pancytopenia and Aplastic Anemia

A. **Definition.** Pancytopenia is defined as low white blood cells (WBCs), RBCs, and platelets and implies **bone marrow failure.**

B. **Pancytopenia** may be **congenital or acquired.**

1. **Congenital aplastic anemia** is also known as **Fanconi anemia.**
    a. **Etiology.** Inheritance is **autosomal recessive.**
    b. **Clinical features**
        1. Onset of bone marrow failure occurs at a **mean age of 7 years.** Typical presentation is with ecchymosis and petechiae.
        2. **Skeletal abnormalities,** which include **short stature** in almost all *patients, and* **absence or hypoplasia of the thumb and radius**
        3. **Skin hyperpigmentation**
        4. **Renal abnormalities,** including renal tubular acidosis
    c. **Laboratory findings.** Studies show pancytopenia, RBC macrocytosis, low reticulocyte count, elevated Hgb F, and bone marrow hypocellularity.
    d. **Management.** Treatment includes transfusions of RBCs and platelets as needed, and bone marrow transplant from an HLA-compatible donor, if available. Immunosuppressive therapy (e.g., corticosteroids, cyclosporin) may also help.
2. **Acquired aplastic anemia**
    a. **Etiology.** Causes include **drugs** (e.g., sulfonamides, anticonvulsants, chloramphenicol), **infections** (e.g., human immunodeficiency virus [HIV], Epstein–Barr virus [EBV], cytomegalovirus [CMV], hepatitis), **chemicals,** and **radiation.** These all may damage bone marrow stem cells directly or may induce autoimmune destruction. **Acquired aplastic anemia is most often idiopathic.**
    b. **Clinical features.** Signs and symptoms include bruising, petechiae, pallor, and fatigue, or serious infection as a result of neutropenia.
    c. **Laboratory findings.** Studies show pancytopenia, low reticulocyte count, and hypocellular bone marrow.
    d. **Management.** Treatment includes identifying and stopping the causative agent, transfusions as needed, bone marrow transplant, and immunosuppressive therapy.

III. Polycythemias

A. **Definition.** Polycythemia is defined as an **increase in RBCs relative to total blood volume.** It may also be defined as a hematocrit (Hct) > 60% or as an Hgb or Hct more than 2 standard deviations above normal values for age.

B. **Primary polycythemia (polycythemia vera)** is an extremely rare cause of polycythemia during childhood. This is a myeloproliferative disorder seen typically in older adults.

C. **Secondary polycythemia** is caused by **increased erythropoietin production.** Production may be appropriate or inappropriate.

1. **Appropriate polycythemia** may be caused by **chronic hypoxemia** as a result of **cyanotic congenital heart disease (the most common cause of polycythemia in childhood)**, pulmonary disease, or living at high altitudes.
2. **Inappropriate polycythemia** may be caused by benign and malignant tumors of the kidney, cerebellum, ovary, liver, and adrenal gland; excess hormone production (e.g., corticosteroids, growth hormone, androgens), and kidney disease.
3. **Clinical features** include a ruddy facial complexion with a normal-sized liver and spleen.
4. **Laboratory findings** reveal elevated Hgb and Hct but normal platelet and WBC counts. Erythropoietin levels are high.
5. **Management** is directed toward identifying and treating the underlying cause. Phlebotomy is also used to keep the Hct < 60%.

D. **Relative polycythemia** refers to an **apparent increase in RBC mass** caused by a **decrease in plasma volume.** The most common cause is **dehydration,** and this should be considered in every patient with a high Hgb or Hct. Appropriate fluid management normalizes the Hct.

E. **Complications** of polycythemia include **thrombosis** (vaso-occlusive crisis, stroke, myocardial infarction) and **bleeding.**

IV. Disorders of Hemostasis

A. **General concepts**
   1. **Hemostasis** requires normal function of three important elements: **blood vessels, platelets, and soluble clotting factors. Hemorrhage** may result from deficiency or dysfunction of any of these elements. **Thrombosis** may also occur but is rare during childhood.
   2. **The clotting cascade** is depicted in **Figure 13-2**.
   3. **Clinical features suggesting abnormal hemostasis include the following:**
      a. **Cutaneous bleeding** (e.g., ecchymoses, petechiae)
      b. **Spontaneous epistaxis** that is **severe and recurrent** without an obvious cause
      c. **Prolonged bleeding** after simple surgical procedures, circumcision, trauma, or dental extraction
      d. **Recurrent hemarthroses**
      e. **Deep venous thrombosis**, *pulmonary embolism*, or **stroke**
   4. **Diagnostic studies.** Evaluation for clotting abnormality typically includes these screening tests:
      a. **Complete blood count (CBC)**
      b. **Platelet count**
      c. **Blood smear to evaluate platelet morphology**
      d. **Activated partial thromboplastin time (aPTT)**
      e. **Prothrombin time (PT)**
      f. **Platelet function assay**
      g. **The laboratory and clinical findings of coagulation disorders** are summarized in **Table 13-6.**
   5. **The differential diagnosis of disorders of hemostasis** is summarized in **Figure 13-3.**

B. **Congenital clotting factor disorders.** These disorders include deficiency of factor VIII and von Willebrand disease (both of which are factor VIII–related disorders) and deficiency of factor IX.
   1. **General considerations. Factor VIII disorders** include two inherited disorders, **hemophilia A** and **von Willebrand disease,** which are described in more detail below. These two diseases involve different regions and different functions of the factor VIII molecule.
      a. **Hemophilia A** represents a defect in factor VIII procoagulant activity (antihemophilic factor; factor VIII protein). Platelet function is normal.
      b. In **von Willebrand disease,** factor VIII procoagulant activity is variable, but platelet function is defective because of a decrease or defect in **von Willebrand factor,** a protein required for platelet adhesion to blood vessel wall. It also functions as a carrier protein for factor VIII.
   2. **Factor VIII deficiency—hemophilia A**
      a. **Inheritance** is **X-linked** and occurs in 1 in 5000–10,000 male births. More than 200 different mutations or deletions have been identified in the factor VIII gene.
      b. **Clinical features**
         1. **Hemarthroses** (involving the knees, elbows, and ankles most commonly) and **deep soft tissue bleeding** are the **hallmarks.** Bleeding into the iliopsoas muscle may be especially severe as a result of delayed recognition of the bleeding and the potential for significant blood accumulation. **Risk of serious and life-threatening hemorrhage is lifelong.**
         2. **Severe, moderate, and mild forms** exist based on the activity level of factor

VIII protein.
    a. **Severe: spontaneous bleeding** (<1% factor VIII protein activity)
    b. **Moderate: bleeding only with trauma** (1–5% factor VIII protein activity)
    c. **Mild: bleeding only after surgery or major trauma** (>5% factor VIII protein activity)
  3. **Central nervous system (CNS) bleeding** is the most dreaded complication and is usually the result of head trauma.
- c. **Laboratory findings**
  1. **Prolonged aPTT** (in mild form, aPTT may be normal)
  2. **Normal PT, platelet count,** and **platelet function assay**
  3. **Low factor VIII protein activity** in the presence of normal von Willebrand factor assay
- d. **Management.** Treatment includes prevention of trauma and replacement of factor VIII. Desmopressin acetate (DDAVP) causes the release of stored factor VIII from the patient's own cells and may be useful in mild hemophilia A.

3. **von Willebrand disease.** This group of disorders involves defects or deficiency in the von Willebrand factor (vWf) portion of the factor VIII complex and is the **most common hereditary bleeding disorder.**
- a. **Etiology.** Inheritance is most commonly **autosomal dominant.**
- b. **Categories**
  1. **Type I (classic type):** mild quantitative deficiencies of vWf and factor VIII protein. It is the **most common form.**
  2. Type II: qualitative abnormality in vWf
  3. Type III: absence of vWf; the most severe type
- c. **Clinical features**
  1. **Most patients** have mild to moderate bleeding, usually involving mucocutaneous surfaces. More profound bleeding occurs in type III disease.
  2. **Common signs and symptoms** include epistaxis, **menorrhagia,** bruising, and bleeding after dental extraction or tonsillectomy. Excessive bleeding after trauma may occur.
  3. **Hemarthroses are unusual.**
- d. **Laboratory findings**
  1. **Prolonged bleeding time** and **prolonged aPTT may be present, but not always** (but they are always present in type III disease).
  2. **Quantitative assay for vWf antigen and activity (ristocetin cofactor assay) are diagnostic.**
- e. **Management. DDAVP** induces vWf release from endothelial cells and is used for mild to moderate bleeding and for prophylaxis before surgery. DDAVP is most useful in type I disease and is sometimes effective in type II disease. Cryoprecipitate, which contains intact vWf, may be used for serious bleeding, for extensive surgeries, or for type III disease.

4. **Factor IX deficiency—hemophilia B (Christmas disease).** This **X-linked disorder** has clinical features similar to those of hemophilia A and occurs in 1 in 50,000 males. aPTT is prolonged and low factor IX activity is found. PT and platelet count are normal. Management includes factor IX replacement.

C. **Acquired clotting factor disorders**
1. **Vitamin K deficiency**
- a. **Vitamin K,** a fat-soluble vitamin, is essential for the synthesis of both procoagulant and anticoagulant factors, such as **factors II, VII, IX, and X** and **proteins C and S.**
- b. **Etiology**

1. **Dietary deficiency is unusual,** except during early infancy.
2. Pancreatic insufficiency, biliary obstruction, and prolonged diarrhea may result in diminished ability to absorb vitamin K.
3. **Medications** may interfere with vitamin K metabolism (e.g., cephalosporins, rifampin, isoniazid, warfarin).
4. **Hemorrhagic disease of the newborn** is the result of vitamin K deficiency. It may occur early (within 24 hours after birth), within the first week of life (**classic form**), or late (1–3 months after birth).

c. **Clinical features.** Clinical manifestations include bruising, oozing from skin puncture wounds (e.g., previous blood draw sites), and bleeding into organs. **Hemorrhagic disease of the newborn is characterized by serious bleeding in the early and late forms,** but classic disease generally presents only with cutaneous bleeding, hematemesis, and bleeding from the circumcision site or umbilical cord. CNS bleeding may occur occasionally.

d. **Laboratory findings** include **prolonged aPTT and PT.**

e. **Management.** Treatment includes administration of vitamin K. **Intramuscular administration of vitamin K after birth prevents hemorrhagic disease of the newborn.** In severe disease, fresh-frozen plasma (FFP) may be needed.

2. **Liver disease**

a. The liver is the major site of production of most coagulation factors. Therefore, with liver disease, synthesis of clotting factors is often diminished, with the vitamin K–dependent factors most severely affected [see section IV.C.1.a]. Consumption of clotting factors and platelets may also occur with liver disease.

b. **Laboratory findings.** Laboratory results are the same as those seen in DIC [see section IV.C.3], including **prolonged PT and aPTT, increased fibrin degradation products, and thrombocytopenia.**

c. **Management.** Treatment includes vitamin K, FFP, and platelets as needed.

3. **DIC**

a. **Definition.** DIC refers to a group of laboratory and clinical features indicative of both accelerated fibrinogenesis and fibrinolysis. The initiating event is clotting that leads to consumption of procoagulant factors and resultant hemorrhage.

b. **Etiology.** DIC is a secondary phenomenon that occurs in response to local factors (e.g., large hemangiomas as seen in Kasabach–Merritt syndrome) and systemic factors (e.g., sepsis, hypothermia, malignancy, heat stroke, snakebite, burns).

c. **Clinical features.** Signs include cutaneous and internal organ bleeding.

d. **Laboratory findings.** Studies show **thrombocytopenia, prolongation of PT and aPTT, reduction in clotting factors** (especially **fibrinogen** and factors II, V, and VIII), **elevated fibrin degradation products** (positive D-dimer assay), and fragmented and helmet-shaped RBCs on blood smear.

e. **Management.** Therapy includes treatment of the underlying cause and transfusions of fibrinogen, FFP, and platelets as needed. Heparin may be useful if the underlying defect cannot be corrected.

D. **Disorders of blood vessels.** These diseases affect the integrity of blood vessels and may present with bleeding.

1. **Henoch–Schönlein purpura,** an IgA-mediated vasculitis, presents with **palpable purpura** on the lower extremities and buttocks, renal insufficiency, arthritis, and abdominal pain. **Platelet count is normal.** (See also Chapter 16, section I.)
2. **Hereditary hemorrhagic telangiectasia** is an **autosomal dominant** disorder characterized by locally dilated and tortuous veins and capillaries of the skin and mucous membranes.

3. **Scurvy** is **vitamin C deficiency** and causes impaired collagen synthesis that results in weakened blood vessels.
4. **Inherited disorders of collagen synthesis** (e.g., Ehlers–Danlos syndrome) may result in capillary fragility.
5. **Malnutrition and corticosteroids** may weaken the collagen supporting vessels.

E. **Platelet abnormalities**
1. **General concepts**
   a. **Platelet abnormalities may be quantitative** (i.e., decreased or increased in number) or **qualitative** (i.e., intrinsic abnormality in function).
   b. **Thrombocytopenia** is defined as a decreased number of platelets, generally <100,000/μL. It is the **most common cause of bleeding.**
2. **Quantitative disorders** may be secondary to diminished platelet production or to increased platelet destruction or sequestration (within the spleen). They may also be congenital or acquired.
   a. **Decreased platelet production**
      1. **Congenital disorders**
         a. **Wiskott–Aldrich syndrome** is an **X-linked** disorder characterized by **thrombocytopenia** with unusually small platelets, **eczema,** and *defects in T- and B-cell immunity*.
         b. **Thrombocytopenia–absent radius (TAR) syndrome** is an **autosomal recessive** disorder characterized by thrombocytopenia and limb abnormalities, especially absence of the radius (**note that the thumb is present, in contrast to Fanconi anemia, in which the thumb is absent**; see section II.B.1). Cardiac and renal disease may be present. Thrombocytopenia improves in the second or third year of life.
      2. **Acquired disorders** are generally those that cause pancytopenia, including infiltration of the bone marrow, infections, drugs, and aplastic anemia [see section II.B.2].
   b. **Increased platelet destruction**
      1. **Immune-mediated thrombocytopenias**
         a. **Immune thrombocytopenic purpura (ITP) is the most common acquired platelet abnormality in childhood.**
            1. **Etiology.** ITP may be viral, drug-induced, or **idiopathic**.
            2. **Pathophysiology.** Because ITP often follows a viral infection, it is thought that the virus triggers antibodies that cross-react with platelets, causing their destruction and removal by the spleen.
            3. **Clinical features.** Illness typically occurs 1–4 weeks **after a viral infection.** It begins abruptly with cutaneous bleeding (e.g., petechiae, bruising) or mucous membrane bleeding (e.g., epistaxis, gum bleeding). Internal bleeding into the brain (occurs in <1%), kidneys, or GI tract may occur but are rare.
            4. **Laboratory findings.** Studies reveal thrombocytopenia and a blood smear showing few *large "sticky" platelets*.
            5. **Management.** Treatment includes supportive care. Very low platelet counts (<10,000/μL) or active bleeding warrants treatment with intravenous immunoglobulin (**IVIG**) or corticosteroids. Anti-D immunoglobulin is a second-line agent that may also be effective. This immunoglobulin binds to erythrocyte D antigen (Rh) on RBCs (patients must be Rh-positive). These antibody-coated RBCs are cleared by the spleen, preferentially allowing platelets to escape

destruction. Platelet transfusions are generally avoided because transfused platelets are rapidly destroyed.

6. **Prognosis. Most cases (70–80%) resolve spontaneously within months.** Chronic ITP, which occurs in 10–20%, is diagnosed if ITP lasts >6 months. Chronic ITP results in long-lasting or relapsing thrombocytopenia and is more common in adults and in children older than 10 years. Splenectomy results in a normal platelet count in 75% of patients with chronic ITP, but because of the risk of infection after spleen removal, there is a reluctance to perform a splenectomy on children.

b. **Neonatal immune-mediated thrombocytopenia**

1. **Passive autoimmune thrombocytopenia** occurs when the mother has ITP, and antibodies against her own platelets cross the placenta and destroy the fetus's platelets. **The mother has thrombocytopenia.**
2. **Isoimmune thrombocytopenia** occurs when the mother produces antibodies against her fetus's platelets as a result of sensitization to an antigen that her own platelets lack. **The mother's platelet count is normal.**

2. **Drugs, DIC, and an enlarged spleen** may all cause platelet destruction.
3. **HUS** is characterized by thrombocytopenia, in association with acute renal failure and hemolytic anemia (see Chapter 11, section VII).
4. **Large hemangiomas** may sequester and destroy platelets (e.g., **Kasabach–Merritt syndrome** characterized by an enlarging hemangioma, microangiopathic hemolytic anemia, thrombocytopenia, and consumptive coagulopathy).

3. **Qualitative platelet disorders** (i.e., defect in platelet function despite normal number) may be **congenital** or **acquired.**

a. **Congenital disorders**

1. **Glanzmann thrombasthenia** is an **autosomal recessive** disorder characterized by diminished ability of platelets to aggregate and form a clot as a result of deficient adhesive glycoprotein IIb/IIIa (receptor for fibrinogen) on the platelet cell membrane.
2. **Bernard–Soulier syndrome** is an **autosomal recessive** disorder characterized by decreased platelet adhesion as a result of absence of platelet membrane glycoprotein Ib (receptor for collagen). Severe hemorrhage may occur, and large unusual platelets are seen on blood smear.

b. **Acquired disorders** are usually caused by **drugs** (e.g., **aspirin,** valproic acid) that impair platelet function. **Uremia** and severe **liver disease** may also decrease platelet function.

F. **Hypercoagulability**

1. **Inherited coagulation abnormalities** leading to hypercoagulability most commonly include deficiencies of **proteins C and S or antithrombin III,** or mutations in **factor V** (factor V Leiden) and **prothrombin.**

a. **Protein C deficiency**

1. Protein C is a vitamin K–dependent factor that is the most potent anticoagulant protein known. Homozygous and heterozygous deficiency states have been described, and inheritance may be either autosomal recessive or dominant.
2. **Clinical features**

        a. **Homozygotes** usually have no protein C activity and are detected soon after birth. **Purpura fulminans,** a nonthrombocytopenic purpura, is often the initial presentation. It is characterized by fever, shock, and rapidly spreading skin bleeding and intravascular thrombosis.
        b. **Heterozygotes** often present later with **deep venous or CNS thrombosis.**
    3. **Diagnosis** is by careful family history and specific testing for protein C.
    4. **Management.** Treatment may include heparin, FFP, and warfarin. Purified concentrates of protein C have been used.
  b. **Protein S** and **antithrombin III deficiencies,** and **factor V Leiden and prothrombin mutations** present similarly to protein C deficiency. Specific testing for levels and function of each factor is diagnostic.
2. **Disease states** associated with thrombosis include SS disease, malignancy, inflammatory disease (e.g., ulcerative colitis), liver disease, kidney disease (e.g., nephrotic syndrome), dehydration, vasculitis (e.g., Kawasaki disease), diabetes mellitus, and homocystinuria. Pregnancy and contraceptive use may also be associated with thrombosis.

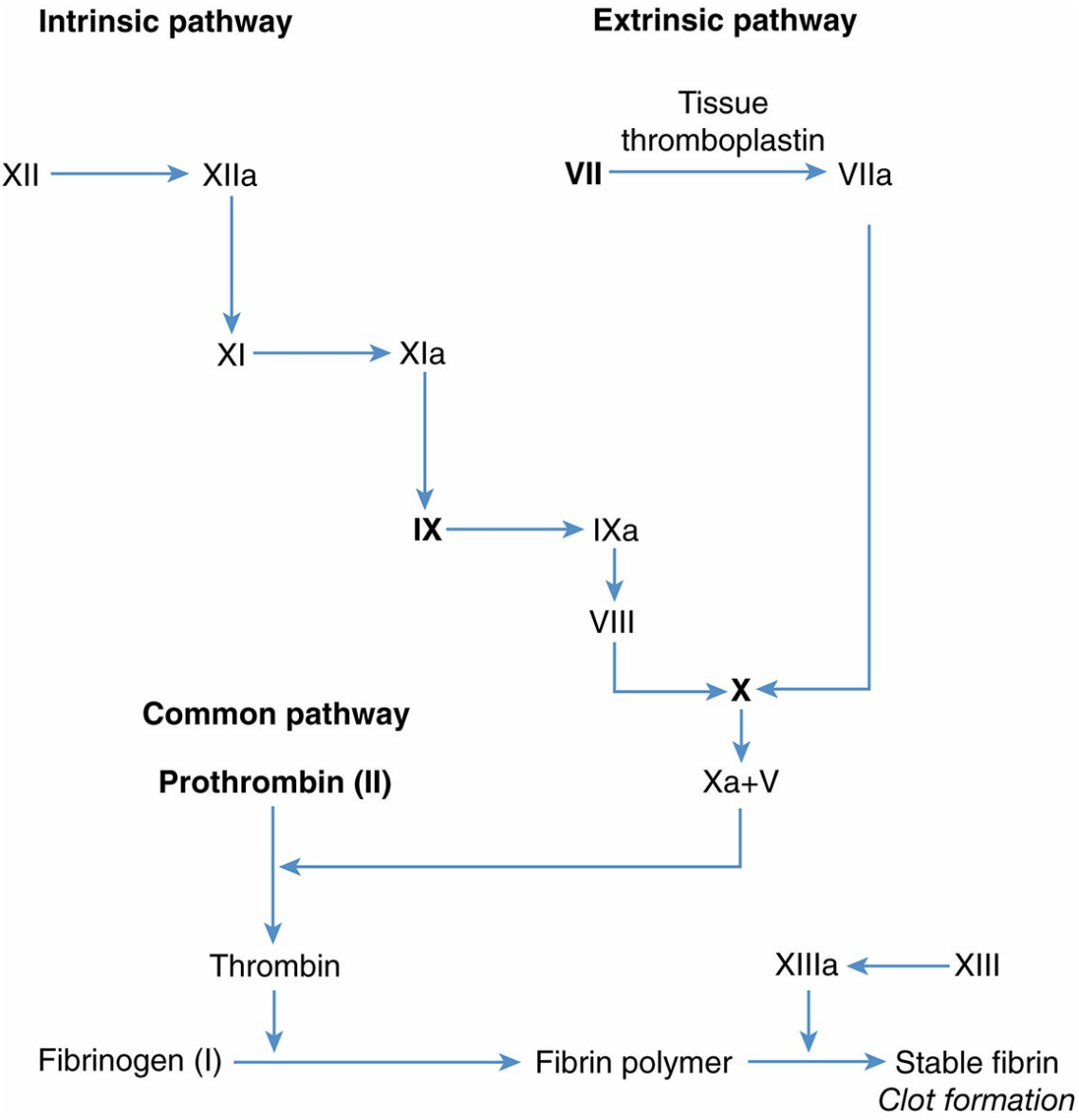

FIGURE 13.2 Coagulation cascade. *Activated partial thromboplastin time* measures the function of the intrinsic pathway and the extrinsic pathway, except for factor VII; the *prothrombin time* measures the function of the extrinsic pathway (factors VII, X, and V), fibrinogen, and prothrombin (factor II). *Factors in bold type are vitamin K–dependent coagulation factors*.

Table 13-6
Laboratory and Clinical Findings in Coagulation Disorders

Disorder	aPTT	PT	Platelet Function Assay	Platelet Count	Petechiae	Hemarthroses
Factor VIII, IX deficiency	Prolonged	Normal	Normal	Normal	No	Yes
von Willebrand	Prolonged	Normal	Abnormal	Normal	No	Rare
Thrombocytopenia	Normal	Normal	*	Low	Yes	No
Platelet function defect	Normal	Normal	Abnormal	Normal	Yes	No
Vitamin K deficiency	Prolonged	Prolonged	Normal	Normal	Yes	Yes
DIC	Prolonged	Prolonged	Abnormal	Low	Yes	Sometimes

*Platelet function assays may be unreliable with thrombocytopenia and therefore are typically not indicated.

aPTT = activated partial thromboplastin time; *PT* = prothrombin time; *DIC* = disseminated intravascular coagulation.

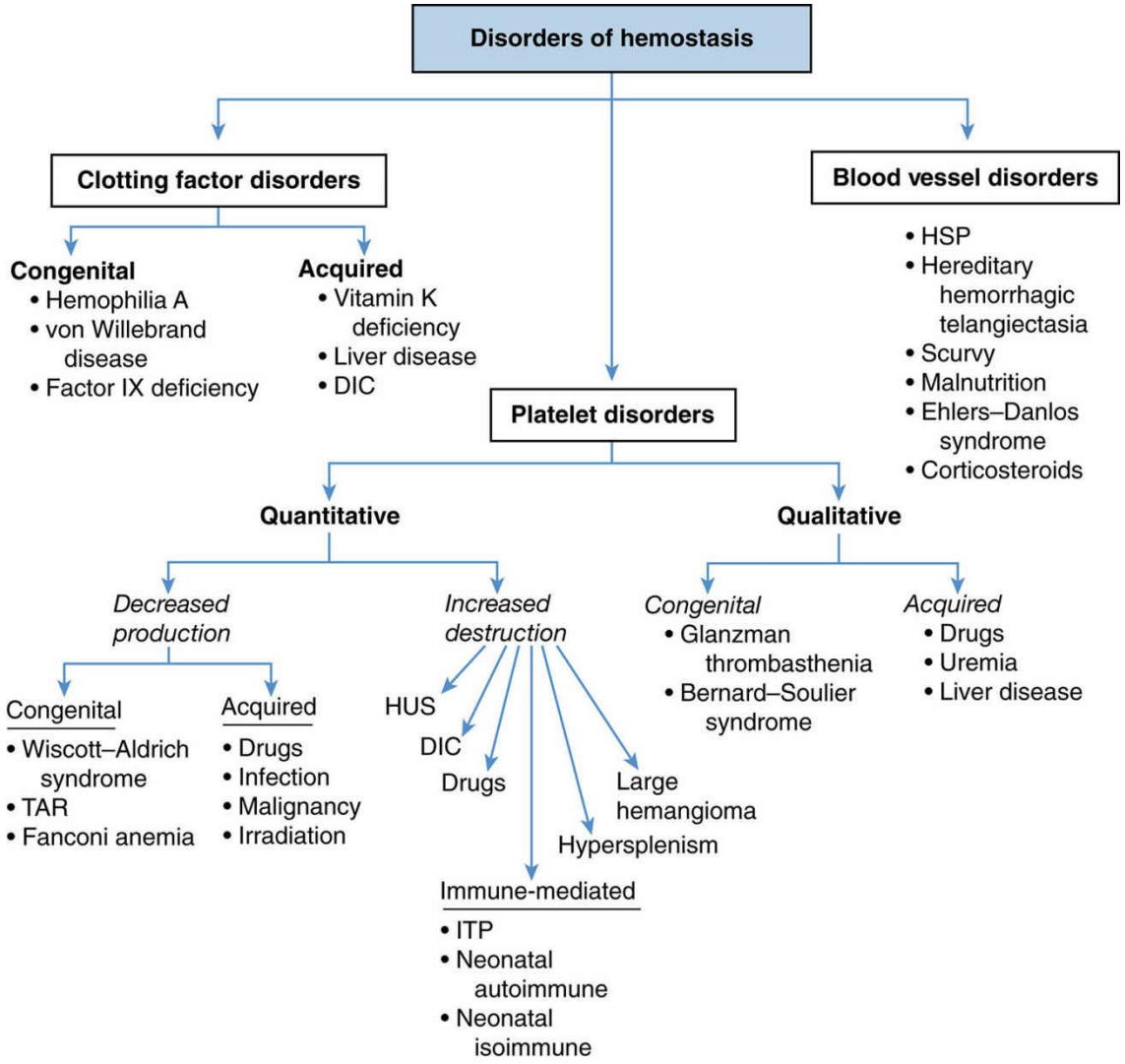

FIGURE 13.3 Overview of the differential diagnosis of disorders of hemostasis. *DIC* = disseminated intravascular coagulation; *HUS* = hemolytic uremic syndrome; *HSP* = Henoch–Schönlein purpura; *TAR* = thrombocytopenia–absent radius syndrome; *ITP* = immune thrombocytopenic purpura.

V. Neutropenia

A. **General concepts**
   1. **Definition.** Neutropenia is a **low absolute number of neutrophils** and is often expressed as the **absolute neutrophil count** (**ANC;** percentage of WBCs that are neutrophils, bands, and immature myeloid cells).
   2. **Risk of infection is directly related to the ANC.**
      a. **Mild neutropenia** is an ANC of 1000–1500 cells/mm^3.
      b. **Moderate neutropenia** is an ANC of 500–1000 cells/mm^3. Infection generally involves the mucous membranes and skin (e.g., stomatitis, cellulitis, gingivitis).
      c. **Severe neutropenia** is an ANC of <500 cells/mm^3. Severe infections may result, such as pneumonia, sepsis, and meningitis. *S. aureus* and Gram-negative bacteria (e.g., *Klebsiella, Serratia, Escherichia coli,* and *Pseudomonas*) are typical organisms.

B. **Neutropenia caused by decreased production**
   1. **Infections are the most common cause of neutropenia during childhood.** Viruses (e.g., HIV, EBV, CMV, hepatitis A and B, influenza A, parvovirus B19), bacteria (e.g., typhus, Rocky Mountain spotted fever), and protozoans (e.g., malaria) may all suppress the bone marrow, marginate neutrophils, or exhaust marrow reserves, resulting in neutropenia.
   2. **Chronic benign neutropenia (CBN) of childhood,** a common cause of neutropenia in children younger than 4 years, refers to a group of acquired and inherited disorders with **noncyclic neutropenia** as the only abnormality. Its etiology is presumed to be autoimmune.
      a. **Clinical features.** CBN has a **variable course,** with most children having an increased incidence of **mild infections,** such as otitis media, sinusitis, pharyngitis, and cellulitis. Severe infections may occur but are uncommon. Children are otherwise healthy, with normal appearance and growth.
      b. **Laboratory findings.** Studies show a low ANC with a normal or slightly low WBC. Bone marrow demonstrates immature neutrophil precursors (development of mature neutrophils is arrested).
      c. **Prognosis.** In most children, CBN resolves spontaneously within months to years.
   3. **Severe congenital agranulocytosis** (**Kostmann syndrome**) is an **autosomal recessive** disorder with frequent and life-threatening pyogenic bacterial infections beginning in infancy. ANC is usually <300 cells/mm^3. These patients must be supported with granulocyte colony-stimulating factor or undergo bone marrow transplant for cure.
   4. **Cyclic neutropenia**
      a. **Clinical features. Cyclic alterations in neutrophil counts** result in **regular episodes of neutropenia** with resultant infections. Fever, oral ulcers, and stomatitis may occur during the neutropenia. Cycles last an average of 21 days in 70% of patients. Some cases are inherited in an autosomal dominant pattern.
      b. **Diagnosis** is made by documenting the cyclic nature of the neutropenia by obtaining **serial neutrophil counts** during a 2- to 3-month period.
      c. **Treatment** is with granulocyte colony–stimulating factor during periods of neutropenia, although some patients spontaneously remit during adolescence.
   5. **Genetic syndromes associated with neutropenia**
      a. **Chédiak–Higashi syndrome** is an autosomal recessive disorder characterized by **oculocutaneous albinism,** large blue-gray granules in the cytoplasm of neutrophils, neutropenia, and **blond or brown hair with silver streaks.** Patients are at high risk for serious infection.
      b. **Cartilage–hair hypoplasia syndrome** is an autosomal recessive disorder

characterized by **short stature, immunodeficiency, fine hair,** and **neutropenia.**

6. **Shwachman–Diamond syndrome** is characterized by **exocrine pancreatic insufficiency** with malabsorption, **short stature** caused by **metaphyseal chondrodysplasia, and neutropenia.** Failure to thrive and recurrent infections (especially otitis media) are common.
7. **Drugs** (e.g., antibiotics, anticonvulsants, aspirin), environmental toxins, radiation, and chemotherapy may all cause neutropenia.
8. **Metabolic diseases,** such as hyperglycinemia, methylmalonic acidemia, and Gaucher disease, may result in neutropenia.

C. **Neutropenia caused by increased destruction**

1. **Infections** (especially viral)
2. **Drugs**
3. **Hypersplenism**
4. **Autoimmune neutropenia** describes a disorder in which **antineutrophil antibodies** are produced in response to infection (e.g., EBV), drugs, SLE, and juvenile rheumatoid arthritis (JRA), or for unknown reasons.
5. **Isoimmune neutropenia** describes the passive transfer of antineutrophil antibodies from the mother to her fetus after maternal sensitization by antigens on the fetal neutrophils. Infants are initially susceptible to infection, but neutropenia resolves by 8 weeks of life.

Review Test

1. You are evaluating a 2-month-old healthy full-term male infant at a routine health care maintenance visit. His mother is concerned because he seems pale. Although your examination is normal, you draw a hemoglobin (Hgb) level to reassure the parents. Which of the following statements is correct regarding the expected Hgb concentration?
   A. Evidence of nutritional iron-deficiency anemia is likely.
   B. The Hgb level is likely at its physiologic lowest point.
   C. Fetal Hgb has disappeared by now, and the Hgb level will be slightly lower than that at birth.
   D. The Hgb level was likely low at birth and is now increasing.
   E. Evidence of macrocytic anemia is likely.
2. A 2-year-old boy is brought to your office with a history of multiple bacterial infections, including six episodes of otitis media, three episodes of sinusitis, and one episode of periorbital cellulitis. He is normal-appearing with normal growth and development. Biweekly laboratory assessments for the past 3 months have revealed consistently low white blood cell counts at 2000–2500 cells/mm^3, with an absolute neutrophil count of 500–1000 cells/mm^3. Which one of the following is the most likely diagnosis?
   A. Chédiak–Higashi syndrome
   B. Shwachman–Diamond syndrome
   C. Chronic benign neutropenia of childhood
   D. Cyclic neutropenia
   E. Kostmann syndrome
3. A 3-year-old girl is brought to the office with petechiae and bruising on the face, chest, back, and lower extremities, which her mother noticed early this morning. The mother states that her daughter has been healthy except for a viral upper respiratory illness 2 weeks ago. Laboratory assessment reveals a platelet count of 25,000/μL. Which of the following statements regarding the likely diagnosis is correct?
   A. Hemarthroses commonly occur in this disorder.
   B. Spontaneous recovery within several weeks to months is expected.
   C. Platelet transfusion should be urgently performed.
   D. Prothrombin time and activated partial thromboplastin time are prolonged.
   E. Considering the girl's young age, this disorder will likely become chronic.
4. A 15-month-old girl has a hypochromic, microcytic anemia (hemoglobin of 10.6 g/dL) on a routine anemia screen performed in the office. History reveals a diet consisting of six 8-oz glasses of whole cow's milk per day since the age of 9 months. Which of the following statements regarding the likely diagnosis is correct?
   A. The anemia is caused by a benign disorder, and there are no physical or intellectual effects.
   B. Low serum ferritin is a late finding.
   C. The reticulocyte count is low, considering the impact of this disorder on the bone marrow.
   D. Transferrin saturation is low.
   E. Free erythrocyte protoporphyrin is low.
5. You are evaluating a term newborn female infant during a routine health maintenance evaluation at 2 weeks of age. You receive the results of a routine newborn screen performed on the second day of life. The results of the newborn screen are normal, with the exception of the sickle cell screen, which reveals that the infant has hemoglobin (Hgb) A, Hgb S, and Hgb F. Which of the following is correct regarding the diagnosis?

A. Mild anemia is expected.
B. A vaso-occlusive crisis involving the hands and feet is likely by 6 months of age.
C. Splenic function is expected to decrease by 3 years of age.
D. Penicillin prophylaxis should be started immediately.
E. Hematuria may be the only manifestation of this disorder.

6. An 8-year-old boy with sickle cell anemia presents with severe right arm pain that began today. His pain has been unresponsive to oral acetaminophen. His mother states that he has been afebrile, and she denies any trauma. On examination, his right arm is mildly tender and is minimally warm along the humerus. Range of motion of the upper extremity is normal. There is no fever. Which of the following is the appropriate initial management?
   A. Obtaining a blood culture
   B. Transfusion of red blood cells with a goal of an Hgb level of 14 g/dL
   C. Bolus with 40 mL/kg of normal saline
   D. Administration of ibuprofen and a narcotic
   E. Magnetic resonance imaging (MRI) to rule out osteomyelitis
7. A 17-year-old girl presents with concerns about her menstrual periods. Menarche occurred at 13 years of age, and for the past 2 years, her menstrual cycles have been regular but characterized by extremely heavy bleeding lasting 7–8 days. She also has a history of frequent nosebleeds since early childhood. She denies bleeding into her joints and has been otherwise healthy. She also denies medications, including aspirin. Based on her history, which of the following is the most likely diagnosis?
   A. Hemophilia A
   B. Hemophilia B
   C. Vitamin K deficiency
   D. Immune thrombocytopenic purpura (ITP)
   E. von Willebrand disease
8. A 7-year-old girl comes to your office for the first time. Her parents bring her to see you because she has had widespread bruising for 3 days. They also believe that she is abnormally pale. On examination, you note that she is pale and has multiple areas of ecchymosis on her arms, legs, and trunk. Her medical history is remarkable for being born with absence of her right thumb and right radius. Laboratory studies reveal a hemoglobin level of 7 g/dL, platelet count of 30,000/μL, and white blood cell count of 800 cells/mm^3. Which of the following statements regarding the likely diagnosis is correct?
   A. The reticulocyte count is elevated.
   B. Spontaneous recovery from this disorder is likely.
   C. The growth chart likely reveals short stature.
   D. Intravenous immunoglobulin should be administered for immune thrombocytopenic purpura (ITP).
   E. Causes of the disorder include drugs, radiation, or chemical exposure.
9. A 10-year-old Italian boy has had chronic anemia since infancy that is characterized by severe hypochromia and microcytosis. Examination reveals a short child, an enlarged liver and spleen, and prominent facial bones, especially the maxilla, forehead, and cheekbones. Which of the following statements regarding the likely diagnosis is correct?
   A. Management should include supplemental iron.
   B. Hemochromatosis is a likely future complication.
   C. His hemoglobin (Hgb) electrophoresis will reveal Hgb S and Hgb F.
   D. The cause of his disorder is deletion of the α-globin chain.
   E. His blood smear will show spherocytes.
10. A 2-year-old girl has anemia with a hemoglobin level of 9.8 g/dL on routine laboratory screening. History reveals a diet consisting of large amounts of goat's milk. Which of the

following statements regarding the anemia is correct?

A. The cause of the anemia is diminished intake of vitamin B_{12}.
B. Spoon-shaped nails may be seen on examination.
C. Smooth red tongue may be seen on examination.
D. The anemia is normochromic and normocytic.
E. Management includes administration of folic acid.

The response items for questions 11–13 are the same. You will be required to select one answer for each item in the set.

A. Thrombocytopenia–absent radius (TAR) syndrome
B. Fanconi anemia
C. Wiskott–Aldrich syndrome
D. Immune thrombocytopenic purpura
E. Hemolytic uremic syndrome
F. Kasabach–Merritt syndrome
G. Glanzmann thrombasthenia
H. Bernard–Soulier syndrome

For each patient, select the likely diagnosis.

1. A 2-year-old boy with thrombocytopenia and a large hepatic hemangioma.
2. A 5-year-old boy with thrombocytopenia, moderate eczema, and both humoral and cell-mediated immunodeficiency.
3. A newborn girl with thrombocytopenia, ventricular septal defect, and absence of a radius. The girl's thumb is present.

The response items for questions 14 and 15 are the same. You will be required to select one answer for each question in the set.

A. Transient erythroblastopenia of childhood
B. Diamond–Blackfan anemia
C. Parvovirus B19 red blood cell aplasia

For each clinical description, select the likely diagnosis.

1. A 6-month-old male infant presents with rapid onset of anemia. He has triphalangeal thumbs on examination. Corticosteroids improve his anemia.
2. A 2-year-old girl develops the gradual onset of significant anemia 2 weeks after a viral upper respiratory infection. Her anemia improves spontaneously.

The response items for questions 16–19 are the same. You will be required to select one answer for each item in the set.

A. Hemophilia B
B. Platelet function defect
C. Vitamin K deficiency
D. Disseminated intravascular coagulation (DIC)
E. von Willebrand disease
F. Immune thrombocytopenic purpura

For each patient, select the most likely diagnosis.

1. A 6-year-old boy with prolonged diarrhea lasting 2 weeks develops a hemarthrosis involving the knee. He has a prolonged prothrombin time and prolonged activated partial thromboplastin time with a normal platelet activation function assay.
2. A 2-year-old boy with newly diagnosed acute lymphocytic leukemia presents with fever, petechiae, and ecchymoses. He has thrombocytopenia, prolonged prothrombin time, prolonged activated partial thromboplastin time, and a prolonged platelet functional assay.
3. A 5-year-old boy presents with a hemarthrosis involving the knee. He has a normal prothrombin time, prolonged activated partial thromboplastin time, and normal platelet function assay.
4. An 8-year-old boy develops severe bleeding following tonsillectomy. He has a normal prothrombin time, prolonged activated partial thromboplastin time, and abnormal platelet function assay.

Answers and Explanations

1. **The answer is B** [I.A.2]. The hemoglobin of a healthy full-term infant is high at birth and decreases during the next several months, reaching its nadir, or physiologic lowest point, by 2–3 months of age. The hemoglobin of a preterm infant is at its physiologic low point at 1–2 months of age. Iron-deficiency anemia does not generally appear until 9–24 months of age, as a result of inadequate iron intake and depletion of iron stores acquired during fetal life. Fetal hemoglobin, a major constituent of red blood cells during early postnatal life, gradually declines and disappears by 6–9 months of age. Macrocytic anemia, caused most commonly by folic acid or vitamin B_{12} deficiency, would not normally occur at 2 months of age.
2. **The answer is C** [V.B.2]. This patient's clinical presentation and age are most consistent with chronic benign neutropenia (CBN) of childhood. This noncyclic neutropenia is most common in children younger than 4 years of age. CBN is characterized by normal appearance and growth and a history of mild infections, such as sinusitis, cellulitis, and otitis media. Absolute neutrophil count (ANC) and white blood cell counts are low. Chédiak–Higashi and Kostmann syndromes are characterized by more severe infections, and Chédiak–Higashi syndrome is also notable for the presence of oculocutaneous albinism. Kostmann syndrome (severe congenital agranulocytosis) is an autosomal recessive disorder with frequent severe infections and a very low ANC. Shwachman–Diamond syndrome is characterized by poor growth, pancreatic insufficiency, and metaphyseal chondrodysplasia. Cyclic neutropenia, as its name suggests, is characterized by regular cycles of neutropenia occurring on average every 21 days.
3. **The answer is B** [IV.E.2.b.(1) and Table 13-6]. The most likely diagnosis is immune thrombocytopenic purpura (ITP) based on the acuteness of the presentation and the classic history of signs and symptoms after a viral infection. Spontaneous recovery is the rule, occurring in 70–80% of patients. Clinical features of ITP most commonly include cutaneous or mucous membrane bleeding, rather than bleeding into joints (hemarthroses). Platelet transfusions are generally not recommended because transfused platelets will be destroyed by the patient's antibodies. Patients with ITP have low platelet counts but normal activated partial thromboplastin time and prothrombin time. Treatment includes supportive care, intravenous immune globulin, or corticosteroids, and sometimes anti-D immunoglobulin. Chronic ITP occurs more commonly in patients older than 10 years.
4. **The answer is D** [I.D.1]. The history of excessive intake of iron-poor cow's milk and the presence of a microcytic, hypochromic anemia at 15 months of age are both consistent with iron-deficiency anemia. In iron-deficiency anemia, findings include increased free erythrocyte protoporphyrin, increased transferrin, and decreased transferrin saturation. Significant physical and intellectual effects may occur in iron-deficiency anemia and include poor weight gain, diminished attention, and diminished abilities to learn. One of the earliest laboratory findings is a low serum ferritin. Reticulocyte count is often elevated, reflecting increased bone marrow activity.
5. **The answer is E** [I.F.3.d]. The presence of both hemoglobin (Hgb) A and Hgb S indicates that this patient has sickle cell trait (all children also have Hgb F at birth). The presence of Hgb A excludes sickle cell disease; affected patients with sickle cell disease have only Hgb S and Hgb F. Patients with sickle cell trait are generally asymptomatic, although during adolescence they may have an inability to concentrate the urine or hematuria. Patients do not have anemia; they are generally free of crises, unless they have severe hypoxemia, and they have normal splenic function. Prophylactic penicillin is unnecessary given the normal splenic function.
6. **The answer is D** [Table 13-3]. Extremity pain in patients with sickle cell disease may be caused by trauma, osteomyelitis, or a vaso-occlusive crisis. Because there is no trauma or fever, a painful bone crisis (a type of vaso-occlusive crisis) is most likely. Appropriate management

includes pain control with a narcotic and a nonsteroidal anti-inflammatory agent. There is no need to obtain a blood culture because the child has no fever. Red blood cell transfusion to a hemoglobin level of 14 g/dL is inappropriate because it will lead to increased blood viscosity that may result in increased vaso-occlusion. If the pain is not well controlled with analgesia and improved hydration, a partial exchange transfusion might be indicated. Because osteomyelitis is less likely given the acute onset of the pain and the absence of fever, magnetic resonance imaging would not be an appropriate initial management step.

7. **The answer is E** [IV.B.3]. von Willebrand disease is characterized by mild to moderate bleeding in most patients. Common signs and symptoms include bruising, epistaxis, menorrhagia (i.e., prolonged or excessive uterine bleeding occurring at regular intervals), and bleeding after surgical procedures or dental extraction. Hemarthroses are unusual and are more typical in hemophilia A and B, in which deep soft tissue bleeding occurs. In addition, these bleeding disorders occur in males; they have X-linked inheritance. Vitamin K deficiency in an adolescent would likely be caused by medications or disorders that cause diminished vitamin K absorption, such as pancreatic insufficiency, biliary obstruction, or prolonged diarrhea. Symptoms would also likely be more severe. Immune thrombocytopenic purpura may present with petechiae, bruising, or nosebleeds. However, the onset of symptoms is generally acute.
8. **The answer is C** [II.B.1]. The patient most likely has Fanconi anemia, or congenital aplastic anemia, on the basis of pancytopenia, her age at presentation, and her history of absence (hypoplasia may also occur) of the thumb and radius. Fanconi anemia is an inherited lifelong disorder that results in bone marrow failure. Almost all patients have short stature, and many also have skin hyperpigmentation and kidney anomalies. Management includes transfusions and bone marrow transplant. Because Fanconi anemia is characterized by bone marrow failure, the reticulocyte count would be expected to be very low. Because the hemoglobin and white blood cell count are also low, this girl does not have immune thrombocytopenic purpura.
9. **The answer is B** [I.D.2.d]. This patient's anemia and physical features suggest β-thalassemia. β-Thalassemia occurs most commonly in patients of Mediterranean background and is caused by deletion of the β-globin chain. If untreated, β-thalassemia results in bone marrow hyperplasia (often noted within the facial bones), delays in growth and puberty, and hepatosplenomegaly. Many children suffer from hemochromatosis (iron overload) as a complication, and therefore iron is contraindicated in these patients. The presence of both hemoglobin S and hemoglobin F is not consistent with β-thalassemia and would instead suggest sickle cell anemia. Spherocytes are not present on blood smear.
10. **The answer is E** [I.E.1]. Feedings exclusively with goat's milk as a sole source of milk protein can lead to folic acid deficiency and a macrocytic anemia. Dietary folic acid is the treatment. Spoon-shaped nails are seen in iron-deficiency anemia, and a smooth red tongue is seen in vitamin B_{12} deficiency.
11. **The answers are F, C, and A, respectively** [IV.E.2.b.(4), IV.E.2.a.(1).(a), and IV.E.2.a.(1).(b)]. The 2-year-old boy has a large hemangioma that sequesters and destroys platelets, which is termed Kasabach–Merritt syndrome. The 5-year-old boy has Wiskott–Aldrich syndrome, which is characterized by eczema, defects in T- and B-cell immunity, and low platelet counts. The newborn girl has thrombocytopenia–absent radius (TAR) syndrome, which is characterized by thrombocytopenia, at times cardiac and renal disease, and absence of the radius. The thumb is present in TAR syndrome, in contrast to Fanconi anemia (pancytopenia with hypoplasia or absence of the radius and thumb).
12. **The answers are B and A, respectively** [Table 13-5]. The 6-month-old infant has Diamond–Blackfan anemia, which is characterized by rapid onset of anemia within the first year of life and physical abnormalities, including triphalangeal thumbs, short stature, and cardiac and

renal anomalies, in one-fourth to one-third of patients. Treatment includes transfusions and corticosteroids. The 2-year-old girl has transient erythroblastopenia of childhood, which is characterized by the slow onset of anemia after the first year of life. The cause is likely a postviral autoimmune reaction, and no treatment is generally required. Parvovirus B19 red blood cell aplasia generally results in no symptoms of anemia in healthy children. Associated features may include a "slapped cheek" red facial rash and upper respiratory symptoms.

13. **The answers are C, D, A, and E, respectively** [Table 13-6]. The clinical characteristics and laboratory abnormalities can differentiate the causes of bleeding in pediatric patients. The 6-year-old boy has vitamin K deficiency, which can occur with pancreatic insufficiency, biliary obstruction, and prolonged diarrhea. Vitamin K deficiency affects the vitamin K–dependent coagulation factors (II, VII, IX, and X) and therefore results in hemarthroses, a prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), and normal bleeding times. The 2-year-old boy has disseminated intravascular coagulation (DIC), which may be caused by malignancy, sepsis, snakebite, heat stroke, and burns. DIC is characterized by abnormalities in all coagulation constituents, including low platelet counts and prolonged aPTT, PT, and bleeding time. Both petechiae and hemarthroses may be present. The 5-year-old boy has hemophilia B, or factor IX deficiency. Hemophilia B is characterized by hemarthroses and prolonged aPTT, but normal PT and bleeding time. The 8-year-old boy has von Willebrand disease, which can present with epistaxis, menorrhagia, and bleeding after tonsillectomy or dental surgery. von Willebrand disease is characterized by prolonged aPTT and prolonged bleeding time, but normal PT. Hemarthroses may sometimes occur.

CHAPTER 14

Oncology

Carol Diamond

I. General Considerations

A. **Incidence.** Approximately 6000–7000 children between 1 and 15 years of age develop cancer each year.
   1. Cancer is the **leading cause of death from disease** in childhood.
   2. Unlike adult cancers, most childhood cancers are not carcinomas. The **most common childhood cancers,** in order of declining incidence, are leukemia, brain tumors, lymphoma, neuroblastoma, soft tissue sarcomas, Wilms tumor, and bone tumors.

B. **Etiology.** The **cause of childhood cancers is often unknown.** However, genetic disorders, immunodeficiency diseases, infections, and environmental factors may predispose to certain cancers.
   1. Ten to fifteen percent of cancers have a familial association or are associated with a genetic disorder. **Table 14-1** lists common genetic syndromes and their associated cancer(s).
   2. **Immunodeficiency diseases** may predispose to cancer, including the following examples:
      a. **Wiskott–Aldrich syndrome,** characterized by B- and T-cell dysfunction, atopic dermatitis, and thrombocytopenia, is associated with lymphoma and leukemia.
      b. **X-linked lymphoproliferative disease,** associated with Epstein–Barr virus (EBV) infection, may result in lymphoma.
   3. **Infectious diseases,** such as EBV infection, which can be associated with Burkitt lymphoma and Hodgkin disease, human papillomavirus (HPV) which can cause cervical, orophayngeal and penile cancer, and human immunodeficiency virus (HIV) infection, which can predispose to Kaposi sarcoma
   4. **Environmental factors,** such as prior chemotherapy and ionizing radiation, may result in malignancy.

C. **Typical presenting features** of childhood cancer
   1. **Persistent fever,** especially if associated with weight loss or night sweats, may be associated with leukemia, lymphoma, and other cancers.
   2. **Palpable or visible mass**
      a. **Abdominal mass** should be considered malignant until proven otherwise. Wilms tumor and neuroblastoma are the two most common malignant abdominal tumors that may present with an abdominal mass.
      b. **Mass on the trunk or extremities** may be caused by rhabdomyosarcoma or bone tumor.
   3. **Bone pain** may reflect metastatic cancer, primary tumors of bone or connective tissue, or leukemic infiltration of bone marrow.
   4. **Supraclavicular lymphadenopathy,** nontender, firm lymph nodes, or enlarging lymph nodes may be caused by leukemia, lymphoma, or metastatic disease.
   5. **Early morning headache** with **vomiting,** or change in gait, may be caused by a space-occupying tumor within the central nervous system (CNS).
   6. **Bruising, petechiae, and pallor** may be caused by tumor infiltration of the bone marrow.
   7. **Leukocoria** (i.e., white reflex in the pupillary area) may be caused by retinoblastoma (see Chapter 18, section VIII.B).
   8. **Hypertension** may be caused by neuroblastoma, Wilms tumor, or pheochromocytoma.

Table 14-1
Genetic Disorders and Their Association with Childhood Cancer

Genetic Disorder	Type of Cancer

Down syndrome	Leukemia (ALL or AML)
Turner syndrome	Gonadoblastoma
Trisomy 13	Leukemia, teratoma
Trisomy 18	Wilms tumor, neurogenic tumors
Klinefelter syndrome	Leukemia, germ cell tumors, breast cancer
Fanconi anemia	Leukemia
Xeroderma pigmentosa	Basal and squamous cell carcinoma, melanoma
Ataxia telangiectasia	Hodgkin and non-Hodgkin lymphoma, leukemia, sarcomas
Bloom syndrome	Leukemia, lymphomas, gastrointestinal malignancies, solid tumors
Beckwith–Wiedemann syndrome	Wilms tumor, hepatoblastoma, rhabdomyosarcoma, adrenocortical carcinoma
Neurofibromatosis type 1	Brain tumors, lymphoma, leukemia, malignant schwannoma
Neurofibromatosis type 2	Acoustic neuroma

ALL = acute lymphocytic leukemia; *AML* = acute myelogenous leukemia.

II. Leukemias

A. **Acute lymphocytic leukemia (ALL)** [acute lymphoblastic leukemia]

1. **Epidemiology**
    a. **ALL accounts for 30% of all pediatric cancers.**
    b. **ALL** represents **80–85%** of childhood leukemias.
    c. **Peak incidence** occurs at **2–6 years of age.** ALL is more common in **males** and in Caucasians.
2. **Etiology.** The cause is generally unknown; however, ALL may be associated with ionizing radiation, chemotherapy, genetic syndromes (e.g., Down syndrome, Bloom syndrome), chemical agents, and immunodeficiency diseases (e.g., ataxia telangiectasia).
3. **Classification** is based on the cell of origin, immunophenotype, and cytogenetic characteristics of the leukemic cells (i.e., lymphoblasts). The immunophenotype classification is as follows:
    a. **T-cell phenotype: 20%**
    b. **Mature B-cell phenotype: <5%**
    c. **Precursor B-cell phenotype: 70–80%.** Pre–B-cell ALL may be further subdivided on the basis of the presence of common acute lymphocytic leukemia antigen (**CALLA**).
        1. CALLA-positive (70%)
        2. CALLA-negative (30%)
4. **Clinical features**
    a. **Fever** and **bone or joint pain** are the **most common symptoms.** Bone or joint pain often manifests as refusal to bear weight.
    b. **Pallor, bruising, hepatosplenomegaly, and lymphadenopathy** are the **most common signs.**
    c. Epistaxis, anorexia, fatigue, testicular pain and swelling, and abdominal pain may also be present.
5. **Diagnosis**
    a. ALL is **suggested** by a complete blood count (CBC) that demonstrates **anemia** and **thrombocytopenia. The white blood cell (WBC) count is variable.**
        1. **WBC** is **high in one-third** of cases (>50,000 cells/mm^3), **normal in one-third** of cases, and **low in one-third** of cases (<10,000 cells/mm^3).
        2. **Leukemic blasts** (i.e., lymphoblasts) are often seen.
        3. **Note: A normal CBC does not rule out leukemia.**
    b. **Confirmation** is by **bone marrow evaluation** demonstrating **marrow replacement by lymphoblasts.** Other normal marrow elements are decreased or absent. Cytogenetics to evaluate for translocations and immunophenotyping must be performed. Spinal fluid must also be obtained to determine the presence of CNS involvement.
    c. **Prognostic factors** for ALL at the time of diagnosis are listed in **Table 14-2.** Most patients have disseminated disease at presentation, so there is no staging system for ALL.
6. **Management.** The best treatment for ALL remains under investigation, and patients should be encouraged to participate in a national clinical trial. Treatment is stratified by risk and initial response to therapy. Management involves **four stages: induction, consolidation, delayed intensification, and maintenance.**
    a. **Induction** aims to destroy as many cancer cells as possible to induce remission.
        1. Drugs vary based on study protocol but typically include corticosteroids, vincristine, and L-asparaginase. **Intrathecal methotrexate** is given to all

children during induction. Other agents are added on the basis of expected prognosis.
2. Remission is induced in 95% of patients.
3. **Minimal residual disease (MRD)**, refers to the small number of leukemic cells that remain in the patient during or after treatment. It is assessed in peripheral blood and marrow by immunophenotyping at the end of induction, is a very powerful indicator of prognosis and guides further therapy.

b. **Consolidation** involves a continuation of systemic chemotherapeutic agents and prophylactic regimens to prevent CNS involvement, because systemic chemotherapy poorly penetrates the blood–brain barrier.
1. **Intrathecal methotrexate** is continued during consolidation.
2. **Cranial irradiation** may be given to high-risk children. Radiation should generally be avoided in children younger than 5 years, if possible, because of the risk of subsequent neuropsychological effects.

c. **Delayed intensification** is commonly used during the first few months of maintenance. It is comprised of regimens similar to those used during induction. Children with higher risk disease may receive longer periods of intensification.

d. **Maintenance** therapy involves daily and periodic chemotherapy during remission for up to 3 years. Chemotherapy is discontinued after 2–3 years if the patient remains disease-free.

e. **Bone marrow transplant** may be performed for very high–risk children and for those who have relapsed or were slow to enter remission after the first several months of therapy. (The bone marrow is the most common site of relapse.)

f. **Complications** during treatment often occur. **Supportive care** is important and includes management of anemia and thrombocytopenia with appropriate blood products and therapy for the following common complications:
1. **Infection associated with neutropenia is potentially life-threatening. Children with fever and severe neutropenia (absolute neutrophil count < 500 cells/mm^3) must be assumed to have a serious bacterial infection, such as sepsis, until proven otherwise.** Common infectious agents include *Staphylococcus aureus, Staphylococcus epidermidis, Pseudomonas aeruginosa,* and *Escherichia coli.* It is necessary to give **empiric treatment with intravenous broad-spectrum antibiotics after appropriate cultures** of blood and urine and any other noticeable sources of infection are obtained.
2. **Opportunistic infections** with organisms, such as herpes simplex virus, *Pneumocystis jiroveci* (i.e., *P. jiroveci* pneumonia [PCP]), and fungi (*Candida albicans, Aspergillus*), may occur as a result of immunosuppression associated with chemotherapy. Fungal infection should be considered in patients with fever lasting longer than 1 week while on intravenous antibiotics. Prophylaxis with trimethoprim–sulfamethoxazole is generally effective in preventing PCP infection.
3. **Metabolic complications** from spontaneous or therapy-induced cell lysis (**tumor lysis syndrome**)
   a. **Hyperuricemia** may result in renal insufficiency.
   b. **Hyperkalemia** may result in cardiac dysrhythmias.
   c. **Hyperphosphatemia** may result in **hypocalcemia** with tetany.
4. Other complications include medication-induced pancreatitis (L-asparaginase and corticosteroids), cardiomyopathy (doxorubicin), and cystitis (cyclophosphamide). Cranial irradiation may result in cognitive impairment, stroke, endocrine problems (e.g., growth delay, hypothyroidism,

hypopituitarism), and secondary malignancy.

7. **Prognosis.** The outlook for patients with ALL is generally good. Overall long-term survival occurs in 85% of patients.

B. **Acute myelogenous leukemia (AML)**
   1. **Epidemiology. AML represents 15–20% of childhood leukemias.**
   2. **Etiology.** The **cause of AML is unknown.** AML is associated with **Down syndrome,** Fanconi anemia, Kostmann syndrome, and neurofibromatosis. It may also be associated with ionizing radiation and occur as a secondary malignancy resulting from chemotherapy.
   3. **Classification** is based on cell of origin, immunophenotype, and cytogenetic characteristics.
   4. **Clinical features** are similar to those of ALL.
      a. **Symptoms and signs include fever, hepatosplenomegaly**, bruising and bleeding, **gingival hypertrophy,** and bone pain. Lymphadenopathy and testicular involvement are uncommon.
      b. **Laboratory findings** may include pancytopenia or leukocytosis and disseminated intravascular coagulation (DIC).
   5. **Diagnosis** is **suggested** by clinical features and blood smear demonstrating **leukemic myeloblasts.** Blasts containing **Auer rods** are consistent with myeloid leukemia. **Confirmation** is by immunophenotyping and cytogenetics of cells obtained by bone marrow evaluation.
   6. **Management.** AML, unlike ALL, requires very intensive myeloablative therapy to induce remission. **Bone marrow transplant** is recommended for most patients in remission, if they have a human leukocyte antigen (HLA)–matched donor.
   7. **Prognosis.** Aggressive chemotherapy is effective in 60% of patients. Bone marrow transplant from a matched sibling is curative in 70% of patients. Megakaryoblastic AML associated with Down syndrome is unusually responsive to chemotherapy and carries an excellent prognosis.

C. **Chronic myelogenous leukemia (CML)**
   1. **Epidemiology.** CML is the **least common** type of leukemia in children, representing 3–5% of childhood leukemia. Males are more commonly affected.
   2. **Classification.** Two forms of CML occur in children.
      a. **Adult-type CML**
         1. **Twice as common as the juvenile form**
         2. Occurs predominantly in **older children and adolescents**
         3. Characterized by the presence of the **Philadelphia chromosome** (reciprocal translocation between the long arms of chromosomes 9 and 22, leading to the fusion gene *BCR/ABL1* that produces the BCR-ABL fusion protein)
      b. **Juvenile chronic myelogenous leukemia** (juvenile myelomonocytic leukemia [**JMML**])
         1. Occurs predominantly in **infants and children** younger than 2 years
         2. Sometimes characterized by abnormalities of chromosome 7 or 8. The Philadelphia chromosome is absent.
   3. **Clinical features.** Signs and symptoms vary based on the type of CML.
      a. **Adult-type CML**
         1. Nonspecific symptoms such as fatigue, weight loss, and abdominal discomfort
         2. **Massive splenomegaly** leading to abdominal distension. CML is typically discovered after an incidental finding of splenomegaly on examination.
         3. **Extremely high WBC (often >100,000 cells/mm^3)**
      b. **JMML**

1. **Fever and malaise**
2. **Chronic eczema-like facial rash**
3. **Suppurative lymphadenopathy**
4. **Petechiae and purpura**
5. **Moderate leukocytosis** (<100,000 cells/mm^3), anemia, and thrombocytopenia

4. **Management.** The first line of therapy for CML is a tyrosine kinase inhibitor (imatinib mesylate), which induces sustained remission in most patients. Bone marrow transplantation (BMT), with either HLA-matched (ideally) or unmatched donor, is reserved for those who do not have a rapid response, fall out of remission, or progress to acute leukemia. Radiation therapy is not effective.
5. **Prognosis**
   a. **Adult-type CML.** With a tyrosine kinase inhibitor, the majority of patients can achieve and maintain a sustained remission, but BMT is still considered curative.
   b. **JMML** is often fatal. Relapse occurs in 60% of cases, even with BMT.

Table 14-2
Prognostic Factors for ALL at Time of Diagnosis

Prognostic Factor	Favorable	Unfavorable
Age	1–9 years of age	<1 or >9 years of age
Sex	Female	Male
Race	White	Black
WBC	<50,000 cells/mm^3	>50,000 cells/mm^3
Ploidy	Hyperploidy (more than 53 chromosomes within leukemic cells)	Low ploidy (fewer than 53 chromosomes within leukemic cells) or extreme hyperploidy
Organ involvement	None	Organomegaly, central nervous system involvement, mediastinal mass
Immunophenotype	CALLA-positive	CALLA-negative

ALL = acute lymphocytic leukemia; *CALLA* = common acute lymphocytic leukemia antigen; *WBC* = white blood cell count.

III. Lymphomas

Lymphomas account for 10–15% of childhood cancers.

A. **Hodgkin disease** is a cancer of the B-cell lineage.
   1. **Epidemiology**
      a. Hodgkin disease can be **associated** with **EBV infection.** Patients with EBV-associated mononucleosis have a two to four times greater risk of developing Hodgkin disease later in life.
      b. Hodgkin disease is more common in older children and adolescents.
   2. **Clinical features.** Most children with Hodgkin disease present with **painless lymphadenopathy,** most commonly in the supraclavicular or cervical regions. **Signs and symptoms** of Hodgkin disease are listed in **Table 14-3.**
   3. **Diagnosis.** The basis of diagnosis is histologic review of tissue obtained by **lymph node biopsy.** The hallmark histologic feature is the **Reed–Sternberg cell,** a large multinucleated cell with abundant cytoplasm.
   4. **Staging.** Classification by the **Ann Arbor system** is the basis for treatment and provides prognostic information. There are four basic stages, and **each stage is subclassified** into "**A**" or "**B,**" reflecting clinical symptoms. **A** refers to lack of systemic symptoms. **B** refers to the presence of systemic symptoms, such as fever, night sweats, or >10% weight loss.
      a. **Stage I:** involvement of a single lymph node or extralymphatic site
      b. **Stage II:** involvement of two or more lymph node regions on the same side of the diaphragm, or extension to an extralymphatic site and one or more lymph node regions on the same side of the diaphragm
      c. **Stage III:** involvement of lymph nodes on both sides of the diaphragm (in this case, the spleen is considered a lymph node)
      d. **Stage IV:** diffuse or disseminated involvement of one or more extralymphatic organs or tissues
   5. **Management.** Treatment is based on the child's age, disease stage, and in some protocols, initial treatment response. Treatment most commonly includes chemotherapy and radiation therapy. **Late complications of therapy** include the following:
      a. **Growth retardation** as a result of radiation therapy
      b. **Secondary malignancies**, including breast cancer, AML, non-Hodgkin lymphoma, and thyroid and skin cancers.
      c. **Hypothyroidism**
      d. **Impaired fertility**
   6. **Prognosis.** Overall, prognosis of stages I and II disease is excellent, with ≥90% long-term survival. More advanced disease carries a long-term survival rate of about 80%.

B. **Non-Hodgkin lymphoma** is an **aggressive** cancer and is 1.5 times more common than Hodgkin disease.
   1. **Epidemiology**
      a. **Male predominance**
      b. Associated with **immunodeficiency states,** such as HIV infection, Wiskott–Aldrich syndrome, ataxia telangiectasia syndrome, and prior EBV infection.
      c. **Increasing incidence after 5 years of age**
   2. **Classification.** There are three major categories of non-Hodgkin lymphoma. (The more **uncommon categories** include anaplastic large cell and large cell, noncleaved immunoblastic lymphoma.)
      a. **Lymphoblastic lymphoma** is histologically similar to the lymphoblast of ALL. It is generally **T cell** in origin. This accounts for about 30% of non-Hodgkin lymphoma.

b. **Small, noncleaved cell lymphoma** includes **Burkitt lymphoma, the most common lymphoma in childhood.** Burkitt lymphoma is **B cell** in origin. This accounts for about 40% of all non-Hodgkin lymphoma.
c. **Large cell lymphoma** is generally **B cell** in origin.

3. **Clinical features (see Table 14-3). Painless lymphadenopathy is the most common presenting feature.**
   a. **Lymphoblastic lymphoma** commonly presents with an **anterior mediastinal mass,** and the patient may develop **superior vena cava syndrome** or **airway obstruction** as a result.
   b. **Small, noncleaved cell lymphoma**
      1. **Intussusception,** abdominal pain, or mass can be the presenting signs or symptoms. **Lymphoma must be considered as a possible cause (lead point) in any child older than 3 years presenting with intussusception.**
      2. **Burkitt lymphoma** is endemic in Africa, where it presents as a **jaw mass and is most often associated with EBV.**
   c. **Large cell lymphoma** commonly presents as enlargement of lymphoid tissue in the tonsils, adenoids, or Peyer patches.
4. **Diagnosis and staging.** The basis of diagnosis is on immunophenotyping, cytogenetics, and morphologic appearance of tissue. Evaluation for dissemination is the basis of staging. This evaluation often includes chest radiograph or chest computed tomography (CT) scan, abdominal and pelvis CT scan, positron emission tomography (PET) scan, bone marrow aspirate and biopsy, and cerebrospinal fluid analysis.
5. **Management. Treatment must be rapid** because of the aggressiveness of this cancer. Management includes surgery to remove or debulk the tumor, chemotherapy specific for the tumor type, prophylaxis for CNS disease, and treatment of tumor lysis syndrome, should it occur. Lymphoblastic lymphoma is treated in a similar way to ALL with at least 2 years of therapy, whereas the other non-Hodgkin lymphomas are treated with a shorter duration of therapy.
6. **Prognosis.** Outlook is **best for localized lymphoma,** with a cure rate >90%. Prognosis is poorest for patients with disseminated disease and for those who do not respond to therapy well initially, but overall greater than 70% of patients are cured with the current regimens used.

Table 14-3
Clinical Features of Hodgkin Disease and Non-Hodgkin Lymphoma

Clinical Feature	Hodgkin Disease	Non-Hodgkin Lymphoma
Symptom onset	Slow, indolent	Rapid
Common location	Cervical and supraclavicular nodes	Abdominal, mediastinal, and supraclavicular nodes
Systemic symptoms*	Relatively common (30%)	Uncommon
Abdominal findings†	Rare	Common
Painless adenopathy	Common	Common
SVC syndrome	Rare	Common
Airway compression	Rare	Common

*Systemic symptoms include fever, drenching night sweats, and weight loss.

†Abdominal findings include abdominal pain, intussusception, abdominal mass, and obstruction.

SVC = superior vena cava.

IV. Brain Tumors

A. **Epidemiology**
   1. Brain tumors are the **second most common childhood cancer** after leukemia and are the **most common solid tumors.**
   2. They account for 20% of all childhood cancers.
   3. Brain tumors may be associated with underlying diseases such as neurofibromatosis, tuberous sclerosis, and von Hippel–Lindau disease.

B. **Classification** is by histology, grade, location, and molecular signature.
   1. **Histology**
      a. **Glial cell tumors are most common** (40–60% of brain tumors) and include astrocytomas. High-grade (i.e., aggressive) tumors often arise in the supratentorial region, and low-grade (i.e., less aggressive) tumors arise in the infratentorial region.
      b. **Primitive neuroectodermal tumors (PNETs)** are the second most common tumor and include medulloblastomas arising from the cerebellum.
      c. **Ependymomas** are the third most common tumor.
      d. **Craniopharyngiomas** are the fourth most common tumor.
   2. **Grade.** The grade of the tumor refers to its aggressiveness.
      a. **High grade:** aggressive, proliferative cells
      b. **Low grade:** less aggressive, more-differentiated cells
   3. **Location. Infratentorial tumors are more common** than supratentorial tumors, except at age extremes of <1 or >12 years.
      a. **Medulloblastoma** is the **most common infratentorial tumor,** followed by cerebellar astrocytoma and brainstem glioma.
      b. **Astrocytoma** is the **most common supratentorial tumor.**

C. **Clinical features.** Signs and symptoms are typically based on the location of the tumor and the child's age.
   1. **Key point: Even benign tumors can be lethal if their location interferes with brain function.**
   2. **Initial nonspecific symptoms are caused by increased intracranial pressure** (and are often **worse during sleep** or **on awakening**). Symptoms commonly subside during the day as venous return from the head improves with upright posture.
      a. **Headache:** diffuse, occipital, or frontal
      b. **Vomiting:** often resolves the accompanying headache
      c. **Drowsiness or irritability**
      d. **Abnormal behavior**
      e. **Ataxia:** associated with cerebellar tumors
      f. **Seizure:** associated with supratentorial tumors
      g. **Head tilt** (torticollis)
   3. **Physical examination findings**
      a. **Enlarged** or **bulging fontanelle** in infants, or enlarged head circumference
      b. **Nystagmus**
      c. **Papilledema**
      d. **Cranial nerve abnormalities,** especially sixth nerve palsy
      e. **Lethargy or irritability**
   4. **Features associated with specific tumors**
      a. **Optic glioma** is associated with diminished vision, visual field deficits, and strabismus.
      b. **Craniopharyngioma** is associated with growth retardation, delayed puberty, visual

changes, diabetes insipidus, and other hormonal problems because of involvement of the hypothalamic–pituitary axis.

D. **Diagnosis**
   1. **Neuroimaging** by magnetic resonance imaging (MRI) is critical for diagnosis and management.
   2. **Cerebrospinal fluid** obtained at surgery is useful for staging and assessment of tumor markers (i.e., α-fetoprotein or β-human chorionic gonadotropin for germ cell tumors; homovanillic acid [HVA], vanillylmandelic acid [VMA], and polyamines for medulloblastoma).

E. **Management**
   1. **Surgery.** Resection or debulking of the tumor is the **principal treatment.**
   2. **Radiation therapy.** Almost all brain tumors are radiosensitive. However, radiation should be reserved, if possible, for children older than 5 years because of the risk of adverse effects [see section II.A.6.f.(4)].
   3. **Chemotherapy.** This method is effective for many tumors and is often used together with radiation therapy and surgery. Stem cell transplant is used, particularly for the younger child, to avoid radiation and thus avoid the late adverse effects of radiation.

F. **Prognosis.** Outlook depends on tumor grade, size, type, and resectability.
   1. **Astrocytomas.** Low-grade, completely resectable astrocytomas have a good prognosis (>80% survival). High-grade astrocytomas have a poor prognosis (35% survival at 3 years) because of their infiltrative nature.
   2. **PNETs.** Survival is >80% if the majority of the tumor can be resected and there are no metastases or extension. Prognosis is worse in children younger than 4 years.
   3. **Brainstem gliomas.** The prognosis is poorest for intrinsic brainstem gliomas, which can respond temporarily to radiation, but are typically fatal.

V. Renal and Suprarenal Tumors

A. **Neuroblastoma.** This malignant tumor of neural crest cells may arise anywhere along the sympathetic ganglia chain and within the adrenal medulla.

1. **Epidemiology**
    a. Neuroblastomas are the **second most common solid tumors,** after brain tumors.
    b. Neuroblastomas are responsible for 8–10% of all childhood cancers.
    c. **Peak incidence is in the first 5 years of life.** Median age at time of diagnosis is 2 years.
    d. Approximately **75% occur in the abdomen or pelvis,** 20% occur in the posterior mediastinum, and 5% occur in the neck.
2. **Etiology.** The cause is unknown; however, chromosomal abnormalities have been detected.
3. **Clinical features.** Signs and symptoms are presented in **Figure 14-1.**
4. **Diagnosis**
    a. Urine excretion of **excessive catecholamines,** including VMA and HVA, is characteristic (found in 90% of patients). **Definitive diagnosis is by tissue biopsy**.
    b. **Staging is achieved with bone marrow biopsy, MRI or CT**, and MIBG (metaiodobenzylguanidine) or PET scanning.
5. **Staging.** The most commonly used staging system is the International Neuroblastoma Staging System.
    a. **Stage 1:** localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes are microscopically negative for tumor
    b. **Stage 2A:** localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes are microscopically negative for tumor
    c. **Stage 2B:** localized tumor with or without complete gross resection, with ipsilateral nonadherent lymph nodes microscopically positive for tumor. Enlarged contralateral nodes must be negative for tumor.
    d. **Stage 3:** unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement, or localized unilateral tumor with contralateral regional lymph node involvement, or midline tumor with bilateral extension by infiltration or by lymph node involvement
    e. **Stage 4:** any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, or skin
    f. **Stage 4S:** localized primary tumor with dissemination limited to the skin, liver, and marrow. Stage 4S is limited to infants.
6. **Management.** In addition to staging, the biologic features of the tumor, which include ploidy, morphology, and n-myc amplification, and the patient's age determine treatment. Except for stage 4S, more aggressive biologic features generally correlate with the disease extent at diagnosis.
    a. **Surgery alone may be curative for stage 1 and 2 disease.**
    b. **Chemotherapy and surgery** are used for intermediate-risk disease (stage 3).
    c. Advanced disease (stage 4) requires chemotherapy, surgery, stem cell transplant, radiation, and immunotherapy.
7. **Prognosis**
    a. **Excellent** prognosis occurs in children younger than 1 year and in patients with stage 1 and 2 disease. **Spontaneous regression without treatment may occur in young infants with stage 4S disease.**

b. Prognosis is good with stage 3 disease, but for stage 4 disease, despite very aggressive treatment, including immunotherapy, only about 65% have long-term survival.

B. **Wilms tumor** (nephroblastoma) is a tumor of the kidney.

1. **Epidemiology**
   a. Wilms tumor is the **most common childhood renal tumor.** It is responsible for 7% of childhood cancers.
   b. Seventy-five percent of cases occur in children **younger than 5 years** (median age at diagnosis is 3 years).
   c. Associated **genetic findings or syndromes** include **Beckwith–Wiedemann** syndrome (hemihypertrophy, macroglossia, and visceromegaly), deletion of the short arm of chromosome 11, and WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation).
2. **Clinical features**
   a. **Abdominal mass,** generally found on routine evaluation, is the **most common presentation.** The mass is smooth and firm and sometimes crosses the midline.
   b. **Abdominal pain** (50% of patients) with or without vomiting
   c. **Hematuria** (25% of patients)
   d. **Hypertension** (25% of patients) secondary to pressure on the renal artery or increased renin secretion by the tumor
   e. **Nonspecific** findings include fever (rare), anorexia, weight loss, and constipation.
   f. Associated congenital anomalies in 15% of cases
      1. **Genitourinary malformations**
      2. **Hemihypertrophy**
      3. **Sporadic aniridia**
3. **Diagnosis.** Wilms tumor should be considered in any child who presents with hematuria or abdominal mass. Wilms tumor is bilateral in 5% of cases. Confirmation is by imaging with abdominal CT or MRI scan and by histologic evaluation of tissue.
4. **Staging.** The National Wilms Tumor Study Group classification is used to stage Wilms tumor.
   a. **Stage I:** tumor limited to the kidney and completely excised intact without rupture
   b. **Stage II:** tumor extends locally but can still be completely excised without residual disease
   c. **Stage III:** residual tumor remains in the abdomen or spillage of tumor occurs during resection
   d. **Stage IV:** distant metastasis to the lung (most common), liver, bone, and brain
   e. **Stage V:** bilateral renal involvement
5. **Management.** Treatment includes prompt surgery for staging and to remove as much tumor as possible. Chemotherapy is used for all stages. Radiation therapy is also used for advanced disease (stages III and IV).
6. **Prognosis.** Outcome is usually **excellent,** with an overall cure rate >90%. Prognosis is dependent on staging and histology. Favorable histology and stage I, II, or III disease result in a 2-year survival rate >95%. Unfavorable histology accounts for 12% of cases but 90% of deaths.

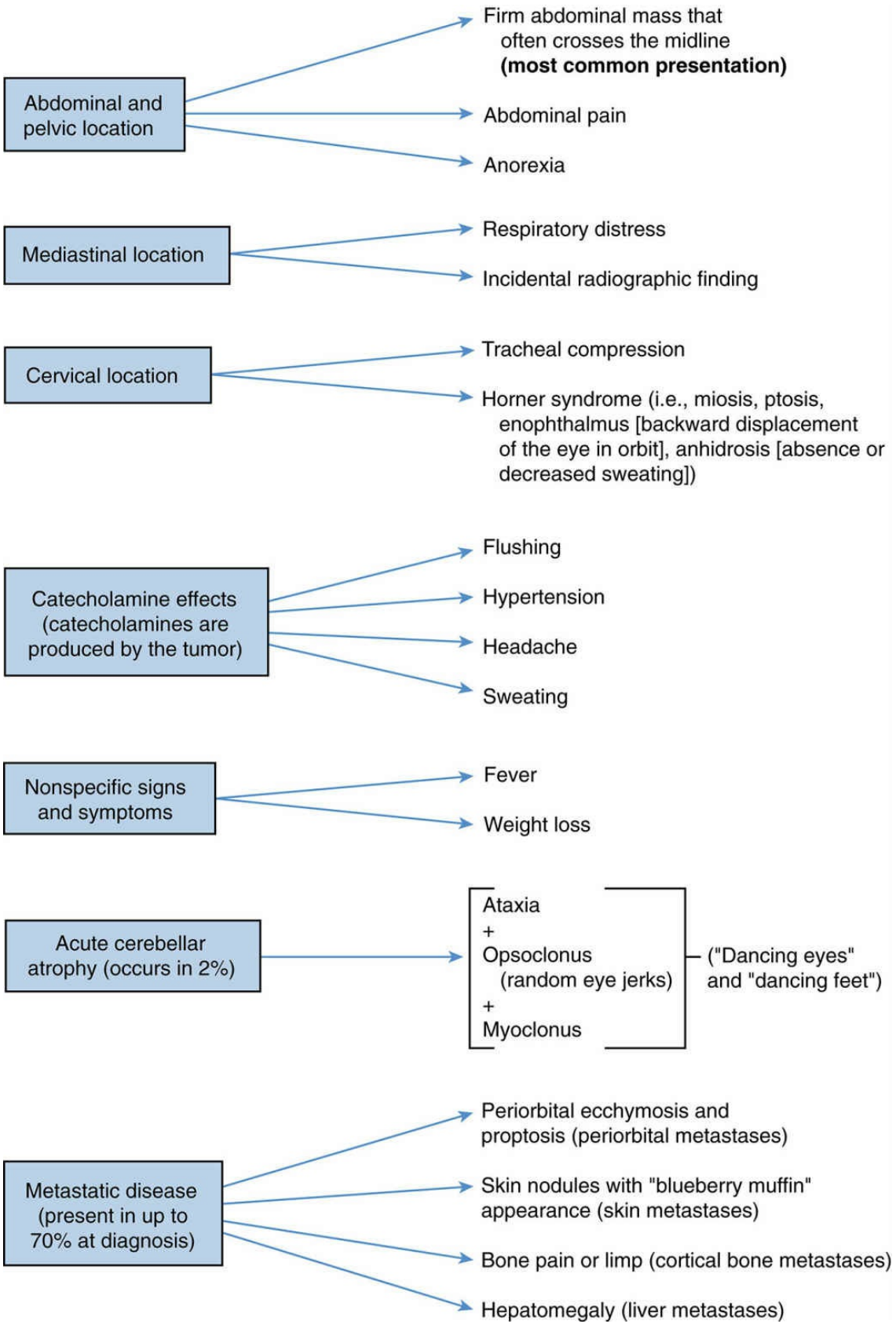

FIGURE 14.1 Clinical features of neuroblastoma.

VI. Soft Tissue Tumors

Rhabdomyosarcoma is the most common soft tissue sarcoma in childhood, and is a malignant tumor of the same embryonic mesenchyme that gives rise to skeletal muscle.

A. **Epidemiology. Two-thirds** of rhabdomyosarcomas occur in children **younger than 10 years.**
B. **Etiology.** The cause is generally unknown. Patients with neurofibromatosis are at higher risk.
C. **Clinical features.** Signs and symptoms depend on the site of involvement. Any part of the body may be affected. The initial presentation is usually a **painless soft tissue mass.**
    1. **Head and neck,** including the orbit, are the **most common sites** of involvement (40% of cases).
        a. **Orbital tumors** typically present with proptosis, chemosis (i.e., conjunctival edema), eyelid swelling, and cranial nerve palsies.
        b. **Nasopharyngeal tumors** typically present with epistaxis, airway obstruction, and chronic sinusitis.
        c. **Laryngeal tumors** typically present with hoarseness.
    2. **Genitourinary tract** is the second most common site of involvement (20% of cases). Tumors in this location typically present with hematuria, urinary tract obstruction, vaginal bleeding, and/or an abdominal mass.
    3. **The extremities** are the third most common site of involvement (18% of cases). Tumors in this location present with a painless growing mass.
    4. **Other sites** of involvement include the trunk, retroperitoneum, mediastinum, and paratesticular and perianal regions.
D. **Diagnosis.** Rhabdomyosarcoma should be considered in any patient presenting with a painless enlarging mass. Imaging studies (CT or MRI) are performed to determine the extent of local extension and to prepare for surgical excision. Immunohistochemistry and cytogenetic evaluation of tissue obtained by biopsy provides a definitive diagnosis.
E. **Management.** Treatment requires chemotherapy and either surgery or surgery and radiation for local control.
F. **Prognosis.** Tumors of the head and neck and the genitourinary tract have the best prognosis, with a cure rate >90% if localized. Poor prognosis is associated with metastases (20% have metastatic disease at time of diagnosis) and with recurrence. Tumors at sites other than the head and neck or the genitourinary tract carry an intermediate prognosis with survival about 70%.

VII. Bone Tumors

A. **Osteogenic sarcoma** is a malignant tumor that forms osteoid or new bone.
   1. **Epidemiology**
      a. Osteogenic sarcoma is the **most common malignant bone tumor in children.**
      b. The incidence of this tumor **peaks during the rapid growth spurt** of adolescence. **Males** are more commonly affected.
   2. **Etiology.** The cause is unknown; however, it is associated with previous retinoblastoma, Paget disease of bone, radiation therapy for cancer, and fibrous dysplasia.
   3. **Clinical features.** About **50% of tumors occur in the distal femur or proximal tibia. Other signs and symptoms** are listed in **Table 14-4,** which compares osteogenic sarcoma with Ewing sarcoma, the second most common malignancy of bone in children.
   4. **Diagnosis.** Diagnosis is suggested by findings on radiographs and MRI. Definitive diagnosis is by tissue biopsy. Bone scan and chest CT scan are performed to evaluate for metastatic disease.
   5. **Management**
      a. **Surgery** to remove the primary tumor is performed by limb amputation or limb salvage procedures after initial chemotherapy.
      b. **Chemotherapy** includes high-dose methotrexate, cisplatin, and doxorubicin.
      c. **Pulmonary metastases** identified at the time of diagnosis are resected if still evident after initial chemotherapy.
   6. **Prognosis.** For nonmetastatic disease, about 70% of patients are cured, and if metastatic at diagnosis, about 50% are cured. Prognosis for those who do not respond to chemotherapy or relapse is very poor.

B. **Ewing sarcoma** is a sarcoma characterized as a small, round, blue cell tumor (undifferentiated, monomorphous cell appearance).
   1. **Epidemiology**
      a. Ewing sarcoma is the **second most common malignant bone tumor.**
      b. It **most commonly occurs during adolescence. Males** are more commonly affected.
      c. It is **rare** in Asians and African Americans.
   2. **Etiology.** The cause is unknown. However, **95% have a chromosomal translocation** between chromosomes 11 and 21 (a similar translocation to that noted in PNET brain tumors).
   3. **Clinical features.** Signs and symptoms are listed in **Table 14-4,** which compares Ewing sarcoma and osteogenic sarcoma. Ewing sarcoma may occasionally develop in soft tissue instead of bone.
   4. **Diagnosis**
      a. **Diagnosis is suggested** by radiographic findings; however, similar findings are found in osteomyelitis, lymphoma, osteogenic sarcoma, and Langerhans cell histiocytosis (LCH).
      b. **MRI** of affected bone can better delineate the tumor and its local extension.
      c. **Definitive diagnosis** is by histologic evaluation of tissue obtained by open biopsy.
      d. Bone scan, chest CT scan, and bone marrow aspiration and biopsy are performed to assess for metastatic disease.
   5. **Management.** Treatment includes multiagent chemotherapy followed by surgical excision, when possible. If the lesion is not surgically resectable, radiation therapy is used for local control. Late complications of radiation therapy include pathologic fractures at the tumor site, retarded bone growth, limb length discrepancy, functional impairment, and secondary malignancy.

6. **Prognosis.** Outcome is good for local disease, with a 3- to 5-year survival rate of 80%. Prognosis is especially poor if metastases are present at diagnosis.

Table 14-4
Clinical and Radiographic Features of Osteogenic Sarcoma and Ewing Sarcoma

Feature	Osteogenic Sarcoma	Ewing Sarcoma
Site	**Metaphysis** of tubular long bones	**Flat bones and diaphysis** of tubular bones; occasionally extraosseous
	50% occur near the knee	
	Most common sites (in order): distal femur, proximal tibia, proximal humerus, proximal femur	Most common sites (in order): axial skeleton (especially pelvis), humerus, femur
Local and systemic findings	Pain, swelling, and soft tissue massSystemic symptoms uncommon	Pain, swelling, and soft tissue mass
		Fever, malaise, and weight loss
		Leukocytosis and elevated ESR
Radiographic findings	Periosteal reaction with **"sunburst"** appearance	Periosteal reaction with **"onion skin"** appearance
	Lytic; or mixed lytic and destructive changes	Destructive changes
Metastases	Occurs in 15% at presentation	Occurs in 25% at presentation
	Lungs (90%) and bone (10%)	Lungs (50%), bone (25%), and bone marrow (25%)

ESR = erythrocyte sedimentation rate.

VIII. Liver Tumors

Liver tumors include **hepatoblastoma** and **hepatocellular carcinoma**.

A. **Epidemiology**
   1. **Hepatoblastoma** is the **most common** type of liver tumor in childhood. It almost always occurs in children younger than 3 years of age. It is also associated with Beckwith–Wiedemann syndrome and familial polyposis, and is more common in children born prematurely.
   2. **Hepatocellular carcinoma** may occur in both young children and in adolescents. It is associated with **chronic active hepatitis B infection,** biliary atresia, glycogen storage disease type I, α_1-antitrypsin deficiency, and hereditary tyrosinemia.

B. **Clinical features.** Signs and symptoms are similar in liver tumors and include presentation with a **right upper abdominal mass,** loss of appetite, and weight loss. Jaundice is generally absent, and quite often patients are asymptomatic.

C. **Diagnosis.** Diagnosis is made by abdominal imaging with CT or MRI scan and finding elevation of the serum tumor marker *α-fetoprotein*.

D. **Management.** Treatment includes surgical resection, if possible, and chemotherapy. Chemotherapy may convert a previously unresectable tumor to one that is amenable to surgery.

E. **Prognosis.** Outcome depends on surgical resectability and chemosensitivity. Nonmetastatic hepatoblastoma carries a cure rate of about 75%, whereas hepatocellular carcinoma carries a cure rate of about 40%.

IX. Retinoblastoma

See Chapter 18, section VIII.B.

X. Germ Cell Tumors (Germinomas)

Germ cell tumors are rare malignancies derived from the cellular precursors of sperm and eggs.

A. **Classification is by location and degree of cell differentiation.** Germ cell tumors may be located in the **gonadal** region (i.e., testis, ovary) or in **extragonadal** regions (i.e., anterior mediastinum, sacrococcygeal area, pineal gland or suprasellar region of the brain, retroperitoneum, neck). Types of germ cell tumors include seminoma (in males), dysgerminoma (in females), teratoma, yolk sac tumor, embryonal cell carcinoma, and choriocarcinoma.

B. **Specific tumors**

1. **Teratomas** are tumors containing more than one of the three primary germ cell layers (i.e., ectoderm, mesoderm, and endoderm). Mature teratomas often contain skin, hair, or teeth, whereas immature teratomas contain fetal- or embryonal-type structures. Teratomas may be benign or malignant. Malignant potential is based on the amount of immature tissue and the presence or absence of other germ cell tumor cells within the teratoma.
    a. **Sacrococcygeal teratoma** is the **most common teratoma during the first year of life.** The majority (75%) occur in **females.** The tumor arises from the coccyx and presents as a **soft tissue mass.** Almost all (95%) are **benign.** Treatment includes surgical excision of both the tumor and the coccyx to prevent recurrence.
    b. **Anterior mediastinal teratomas** are generally **benign** and may present with signs and symptoms of **airway obstruction.**
    c. **Ovarian teratomas** are the **most common ovarian tumor** and are generally **benign.** The teratoma is suggested by the presence of calcium within the tumor on an abdominal radiograph.
2. **Testicular tumors** may be derived from germ cells or stromal cells; 70% of childhood testicular tumors are germinomas.
    a. **Epidemiology**
        1. The most common of these germinomas are yolk sac tumors (60%), followed by teratomas (15%) and, rarely, seminomas and embryonal carcinoma. (See also Chapter 3, section IX.C.1.)
        2. Peak ages are *younger than 5 years and during adolescence*.
        3. There is an association with **cryptorchid testes.**
        4. **One-third of testicular tumors in childhood are benign,** unlike in adults, in whom almost all testicular tumors are malignant.
        5. **Germ cell tumors are more common in patients with sex chromosome abnormalities.**
    b. **Clinical features.** Signs and symptoms include a solid, firm, painless testicular mass or generalized testicular swelling. Serum **α-fetoprotein is elevated** in yolk sac tumors. Malignant tumors may extend locally or may metastasize to retroperitoneal lymph nodes, lung, or liver.
    c. **Management.** Treatment is based on the tumor type and size. Treatment of yolk sac tumors involves radical orchiectomy and, if necessary, retroperitoneal lymph node dissection.
3. **Ovarian tumors** most commonly include yolk sac tumors, teratomas, and dysgerminomas.
    a. **Epidemiology**
        1. **One-third are malignant.** The younger the child, the more likely it is that the tumor will be malignant.

2. **Tumors** increase in frequency during puberty.

b. **Clinical features.** Signs and symptoms include abdominal mass, abdominal pain caused by torsion of the tumor together with the ovary, and vaginal bleeding. As with males, serum **α-fetoprotein is elevated** in yolk sac tumors in females.

c. **Management.** Treatment is based on tumor type and typically includes surgical resection, chemotherapy, and, sometimes, radiation therapy.

XI. Langerhans Cell Histiocytosis (LCH)

A. **Definition.** LCH is characterized by infiltration of organs with Langerhans cells.
B. **Etiology.** The cause is unknown. It appears that some cases represent clonal cellular proliferation, whereas others represent immunologic dysregulation.
C. **Clinical features** are highly variable.
    1. **Skeletal involvement** occurs in 80% of patients.
        a. **The skull is most commonly involved.**
        b. **Single or multiple bony lesions** may be present and may be painful, palpable, and associated with swelling.
        c. Pathologic fractures may occur.
        d. **Chronic draining ears** may indicate LCH involving the mastoid.
    2. **Skin involvement** occurs in 50% of patients. It typically manifests as **seborrheic dermatitis of the diaper area and scalp** (it mimics cradle cap) and is most common in intertriginous areas.
    3. **Pituitary** or **hypothalamic involvement** may lead to growth retardation, diabetes insipidus, hypogonadism, and panhypopituitarism.
    4. Other features include lymphadenopathy, hepatosplenomegaly, exophthalmos, anemia, and pulmonary infiltrates.
    5. **Nonspecific systemic features** are very uncommon and include weight loss, fatigue, fever, and failure to thrive.
D. **Diagnosis** is by identifying the typical histologic features on biopsy of skin or bone lesions. There are characteristic morphologic features and immunohistochemical markings.
E. **Management**
    1. Therapy is geared to abort organ destruction or dissemination.
    2. Corticosteroids and chemotherapeutics are considered standard of care. If a single lesion or organ is involved, local curettage may be used.
F. **Prognosis** varies with the extent and location of disease**.** Single lesions may spontaneously resolve after curettage. Response rate to current treatments is high. Long-term complications include growth impairment, learning problems, hearing loss, orthopedic deformities, and chronic lung disease.

Review Test

1. A 3-year-old Caucasian girl is brought to your office with a 3-week history of bruising, left elbow pain, and fever. Her white blood cell (WBC) count is 25,000 cells/mm^3. You refer her to a pediatric oncologist who performs a bone marrow aspirate, which confirms your suspicion that she has acute lymphocytic leukemia (ALL). Immunophenotyping reveals that the leukemic cells have pre–B-cell phenotype and are common acute lymphocytic leukemia antigen (CALLA) negative. In addition, the leukemic cells demonstrate hyperploidy (>53 chromosomes). Which of the following characteristics predict an unfavorable prognosis in this patient?
   A. Leukemic cells that are CALLA-negative
   B. WBC count at diagnosis <50,000 cells/mm^3
   C. Female sex
   D. Leukemic cells that demonstrate hyperploidy
   E. Age of 3 years
2. A 10-year-old girl has started induction chemotherapy for acute lymphocytic leukemia (ALL). Which of the following statements regarding the treatment of childhood ALL and its complications is correct?
   A. Remission is induced in 25% of patients.
   B. Fever associated with neutropenia is an anticipated complication of treatment and may be managed with acetaminophen alone.
   C. Intrathecal methotrexate is used only for children with an unfavorable prognosis at the time of diagnosis.
   D. Intracranial radiation is generally safe and free from side effects in children older than 1 year.
   E. Tumor lysis syndrome may include hyperkalemia, hyperphosphatemia, and hyperuricemia.
3. A 4-year-old boy has fever of unknown origin, enlargement of the spleen and liver, and gingival hypertrophy. A complete blood count shows leukemic myeloblasts. Which of the following statements regarding this patient's diagnosis is correct?
   A. Further examination would likely reveal generalized lymphadenopathy and testicular swelling.
   B. A blood smear may demonstrate Auer rods within his leukemic blasts.
   C. Evaluation of the chromosomes would reveal the Philadelphia chromosome.
   D. Bone marrow transplant is usually not necessary for treatment, given the high cure rate with standard chemotherapy.
   E. If this boy had Down syndrome, his leukemia would be very difficult to treat and would likely be fatal.
4. A 15-year-old boy has a 3-month history of fever and weight loss. Physical examination reveals posterior cervical and supraclavicular lymphadenopathy. You refer the patient to a pediatric general surgeon, who performs a lymph node biopsy. The diagnosis is Hodgkin disease. Which of the following statements regarding this diagnosis is correct?
   A. The cancer would be classified as stage IA.
   B. Airway obstruction is a common complication of this type of cancer.
   C. Associated infertility is rare.
   D. Prognosis is poor.
   E. The biopsy likely shows Reed–Sternberg cells.
5. A 6-year-old girl has a 1-month history of vomiting in the early morning on awakening, occipital headache, and an unsteady gait. Physical examination is normal with the exception of

a noticeable wide-based gait with ataxia. Although you were unable to view her optic discs to determine whether papilledema is present, you suspect that she may have a brain tumor. Which of the following statements regarding her probable diagnosis and her evaluation is correct?

A. She most likely has a high-grade astrocytoma.
B. She likely has a medulloblastoma in the infratentorial region.
C. A head computed tomography (CT) is the best imaging modality for diagnosis.
D. Combination chemotherapy and radiation therapy are the principal treatments for suspected brain tumor.
E. The cerebrospinal fluid tumor markers homovanillic acid and vanillylmandelic acid will be absent on evaluation.

6. A 15-year-old boy has a routine health maintenance examination. A firm, painless right testicular mass is found. Which of the following statements regarding a testicular tumor in this boy is correct?

A. The tumor is most likely benign.
B. Teratoma is the most common type of testicular tumor.
C. Metastasis most commonly occurs to bone.
D. A history of unilateral cryptorchid testes has put this patient at higher than usual risk for a testicular tumor.
E. Chemotherapy and radiation therapy are the most appropriate initial treatments.

7. A 7-year-old boy with a history of biliary atresia managed with a Kasai portojejunostomy performed at 5 weeks of age now presents with a 10-pound weight loss during a 4-month period. His parents state that his appetite has been very poor. Physical examination shows a mass in the right upper quadrant of the abdomen. You suspect hepatocellular carcinoma given his prior history of biliary atresia. Which of the following statements regarding this type of cancer in childhood is correct?

A. The malignancy is also associated with chronic active hepatitis B infection.
B. Careful examination of the conjunctiva would likely reveal evidence of jaundice.
C. A liver transplant is recommended because of the poor prognosis associated with this malignancy.
D. Urine catecholamines are elevated.
E. Human chorionic gonadotropin is elevated and diagnostic.

The response items for statements 8–11 are the same. You will be required to select one answer for each statement in the following set.

A. Acute myelogenous leukemia
B. Retinoblastoma
C. Burkitt lymphoma
D. Wilms tumor
E. Neuroblastoma
F. Brain tumor
G. Acoustic neuroma

For each patient with a genetic syndrome or infection, select the associated malignancy.

1. A 7-year-old African boy with a history of Epstein–Barr virus infection.
2. A 2-year-old girl with Down syndrome.
3. A 6-year-old boy with Beckwith–Wiedemann syndrome.
4. A 10-year-old boy with neurofibromatosis type 2.

The response items for statements 12–16 are the same. You will be required to select one answer for each statement in the following set.

A. Osteogenic sarcoma
B. Ewing sarcoma
C. Rhabdomyosarcoma
D. Langerhans cell histiocytosis
E. Yolk sac tumor
F. Teratoma
G. Non-Hodgkin lymphoma

For each patient, select the most likely diagnosis.

1. A 4-year-old boy with a painless, growing, soft tissue mass within the orbit, with accompanying proptosis and eyelid swelling.
2. A 14-year-old boy with a painful, growing, soft tissue mass at the distal femur. Radiography reveals periosteal elevation with a "sunburst" appearance.
3. A 5-month-old girl with a soft tissue mass in the lower portion of the back near the coccyx.
4. A 5-year-old boy with a painful, growing mass behind the right ear with chronic right ear discharge.
5. A 16-year-old girl with a painful, growing, soft tissue mass involving the right pelvis. Radiography reveals periosteal elevation with an "onionskin" appearance.

Answers and Explanations

1. **The answer is A** [Table 14-2]. Factors at the time of diagnosis that predict a favorable prognosis include female sex, age between 1 and 9 years, Caucasian race, white blood cell (WBC) count <50,000 cells/mm^3, hyperploidy of leukemic cells, absence of chromosomal translocation, and lack of involvement of the central nervous system, liver, spleen, and other organs. However, a common acute lymphocytic leukemia antigen (CALLA) negative immunophenotype is an unfavorable prognostic indicator, whereas CALLA-positive is a favorable prognostic indicator.
2. **The answer is E** [II.A.6.f]. Many complications may result from therapy for leukemia. Tumor lysis syndrome occurs when cells break apart spontaneously or after chemotherapy and release uric acid, potassium, and phosphate into the circulation. Therefore, hyperuricemia, hyperkalemia, and hyperphosphatemia may be seen. Induction chemotherapy induces remission in approximately 95% of patients. Fever associated with neutropenia is a feared complication that mandates immediate therapy with intravenous antibiotics because of the higher than usual risk of serious bacterial infection in immunosuppressed patients. Intrathecal methotrexate is administered to all patients, regardless of prognosis, during induction as prophylaxis against central nervous system involvement, and to all patients during the consolidation phase of chemotherapy. Intracranial radiation is associated with many long-term complications and should generally be avoided, if possible, in children younger than 5 years.
3. **The answer is B** [II.B.5–7]. This patient's clinical presentation and the finding of leukemic myeloblasts are consistent with the diagnosis of acute myelogenous leukemia (AML). Auer rods found within the leukemic blast cells are consistent with the diagnosis of AML. AML is generally more difficult to treat than acute lymphocytic leukemia (ALL), and remission occurs with aggressive chemotherapy in only approximately 50% of patients. Bone marrow transplant is one of the mainstays of therapy in AML. Patients with AML may present with fever, hepatosplenomegaly, bruising, bone pain, and gingival hypertrophy, but testicular involvement and lymphadenopathy are not common clinical features. The Philadelphia chromosome is found in adult-type chronic myelogenous leukemia, rather than in AML. AML associated with Down syndrome is highly treatable.
4. **The answer is E** [III.A.2–4 and Table 14-3]. Patients with Hodgkin disease most commonly present with painless lymphadenopathy, generally in the cervical or supraclavicular regions. Systemic features, such as weight loss, night sweats, and fever, may also be present. Diagnosis is proven on the basis of the finding of Reed–Sternberg cells on lymph node biopsy. From the involvement of two lymph node regions on the same side of the diaphragm and systemic features in this patient, his cancer would be classified as stage IIB, rather than stage IA (in which only one lymph node region is involved and there would be no systemic manifestations such as fever and weight loss). Airway obstruction caused by involvement of anterior mediastinal nodes is more common in non-Hodgkin lymphoma. Impaired fertility is common in Hodgkin disease. Prognosis for stage II disease is excellent.
5. **The answer is B** [IV.B–D]. The clinical presentation is consistent with a brain tumor. Between 1 and 12 years of age, infratentorial brain tumors are most common. In addition, the ataxia suggests an infratentorial tumor. Medulloblastoma, a primitive neuroectodermal tumor, is the most common infratentorial tumor and would therefore be the most likely tumor in this patient. Astrocytoma is the second most common infratentorial tumor, and brainstem glioma is the third most common infratentorial tumor. Although astrocytomas are possible tumors in the infratentorial region, they tend to be low-grade, rather than high-grade, tumors. Magnetic resonance imaging is the preferred diagnostic imaging study because of the likely cerebellar

location of the medulloblastoma. The principal treatment is surgical resection, if it is possible. The tumor markers, homovanillic acid and vanillylmandelic acid, which are secreted by medulloblastomas, are detectable in the cerebrospinal fluid.

6. **The answer is D** [X.B.2]. Cryptorchid testes (testes that fail to descend into the scrotum) are at much higher than usual risk for malignancy. Two-thirds of testicular tumors in childhood are malignant and one-third are benign. Teratomas account for approximately 15% of testicular tumors. In contrast, yolk sac tumors account for 60% of testicular tumors and are the most common testicular tumor. Management of testicular tumors is based on the tumor type, size, and presence of metastases that may involve the retroperitoneal lymph nodes, liver, or lung. Metastasis to bone is more unusual. Treatment of yolk sac tumors involves radical orchiectomy and retroperitoneal lymph node dissection, if necessary.
7. **The answer is A** [VIII.A.2]. Hepatocellular carcinoma is associated with chronic active hepatitis B infection, biliary atresia, α_1-antitrypsin deficiency, and glycogen storage disease type I. Typical presentation includes a right upper quadrant abdominal mass, weight loss, and anorexia; however, jaundice is generally absent. Liver transplant is not curative because of the high rate of metastatic disease. Diagnosis is based on findings on abdominal imaging and elevation of the serum marker α-fetoprotein. Urine catecholamines are not present, and human chorionic gonadotropin is not elevated.
8. **The answers are C, A, D, and G, respectively** [Table 14-1, II.B.2, I.B.2.b, and I.B.3]. Genetic syndromes and infections may predispose to childhood cancers. Epstein–Barr virus infection may predispose to both Hodgkin disease and non-Hodgkin lymphoma, including Burkitt lymphoma, which is endemic in Africa. Down syndrome may predispose to both acute myelogenous leukemia and acute lymphocytic leukemia. Beckwith–Wiedemann syndrome may predispose to Wilms tumor, rhabdomyosarcoma, and hepatoblastoma. Neurofibromatosis type 2 may predispose to acoustic neuroma, whereas neurofibromatosis type 1 may predispose to brain tumors and lymphoma.
9. **The answers are C, A, F, D, and B, respectively** [VI.C.1.a, Table 14-4, XI.C.1.d, and X.B.1.a]. Rhabdomyosarcoma is the most common soft tissue sarcoma and typically presents as a painless soft tissue mass. The head and neck are involved 40% of the time, and if the orbit is involved, the patient may present with proptosis, eyelid swelling, or cranial nerve palsies. Both osteogenic sarcoma and Ewing sarcoma present as painful soft tissue masses. Osteogenic sarcoma generally involves the metaphysis of tubular long bones, especially the distal femur and proximal tibia. Ewing sarcoma more commonly involves flat bones and the diaphysis of tubular bones. The axial skeleton, including the pelvis, is most commonly involved. Radiographic appearances of both osteogenic sarcoma and Ewing sarcoma reveal periosteal elevation; however, osteogenic sarcoma has a more typical "sunburst" appearance (question 13), whereas Ewing sarcoma has a more typical "onionskin" appearance (question 16). Langerhans cell histiocytosis often presents as bony lesions. If the mastoid bone is involved, a child may present with a mass behind the ear and chronic ear drainage. Sacrococcygeal teratoma, the most common teratoma in infancy, occurs as a soft tissue mass in the area of the coccyx. The majority (75%) of these teratomas occur in females.

CHAPTER 15

Allergy and Immunology

Rajashri Shuba, Iyengar

I. Anaphylaxis

A. **Definition.** Anaphylaxis is a potentially life-threatening, **acute systemic IgE-mediated reaction (**type 1 hypersensitivity). Antigen binding to IgE on the surface of primed mast cells and basophils results in the release of potent mediators that affect vascular tone and bronchial reactivity.

B. **Etiology.** Anaphylaxis is a systemic reaction that occurs most commonly to **drugs, insect venom, foods, latex, and biologic agents.**

C. **Clinical features.** Anaphylaxis involves two or more organ systems, and some cutaneous and mucosal involvement is present 90% of the time.
   1. **Pruritus, flushing, urticaria, and angioedema**
   2. **Dyspnea and wheezing**
   3. **Nausea, vomiting, diarrhea,** and crampy abdominal pain
   4. **Cardiovascular symptoms,** ranging from mild hypotension to shock

D. **Diagnosis** is on the basis of the presence of **clinical signs and symptoms,** which occur **within 30–90 minutes** after exposure to the offending agent.

E. **Management**
   1. **Epinephrine is the principal treatment** for acute respiratory and cardiovascular complications.
   2. **Systemic antihistamines, corticosteroids, and β-adrenergic agonists** are also used to treat the signs and symptoms of anaphylaxis.

II. Allergic Rhinitis

A. **Definition.** Allergic rhinitis is an **IgE-mediated inflammatory response** in the nasal mucosa to inhaled antigens.
B. **Epidemiology.** Allergic rhinitis affects 10–20% of children. It is one of the most common allergic conditions of childhood *(**Figure 15-1**)*.
C. **Etiology.** Allergic rhinitis may be seasonal or perennial.
    1. **Seasonal rhinitis** occurs in specific seasons in response to **tree, grass, or weed pollens** (e.g., tree pollen in the spring, grass pollen in the summer, ragweed pollen in the fall).
    2. **Perennial rhinitis** occurs across seasons in response to **indoor allergens,** most commonly dust mites, molds and animal dander. Molds and dust mites are associated with high-humidity indoor environments.
D. **Pathophysiology**
    1. **Sensitization** to airborne allergens induces IgE formation.
    2. **Allergen-specific IgE** binds to receptors on **mast cells** and basophils in the nasal mucosa.
    3. **Subsequent exposure (known as "priming")** produces an **IgE-mediated inflammatory response,** which occurs within minutes. **Primed mast cells degranulate** and release histamine, leukotrienes, kinins, and prostaglandins.
E. **Clinical features**
    1. **Signs and symptoms** include sneezing, nasal congestion, rhinorrhea, nasal itching, and pale nasal mucosa.
        a. **Allergic shiners** are dark circles under the eyes caused by venous congestion.
        b. **Dennie lines** are creases under the eyes as a result of chronic edema.
        c. **Allergic salute** occurs when the patient uses the palm of the hand to elevate the tip of the nose to relieve itching. This can lead to a transverse crease or line noted between the upper two-thirds and lower one-third of the nasal bridge.
    2. **Allergic rhinitis is commonly associated with** asthma, chronic sinusitis, otitis media with effusion, and nasal polyps.
F. **Diagnosis.** The diagnosis of allergic rhinitis is on the basis of **clinical signs and symptoms.**
    1. **Medical history** may include multiple episodes of otitis media, sinusitis, atopic dermatitis (eczema), and food or drug allergies.
    2. **Laboratory evaluation**
        a. **Total IgE concentration may be elevated.**
        b. **Allergen skin testing (prick or intradermal testing)**
            1. **Skin tests** using purified allergens are the **preferred method** to diagnose and identify causes of allergic rhinitis. **Radioallergosorbent (RAST) tests** can identify serum IgE antibodies to specific allergens but are not as sensitive as skin testing.
            2. **To avoid false-negative results, patients must discontinue antihistamines** 4–7 days before skin testing.
        c. **Nasal smear for cytology** may be helpful in differentiating allergic rhinitis from other disorders.
            1. **More than 10% eosinophils suggests allergic rhinitis.**
            2. **A preponderance of polymorphic leukocytes suggests an infectious cause.**
G. **Management**
    1. **Allergen avoidance** is the first step in the management of allergic rhinitis.
        a. **Avoidance measures**
            1. The **child's bedroom should be free of allergens** to the extent possible.
            2. **Remove pets** or keep them outdoors.

3. **Dust mite control measures** include the use of zippered allergen-proof mattress and pillow covers and the removal of carpets and stuffed animals from the bedroom.
4. **Reduce humidity to less than 50% to inhibit growth of dust mites and mold.**
5. **Avoid open windows** during pollen season.

b. IgE antibody production may decrease with time in the absence of continual antigen exposure.

2. **Pharmacotherapy**
   a. **Intranasal steroids** are the **most effective** class of drugs for controlling rhinitis symptoms. Side effects include local irritation, which may be minimized by careful technique of administration. Systemic absorption is minimal. The hypothalamic–pituitary–adrenal axis is not measurably affected at recommended doses.
   b. **Antihistamines**
      1. **First-generation antihistamines** (over-the-counter products [e.g., diphenhydramine]) are often first-line therapy; however, they may cause sedation and impair academic performance.
      2. **Second-generation antihistamines** (e.g., cetirizine, fexofenadine, loratadine) are **safer and better tolerated than first-generation agents but no more effective.**
      3. **Intranasal antihistamines** may be effective.
   c. **Intranasal cromolyn sodium prevents mast cell degranulation** and can be helpful.
   d. **Decongestants** (e.g., pseudoephedrine) cause vasoconstriction and relieve nasal congestion. Because **side effects include insomnia, nervousness, and rebound rhinitis,** decongestants should be used judiciously and only for short periods of time (<48–72 hours).
   e. Leukotriene receptor antagonists are emerging as effective therapy.
3. **Immunotherapy is effective** for allergic rhinitis, allergic asthma, and insect venom allergy.
   a. **The principle of immunotherapy is that repeated injections of allergens at escalating doses with time lead to better tolerance of the allergen by the patient.**
   b. **Indications**
      1. Other therapies are ineffective in controlling symptoms.
      2. Environmental controls have been tried and failed, or exposure is unavoidable.
4. **Patient education** should include written instructions to enhance compliance.

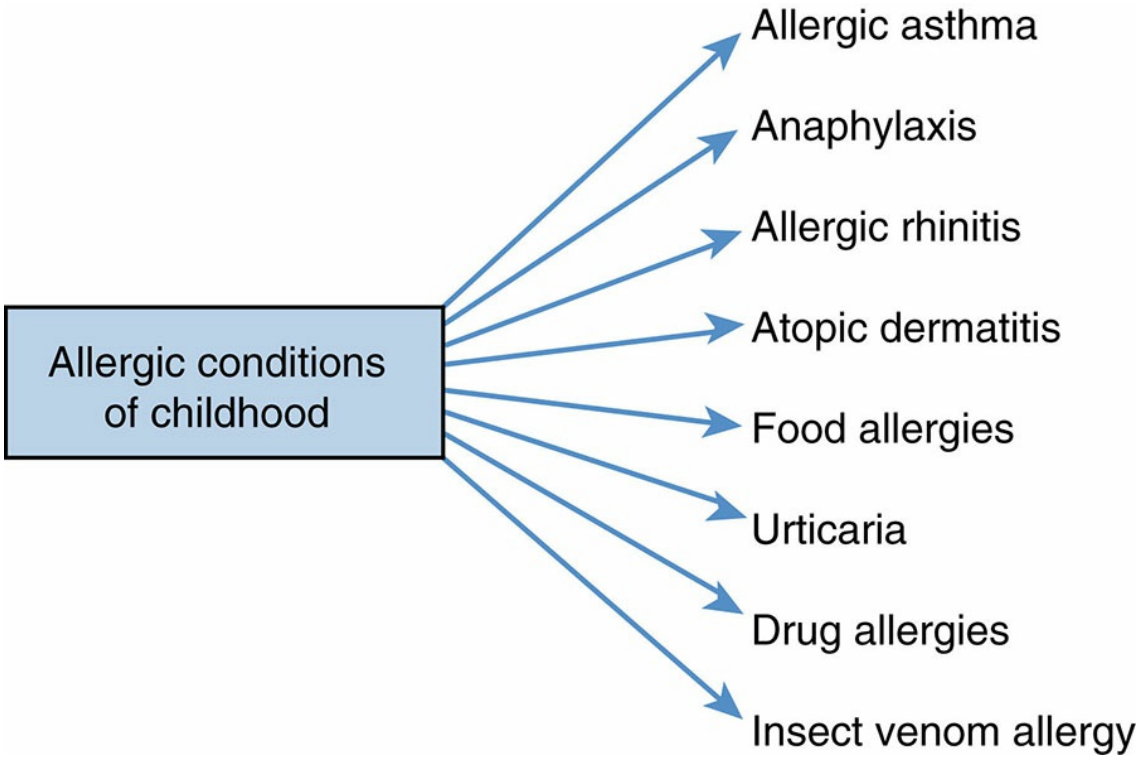

FIGURE 15-1 Allergic conditions of childhood.

III. Atopic Dermatitis

A. **Definition.** Atopic dermatitis is a **chronic inflammatory dermatitis** (also known as **eczema**) characterized by **dry skin** and **lichenification** (i.e., thickening of the skin). The skin is overly sensitive to many stimuli that produce **pruritus,** which leads to scratching, which causes many of the skin manifestations.

B. **Epidemiology**
   1. **Atopic dermatitis affects 5–8% of children.**
   2. Atopic dermatitis typically begins in early infancy, and 85% of patients have signs and symptoms before 5 years of age.
   3. Atopic dermatitis is often worse in winter (i.e., dry, cold weather) or with extremes of temperature.
   4. **Family history** commonly reveals family members with atopic dermatitis, asthma, or other allergic diseases.

C. **Clinical features**
   1. **Pruritus is universal.**
   2. **Skin manifestations** may be acute or chronic *(Table 15-1)*.
      a. **Acute changes** include **erythema, weeping and crusting,** and secondary bacterial (*Staphylococcus aureus*) or viral (herpes simplex virus) infection.
      b. **Chronic changes** include **lichenification,** dry scaly skin, and **pigmentary changes** (most commonly, hyperpigmentation; less commonly, hypopigmentation).
   3. **Clinical presentation varies with age.**
      a. **Infantile form. Truncal and facial areas, along with the scalp,** are involved. **Extensor surfaces** are more involved than flexural surfaces.
      b. **Early childhood. Flexural surfaces** are more severely involved, and **lichenification,** the **hallmark of chronic itching,** is seen.
      c. **Late childhood.** Disease may be more localized, or there may be a tendency toward remission.

D. **Diagnosis**
   1. **Three of four major criteria** should be present:
      a. **Pruritus**
      b. **Personal or family history of atopy**
      c. **Typical morphology and distribution**
      d. **Relapsing or chronic dermatitis**
   2. **Minor criteria,** such as xerosis (i.e., abnormal dryness), pruritus with sweating, wool intolerance, **dermatographism** (stroking of the skin with a dull instrument that produces a pale wheal with a red flare), or skin infections are also helpful in making the diagnosis.

E. **Management**
   1. **Known triggers,** which may include wool, foods (especially eggs, milk, and peanuts), excessive heat or cold, and harsh chemicals or soaps, should be avoided.
   2. **Low- to medium-potency topical corticosteroids** are indicated as needed on affected areas. Systemic corticosteroids are used in severe cases.
   3. **Antihistamines** may be used at bedtime to decrease the itch–scratch cycle.
   4. **Baths** should be in tepid water. After bathing, the patient should blot the skin dry with absorbent towels, and skin lubricants should be applied.

Table 15-1
Acute Versus Chronic Manifestations of Atopic Dermatitis

Acute	Chronic

Erythema	Lichenification
Weeping and crusting	Dry, scaly skin
Secondary bacterial or viral infection	Pigmentary changes

IV. Food Allergy

A. **Definition.** Food allergy is an **IgE-mediated** response to food antigens.
B. **Etiology.** *Most allergic reactions* to food (85–90%) are caused by **egg, milk, peanut, tree nuts, soy, wheat, and fish.**
C. **Clinical features**
    1. **Skin involvement** such as **acute urticaria and angioedema (approximately 90% of reactions)**
    2. **Oral symptoms** such as itching and swelling of the lips, tongue, or throat
    3. **Gastrointestinal (GI) symptoms** such as nausea, vomiting, diarrhea, and abdominal pain
    4. **Respiratory symptoms** such as nasal congestion, rhinorrhea, sneezing, and wheezing
    5. **Key point: When these symptoms involve two or more organ systems (i.e., skin and GI tract), the reaction is called anaphylaxis.**
D. **Diagnosis**
    1. **History** should elicit the types of symptoms, the timing of symptoms in relation to food ingestion, and the reproducibility and severity of symptoms. Histories are often not specific, and there may be confusion between a true immediate allergic reaction (IgE-mediated) and a late reaction to a food (non-IgE mediated).
    2. **Laboratory evaluation**
        a. **Skin tests** may be helpful in identifying foods responsible for IgE-mediated hypersensitivity reactions.
        b. **RAST tests** identify serum IgE antibodies to specific food antigens.
    3. **Provocative oral food challenge** is necessary to determine whether a patient has true food hypersensitivity. **Double-blind placebo-controlled food challenge is the gold standard.**
E. **Management**
    1. **Strict avoidance** of the responsible food allergen is the best therapy.
    2. **Injectable epinephrine** should be carried by food-allergic patients who have a history of severe reactions to foods.

V. Insect Venom Allergy

A. **Definition.** Insect venom allergy is an **IgE-mediated** response to the venom of stinging or biting insects.
B. **Etiology.** The venom of many insects, including yellow jackets, hornets, wasps, bees, and fire ants, may cause allergic reactions.
C. **Clinical features** range from localized erythema and swelling to urticaria and to anaphylaxis.
D. **Management**
    1. **Local skin reactions** can be treated with cold compresses, analgesics, and antihistamines.
    2. **Diffuse urticaria** can be treated with antihistamines, but may require treatment with systemic cortico steroids.
    3. **Anaphylaxis** can be treated as described in section I.E.
    4. **Immunotherapy** is effective.

VI. Urticaria (Hives)

A. **Definition.** Urticaria is **circumscribed, raised, evanescent (vanishing) areas of edema and erythema that are almost always pruritic.** Hives are usually symmetric and **migratory.**

B. **Etiology.** The **causes of urticaria** are extensive, and some are listed in *Table 15-2*.

C. **Classification.** There are two types of urticaria.

1. **Acute urticaria** is often precipitated by exercise, heat, cold, pressure, occupational exposure, medications, insect bites, foods, or recent infections. Health care workers and patients with **myelomeningocele** (who are commonly exposed to latex because of the need for repeated urinary catheterization) are at risk for **latex allergy,** which can present as urticaria.
2. **Chronic urticaria (urticaria that lasts >6 weeks)** may be associated with **underlying conditions** such as malignancy and rheumatologic diseases. A substantial proportion of patients with chronic urticaria have an **IgG antibody to the IgE receptor.**

D. **Management.** The **precipitating factor should be avoided,** if it can be identified.

1. **Antihistamines** are the mainstays of therapy.
2. **Further evaluation** for underlying systemic disease is indicated in patients with chronic urticaria, especially if the urticaria is associated with other symptoms such as fever, arthralgias, weight loss, or abdominal pain.

Table 15-2
Causes of Urticaria

Acute	Chronic
Drugs	Malignancy
1. Penicillin	Rheumatologic disease 1. Systemic lupus erythematosus 2. Rheumatoid arthritis
1. Aspirin	
1. Nonsteroidal anti-inflammatory drugs	
Foods and food additives	1. IgG antibodies to IgE receptors 2. Idiopathic 3. Thyroid disease
1. Eggs	
1. Shellfish	
1. Milk	
1. Nuts	
Contactants	
1. Animal dander	
1. Latex	
Idiopathic	
Infection	

1. Group A β-hemolytic streptococcal pharyngitis	
1. Infectious mononucleosis	
1. *Mycoplasma pneumoniae*	
1. Hepatitis	
1. Coxsackievirus	
Insect venoms	
Transfusion reaction	
Heat and cold	
Skin pressure	
Exercise	

VII. Drug Allergy

A. **Definition.** Reactions to drugs are **mediated by IgE or by direct mast cell degranulation (**also known as **"anaphylactoid"**).

B. **Etiology.** *Many pharmaceutical agents* have been documented to cause allergic reactions or anaphylaxis. The most common offending agents include **penicillin,** sulfonamides, cephalosporins, **aspirin and other nonsteroidal anti-inflammatory drugs,** and narcotics**.**

C. **Clinical features include urticaria, angioedema, and anaphylaxis.** (Angioedema is a vascular reaction of the deep dermis or subcutaneous tissue, associated with localized edema from dilated capillaries with increased permeability, and characterized by giant wheals.)

D. **Diagnosis** is made by clinical features and history of drug ingestion.

E. **Management**

1. **Antihistamines** may be effective.
2. **Anaphylaxis** should be treated as described in section I.E.
3. **Medical alert bracelets** should be worn by patients with previously identified significant drug reactions.

VIII. Asthma

Asthma (see , section IV.A) may be precipitated by an allergic cause in some patients.

IX. Immunology Overview

A. **Main components of the immune system.** The immune system is a complex organization of cells and molecules that serves to protect the host from infection. The components of the immune system can be divided functionally into innate and adaptive components.
   1. **Innate responses** are the first defense against infection. The cells and molecules of the innate system include **phagocytic cells, natural killer cells, toll-like receptors, mannose-binding protein, and the alternative pathway of complement.**
   2. **Adaptive responses** develop more slowly, are highly specific, and improve with repeated exposure to an antigen. The adaptive system includes **T cells, B cells, and immunoglobulin molecules.**

B. **Immunodeficiency states may be primary or secondary** *(Table 15-3)*.

C. In the evaluation of a patient with a suspected immunodeficiency, there are a variety of diagnostic tests used to identify the type of primary immunodeficiency state *(Table 15-4)*.

Table 15-3
Categories of Immunodeficiency States

Primary	B-cell defects (disorders of humoral immunity)
T-cell defects (disorders of cell-mediated immunity)	
Disorders of granulocytes	
Complement deficiencies	
Secondary	Acquired immunodeficiency syndrome (AIDS)
Medications (steroids, chemotherapy)	
Malnutrition	
Nephrotic syndrome	

Table 15-4
Laboratory Evaluation of Primary Immunodeficiency States

Type of Test	Cells Being Tested	Types of Recurrent Infections Seen	Specific Tests
Humoral immunity	B cells	Bacterial (i.e., recurrent otitis media, pneumonia, sinus infection, meningitis)	Quantitative immunoglobulin levels (e.g., IgG, IgA, IgM, IgE)
B-cell subsets			
Antibody titers to immunization (diphtheria, tetanus)			
Isohemagglutinin titers (antibodies to polysaccharides of gut flora that cross-react to red blood cell [RBC] antigens and are a marker for a defect in antibody production)			
Cell-mediated immunity	T cells	Severe viral, fungal, and opportunistic infections	Peripheral smear (to look for lymphopenia)
Anergy panel (delayed type hypersensitivity skin testing)			
T-cell subsets (CD3, CD4, CD8)			
In vitro T-cell proliferative responses to mitogens and antigens			
Phagocyte function	Neutrophils	Skin infections	Peripheral smear (to look for neutropenia)
Dihydrorhodamine (DHR) flow cytometry test			
Measurements of neutrophil chemotaxis			
Complement	Complement	Encapsulated organisms such as *Haemophilus influenzae*, *Streptococcus pneumonia*, and	Total hemolytic complement (CH_{50})

		Neisseria species		
Components	Assays of specific components of complement			

X. Disorders of Lymphocytes (Figure 15-2)

Abnormalities of B cells and T cells may lead to **deficiencies of antibody production, T-cell function, or both.** Whereas pure B-cell defects are uncommon, **hypogammaglobulinemia** is a feature of most disorders involving lymphocyte function. Thus, 75% of all primary immunodeficiency diseases involve abnormalities of antibody concentration or function.

A. **IgA deficiency**
   1. **Definition. Selective IgA deficiency** is characterized by **serum IgA concentrations <7 mg/dL** but usually normal levels of other immunoglobulin isotypes. However, IgA deficiency may be associated with other defects in many patients. Fifty percent of patients with IgA deficiency have IgG deficiency and 20–30% have IgG_2 and IgG_4 subclass deficiencies.
   2. **Epidemiology. IgA deficiency is the most common immune deficiency,** with a prevalence of 1 in 500–1000.
   3. **Etiology.** A genetic basis for IgA deficiency is sometimes present, but for most patients, the precise cause is usually unclear.
   4. **Clinical features**
      a. **Respiratory infections,** such as sinusitis, pneumonia, and otitis media
      b. **GI manifestations,** such as chronic diarrhea and infection with *Giardia lamblia*
      c. **Autoimmune and rheumatic diseases,** such as systemic lupus erythematosus, juvenile rheumatoid arthritis, and celiac disease may be associated with IgA deficiency.
      d. **Atopic diseases,** such as allergic rhinitis, eczema, urticaria, and asthma, may occur in up to 50% of patients with IgA deficiency.
   5. **Diagnosis. Quantitative measurement of serum immunoglobulins,** which reveals the deficiency of IgA (<7 mg/dL), is the basis of diagnosis.
   6. **Management.** IgA cannot be replaced; thus **management of infections and other complications** are the mainstays of therapy. Intravenous immune globulin (IVIG) is not indicated (it contains almost all IgG). Patients with IgA deficiency can mount an antibody reaction to IgA and therefore should receive blood transfusions without IgA.

B. **Common variable immunodeficiency**
   1. **Definition.** This heterogeneous group of disorders is characterized by **hypogammaglobulinemia.** Most patients have normal numbers of B and T cells but have variable degrees of T-cell dysfunction. Most commonly diagnosed in patients who present with **infections occurring after infancy** when the protective maternal antibodies decrease. This is unlike severe combined immunodeficiency disease (SCID) which usually presents in the first few months of life [see section X.C].
   2. **Epidemiology.** Most cases are sporadic, with prevalence between 1 in 10,000 and 1 in 100,000.
   3. **Etiology.** A variety of defects in B-cell function or in B cell–T cell interaction can produce the clinical picture of common variable immunodeficiency. The genetic basis of this disorder is largely unknown, but a number of genetic defects have recently been elucidated.
   4. **Clinical features**
      a. **Respiratory infections** (frequently caused by *Haemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae*) and **GI infections** accompanied by chronic diarrhea (often caused by *G. lamblia* and *Campylobacter jejuni*)
      b. **Autoimmune disorders,** such as rheumatoid arthritis, autoimmune thyroiditis, autoimmune thrombocytopenia, and autoimmune hemolytic anemia

c. **Increased risk of malignancy**

5. **Diagnosis**
   a. **Quantitative immunoglobulin measurement** shows decreased serum immunoglobulin concentrations.
   b. **Diminished antibody function** may be assessed by measuring titers generated in response to childhood immunizations (i.e., diphtheria, tetanus, and pneumococcus).
   c. T-cell proliferation to mitogens (nonspecific stimulators of lymphocyte production) may be diminished.
6. **Management**
   a. **Monthly IVIG** replacement
   b. **Aggressive management of infections** with antibiotics
   c. **Chronic diarrhea management** including nutritional support

C. **SCID**

1. **Definition.** SCID is a group of inherited disorders characterized by profoundly **defective T-cell and B-cell function.**
2. **Etiology.** More than 12 distinct genetic abnormalities that produce SCID have been identified.
   a. **X-linked SCID,** caused by deficiency of the common gamma chain of the receptor for cytokines interleukin (IL)-2, IL-4, IL-7, IL-9, and IL-15, accounts for about 50% of all cases of SCID.
   b. **Autosomal recessive SCID** is caused by a variety of genetic defects involving T-cell ontogeny or function. Adenosine deaminase deficiency accounts for approximately 30% of cases of autosomal recessive SCID.
3. **Clinical features**
   a. Increased susceptibility to **infection within the first few months of life** with common pathogens and with opportunistic organisms, such as *Candida albicans* and *Pneumocystis jirovecii*
   b. **Chronic diarrhea** and **failure to thrive** are common.
4. **Diagnosis**
   a. **Persistent lymphopenia** (<1500 lymphocytes/mL) is a nearly constant feature in patients with SCID.
   b. **Enumeration of lymphocyte populations** by flow cytometry shows decreased numbers of T-cells.
   c. **Quantitative measurement of serum immunoglobulins** shows severe hypogammaglobulinemia.
   d. **T-cell responses to mitogens and antigens** are severely depressed.
5. **Management**
   a. **Supportive care** with appropriate antibiotics, nutritional interventions, and psychosocial support is necessary.
   b. **Blood products should be irradiated** to prevent graft-versus-host disease.
   c. **Monthly IVIG replacement** is administered to maintain a normal serum IgG level.
   d. ***P. jirovecii* pneumonia (PCP) prophylaxis** with trimethoprim–sulfamethoxazole is indicated.
   e. **Bone marrow transplant can be curative.** Complications include graft-versus-host disease, infection, and medication toxicity. Other options include cord blood stem cell or peripheral blood stem cell transplant.
   f. **Gene therapy** is a potential future cure.

D. **Ataxia telangiectasia**

1. **Definition.** Ataxia telangiectasia is an **autosomal recessive** disorder characterized by **combined immunodeficiency, cerebellar ataxia, oculocutaneous telangiectasias, and**

predisposition to malignancy.

2. **Etiology.** Ataxia telangiectasia results from a mutation of a gene on the long arm of **chromosome 11.** The gene product is involved in cell cycle control, DNA recombination, and cellular responses to DNA damage.
3. **Clinical features**
    a. **Variable degrees of immunodeficiency** that most commonly manifests as **chronic sinopulmonary infections**
    b. **Severe progressive cerebellar ataxia** that results in a need for wheelchair assistance by early adolescence in most patients
    c. **Telangiectasias** that appear on the bulbar conjunctiva between 2 and 5 years of age and later on exposed skin and areas of trauma
    d. **High risk of malignancy,** particularly lymphoma and carcinoma, owing to defects in DNA repair
    e. **Other clinical features** such as café-au-lait spots, vitiligo, prematurely gray hair, and multiple endocrine abnormalities
4. **Diagnosis**
    a. **Quantitative measurement of serum immunoglobulins** reveals IgG deficiency in 85% of patients and IgA deficiency in 75% of patients.
    b. **Evaluation of T-cell function** may reveal skin test anergy and diminished T-cell proliferation to mitogens.
5. **Management**
    a. **Treat the neurologic complications**
    b. **Aggressively treat infections**
    c. **Monitor for malignancies**
    d. **Avoid ionizing radiation,** which exacerbates DNA breakage and repair, thus increasing the risk of malignancy.

E. **DiGeorge syndrome** is a congenital immunodeficiency syndrome characterized by **c**ardiac defects, **a**bnormal facies, **t**hymic hypoplasia, **c**left palate, and **h**ypocalcemia because of a **submicroscopic deletion** on **chromosome arm 22q11 (mnemonic: CATCH-22).** See , section IV.D.1.

F. **Wiskott–Aldrich syndrome**
1. **Definition.** Wiskott–Aldrich syndrome is an **X-linked** disorder characterized by **combined immunodeficiency, eczema, and congenital thrombocytopenia** with small platelets.
2. **Etiology.** Wiskott–Aldrich syndrome is caused by the mutation of a gene on the **short arm of the X chromosome.** The gene product is important in T-cell receptor signaling and cytoskeletal organization.
3. **Clinical features**
    a. **Susceptibility to infections with encapsulated organisms, such as *H. influenzae* and *S. pneumoniae*,** because patients do not produce antibodies to polysaccharide antigens.
    b. **Thrombocytopenia characterized by small defective platelets.** Bleeding episodes are frequent and are associated with a risk of intracranial hemorrhage.
    c. **Eczema,** which predisposes to skin infections
4. **Diagnosis**
    a. **Complete blood count** reveals **thrombocytopenia and small platelets.**
    b. **Decreased IgM** is demonstrated by measurement of immunoglobulins.
    c. **Antibody response to polysaccharide antigens** (i.e., polysaccharide vaccines) **is diminished.**
    d. **Cellular immune function is defective** and **anergy** is present. Patients have near-

normal numbers of T cells, but they respond poorly to antigens and **do not develop antigen-specific cytotoxic T cells.**

5. **Management**
    a. **Human leukocyte antigen (HLA)—matched bone marrow transplantation is the therapy of choice.**
    b. **IVIG** is administered for hypogammaglobulinemia.
    c. **Splenectomy** cures the thrombocytopenia in more than 90% of patients. Quality of life is improved, and medical management is simplified. **Prophylactic antibiotics or IVIG must be administered regularly after splenectomy.**

G. **X-linked (Bruton) agammaglobulinemia**

1. **Definition.** X-linked agammaglobulinemia is characterized by **severe hypogammaglobulinemia and a paucity of mature B cells (<1% B cells in peripheral blood) with normal T-cell number and function.**
2. **Etiology.** X-linked agammaglobulinemia is due to mutations in the **Bruton tyrosine kinase (*BTK*) gene** on the X chromosome. The *BTK* gene is critical to normal B-cell ontogeny. Mutations lead to a block in the development from pre–B cell to mature B cell.
3. **Clinical features.** Increased susceptibility to **infections with encapsulated bacteria** (*S. pneumoniae, H. influenzae, S. aureus)* and chronic enteroviral infection may occur.
4. **Diagnosis**
    a. **Quantitative immunoglobulin** measurement reveals profound decreases in all immunoglobulin isotypes.
    b. **B cells are absent** or greatly diminished.
    c. **T cells are present,** and cell-mediated functions are preserved.
    d. **Mutations in the *BTK* gene** are demonstrated by mutation analysis.
5. **Management.** Treatment includes **monthly IVIG replacement** to prevent infection.

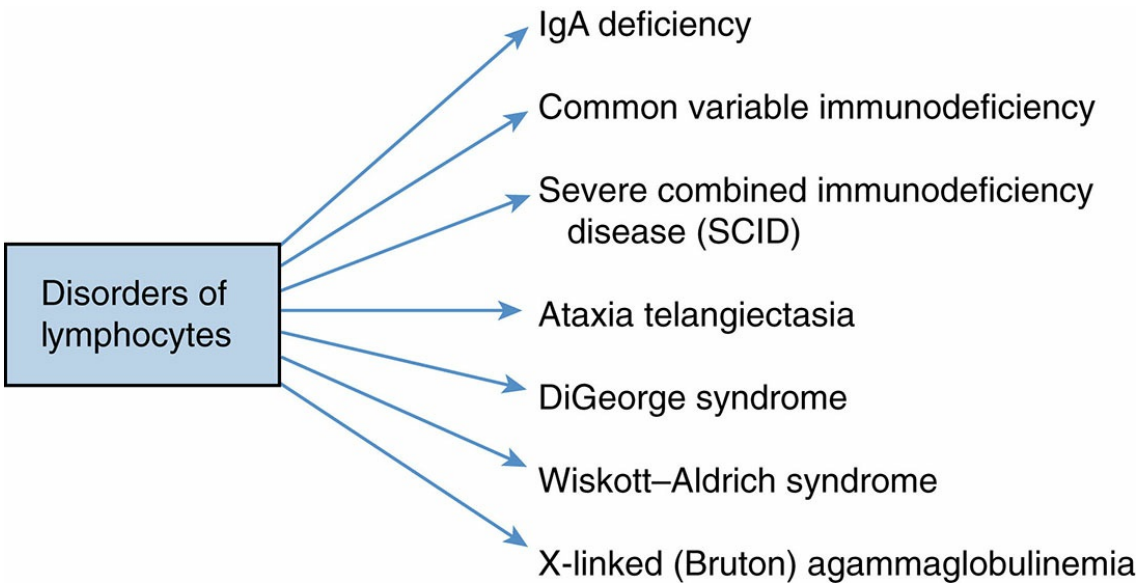

FIGURE 15-2 Disorders of lymphocytes.

XI. Disorders of Granulocytes (Figure 15-3)

A. **Chronic granulomatous disease (CGD)**
   1. **Definition.** CGD is a group of disorders characterized by **defective neutrophil oxidative metabolism** as a result of defects in the multicomponent-reduced nicotinamide–adenine dinucleotide phosphate (NADPH) oxidase system. Defective oxidative metabolism results in **severely impaired intracellular killing of catalase-positive bacteria and some fungal pathogens.**
   2. **Etiology.** The inheritance of CGD is predominantly **X-linked** (70%).
   3. **Clinical features**
      a. **Increased susceptibility to infections** involving the lungs, lymph nodes, liver, spleen, bones, and skin. **Abscess formation** is characteristic.
      b. **Major pathogens** include *S. aureus, Pseudomonas aeruginosa, Salmonella* species, *Klebsiella pneumoniae, Serratia marcescens, Escherichia coli, C. albicans,* and *Aspergillus* species.
   4. **Diagnosis.** Tests demonstrate defective neutrophil oxidative burst. The **nitroblue tetrazolium (NBT)** test was the classic test and has been replaced by the **dihydrorhodamine (DHR) flow cytometry test.**
   5. **Management**
      a. **Abscesses** often require surgical drainage and antibiotics.
      b. **Prophylactic trimethoprim–sulfamethoxazole** reduces the incidence of serious infections.
      c. **Prophylactic itraconazole** reduces the incidence of *Aspergillus* infections.
      d. **Interferon-**γ is given prophylactically.
      e. **Bone marrow transplantation** is curative.
      f. **Gene therapy** is a potential future cure.

B. **Disorders of adherence and motility**
   1. **Shwachman–Diamond syndrome.** This syndrome is an autosomal recessive condition characterized by **decreased neutrophil chemotaxis, neutropenia, and pancreatic exocrine insufficiency.** Patients present with **recurrent soft tissue infection, chronic diarrhea, short stature and failure to thrive.** (See also , section V.B.6.)
   2. **Chédiak–Higashi syndrome.** This syndrome is characterized by variable **neutropenia and thrombocytopenia** and *giant lysosomal granules in neutrophils*. Neutrophils and monocytes have functional defects, and natural killer cell function is impaired. ***S. aureus*** causes the majority of infections. Patients also have **partial oculocutaneous albinism** (see also , section V.B.5.a).
   3. **Lymphocyte adhesion defects** (LAD). This is a clinical syndrome characterized by **delayed umbilical cord separation and skin healing, leukocytosis**, (with elevated neutrophil counts of 20,000–100,000/dL), **gingival inflammation,** as well as **recurrent necrotic infections of skin, mucous membranes**, and **GI tract.** Despite the leukocytosis, few leukocytes are found in the large ulcerative lesions because of defect in neutrophil migration due to the absence of an adhesion molecule (lymphocyte function-associated antigen 1 [LFA-1]).

C. **Neutropenia** is discussed in , section V.

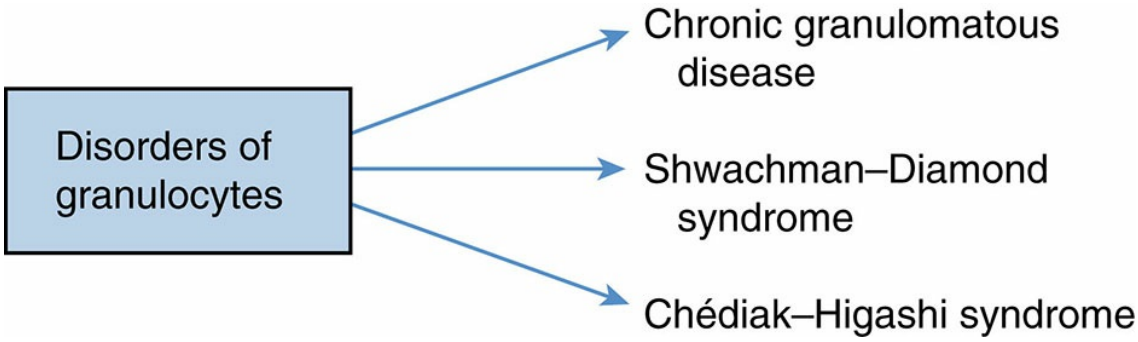

FIGURE 15-3 Disorders of granulocytes.

XII. Disorders of the Complement System

The complement system is composed of **plasma proteins and cellular receptors** functioning in an integrated series of reactions to prevent infections.

A. **Definition.** These disorders involve absence or dysfunction of individual complement components or regulatory proteins.
B. **Etiology.** Complement deficiencies are genetically determined. **Most are autosomal recessive.**
C. **Clinical features** are **variable** and depend on the biologic function of the components that are deficient.
    1. **Deficiencies of the early components** of the classic pathway (C1q, C2, and C4) are associated with **autoimmune diseases**, such as systemic lupus erythematosus.
    2. **Deficiencies of the late components** of the classic pathway (C5, C6, and C8) are associated with increased susceptibility to disseminated **meningococcal and gonococcal infections.**
    3. **Deficiency or dysfunction of C1 esterase inhibitor causes hereditary angioedema.** Patients may experience episodic swelling of various body parts, especially the hands and feet. The bowel wall may also swell, leading to severe abdominal pain. Angioedema affecting the airway can be fatal.
D. **Diagnosis**
    1. **Quantitative.** Specific assays measure levels of specific components.
    2. **Qualitative.** A normal **total serum hemolytic complement (CH_{50})** indicates that all components of the classic complement pathway are present and functional.
E. **Management**
    1. **Prompt diagnosis and treatment** of bacterial infections
    2. **Management of autoimmune disease**
    3. **Therapy with fibrinolysis inhibitors and attenuated androgens** (such as danazol) for hereditary angioedema

Review Test

1. An 8-year-old boy presents to the emergency department in acute severe respiratory distress after being stung by a bee. Vital signs are notable for a respiratory rate of 60 breaths/minute, heart rate of 120 beats/minute, and a blood pressure of 70/50 mm Hg. Physical examination shows severe respiratory distress, wheezing, and a diffuse urticarial eruption on the trunk and extremities. Which of the following is the best initial treatment for this patient?
   A. Antihistamines
   B. Systemic corticosteroids
   C. Epinephrine
   D. β-Adrenergic agonists
   E. Inhaled corticosteroids
2. A 10-year-old girl presents with a history of chronic rhinorrhea, nasal itchiness, and sneezing. Physical examination reveals dark circles under her eyes and pale boggy nasal mucosa. Which of the following categories of medications is the most effective for controlling this patient's signs and symptoms?
   A. First-generation antihistamines
   B. Second-generation antihistamines
   C. Intranasal steroids
   D. Intranasal cromolyn sodium
   E. Decongestants
3. During a routine health maintenance visit, the mother of a 1-year-old girl is particularly concerned about the family's history of food allergies. Which of the following are most likely to cause food allergic reactions?
   A. Soy
   B. Citrus fruits
   C. Chocolate
   D. Tomatoes
   E. Cruciferous vegetables such as broccoli, brussels sprouts, cabbage, and cauliflower
4. The parents of a 5-year-old boy are concerned that their son may have food allergies. On two separate occasions, he exhibited a transient erythematous papular itchy rash and a stuffy nose within several hours after eating fish. Which of the following is the most definitive method for diagnosis of food allergy?
   A. Skin tests using extracts from the suspected offending food
   B. Radioallergosorbent testing (RAST) to identify IgE-specific food antibodies
   C. Double-blind, placebo-controlled provocative oral food challenge
   D. Total serum IgE measurements
   E. Parental reports of the suspected food allergy
5. A 12-year-old girl presents with a 9-month history of chronic diarrhea and an increased susceptibility to infections. During this period, she has had two episodes of pneumonia and multiple prolonged episodes of diarrhea. Physical examination is normal. You suspect an immunodeficiency disorder. Laboratory evaluation reveals normal numbers of B cells and platelets; decreased serum concentrations of IgG, IgA, and IgM; low antibody titers in response to immunizations; and poor T-cell function. The total serum hemolytic complement (CH_{50}) is normal. Which of the following is the most likely diagnosis?
   A. Severe combined immunodeficiency disease
   B. Common variable immunodeficiency disease
   C. Chronic granulomatous disease
   D. Complement deficiency

E. Wiskott–Aldrich syndrome

6. A 4-year-old boy presents with a one-day history of fever (temperature up to 103°F [39.4°C]), a stiff neck, and altered mental status. Gram stain of the cerebrospinal fluid shows Gram-negative bacteria. His parents are concerned because he was also hospitalized with meningococcal sepsis at 2 months of age. Which of the following immunodeficiency disorders is the most likely diagnosis?
   A. Chédiak–Higashi syndrome
   B. Chronic granulomatous disease
   C. Selective IgA deficiency
   D. Ataxia telangiectasia
   E. Complement deficiency
7. A 1-year-old boy has a history of multiple episodes of otitis media, sinusitis, and pneumonia. He has not had any fungal, protozoan, or mycobacterial infections. You suspect a disorder of humoral immunity. Which of the following is the best initial screening test?
   A. Dihydrorhodamine (DHR) flow cytometry test
   B. Quantitative serum immunoglobulins
   C. Examination of the peripheral blood smear
   D. Total hemolytic complement (CH_{50})
   E. Anergy panel
8. A 10-year-old boy presents with rhinorrhea, sneezing, and an early morning cough, which is present throughout the year. He sleeps with a collection of stuffed monkeys, and his bedroom is carpeted. There are no pets in the household. Physical examination reveals Dennie lines and an allergic salute. Nasal smear shows 90% eosinophils. Which of the following is the most likely cause of his allergies?
   A. Dust mites
   B. Tree pollens
   C. Weed pollens
   D. Molds
   E. Grasses
9. A 1-year-old girl has erythema and dry patches on her trunk, face, scalp, and extensor surfaces. She scratches frequently and seems sensitive to wool. Her parents also note that at times her cheeks get red, cracked, and weepy. Which of the following is the most likely diagnosis?
   A. Early childhood eczema
   B. Infantile eczema
   C. Idiopathic urticaria
   D. Drug allergy

The response options for statements 10–13 are the same. You will be required to select one answer for each statement in the following set.

A. Ataxia telangiectasia
B. Deficiencies of the early components of the complement cascade
C. Deficiencies of the late components of the complement cascade
D. Adenosine deaminase deficiency
E. Shwachman–Diamond syndrome
F. DiGeorge syndrome
G. Chronic granulomatous disease
H. Wiskott–Aldrich syndrome

For each patient, select the most likely diagnosis.

1. A 1-year-old boy with a history of recurrent pneumonia, chronic diarrhea, and failure to thrive has a white blood cell count of 1500 cells/mm^3.
2. A 2-year-old boy with a history of recurrent cervical adenitis and pneumonia presents with a perianal abscess.
3. An 18-month-old boy has a history of recurrent pneumococcal pneumonia, severe eczema, and a petechial rash on her trunk and face.
4. A 3-month-old boy with a history of chronic diarrhea and failure to thrive presents with *Pneumocystis carinii* pneumonia.

Answers and Explanations

1. **The answer is C** [I.E]. This patient's clinical presentation is consistent with anaphylaxis, a life-threatening, acute IgE-mediated reaction that occurs within 30–90 minutes after exposure to an offending agent. The most common causative agents are foods, drugs, insect venoms, latex, and biologic agents. Immediate administration of epinephrine is the principal initial treatment indicated for the hypotension, wheezing, and respiratory distress. Antihistamines, systemic corticosteroids, and β-adrenergic agonists are additional treatments for anaphylaxis. Inhaled corticosteroids are not helpful.
2. **The answer is C** [II.G.2]. The diagnosis of allergic rhinitis is made on the basis of the clinical signs and symptoms, which often include sneezing, nasal congestion, rhinorrhea, nasal itchiness, pale nasal mucosa, and allergic shiners (dark circles under the eyes caused by venous congestion). Intranasal steroids are the most effective therapy for allergic rhinitis. First-generation antihistamines (sedating) and second-generation antihistamines (nonsedating) are also frequently very effective. Intranasal cromolyn sodium is an alternative therapeutic option. Decongestants may cause insomnia, agitation, and rebound rhinitis; therefore, they should only be used for short periods.
3. **The answer is A** [IV.B]. Egg, milk, peanut, tree nuts, soy, wheat, and fish cause 85–90% of food allergies in children. Although allergies to citrus fruits, chocolate, and tomatoes may occur, these foods do not commonly induce allergy. Cruciferous vegetables are unlikely to cause food allergy reactions.
4. **The answer is C** [IV.D]. Provocative food challenges, which should be double-blinded and placebo-controlled, are the most definitive tests to confirm the cause of food allergy reactions. Skin tests and radioallergosorbent tests (RAST) can be helpful in evaluating food allergy but are not definitive. Total serum IgE is not specific and is therefore not helpful. Parental reports of suspected food allergy are helpful but are neither specific nor definitive. Parents may confuse food allergy with a non-IgE mediated late reaction to food.
5. **The answer is B** [X.B.1, X.B.4, and X.B.5]. This patient's clinical presentation and laboratory findings are most consistent with common variable immunodeficiency disease. Patients with common variable immunodeficiency disease have increased susceptibility to respiratory and diarrheal infections. Laboratory evaluation shows variable degrees of hypogammaglobulinemia and T-cell dysfunction. Most have normal B-cell and T-cell numbers. Patients with severe combined immunodeficiency disease tend to present early in infancy with repeated infections, chronic diarrhea, and failure to thrive. Chronic granulomatous disease is a disorder of neutrophils and involves defective oxidative metabolism. It classically presents with abscesses and multiple infections. Complement deficiency is ruled out by the normal total hemolytic complement (CH_{50}). Wiskott–Aldrich syndrome is characterized by thrombocytopenia and is therefore ruled out by the normal platelet count.
6. **The answer is E** [XII.C.2]. This patient's clinical presentation suggests complement deficiency, particularly a deficiency of one of the late components of the classic complement pathway (C5, C6, C8). Patients with deficiencies of late complement components often present with meningococcal sepsis or meningitis. Chédiak–Higashi syndrome is characterized by neutropenia, thrombocytopenia, and partial oculocutaneous albinism. The majority of infections are caused by *Staphylococcus aureus.* Patients with chronic granulomatous disease tend to present with infections of the skin, bone, lymph nodes, and liver as a result of *S. aureus*, *Aspergillus,* and Gram-negative enteric organisms. Selective IgA deficiency presents with respiratory and gastrointestinal illnesses. Patients with ataxia telangiectasia present with cerebellar ataxia, telangiectasias on the bulbar conjunctiva and later on the skin, and chronic

sinopulmonary infections.

7. **The answer is B** [Table 15-4 and X.A.5]. Most primary immunodeficiency diseases involve abnormalities of immunoglobulin concentration or function (humoral immunity). The hallmark of immunoglobulin deficiency is increased susceptibility to sinopulmonary infections caused by encapsulated bacteria. Serum immunoglobulin concentrations should be measured in such patients. The dihydrorhodamine (DHR) flow cytometry test is used to diagnose chronic granulomatous disease, a disorder of phagocyte oxidative metabolism. Examination of the peripheral smear can yield valuable information about neutropenia, lymphopenia, or thrombocytopenia, which is useful and adjunctive but does not provide a definitive diagnosis. Total hemolytic complement assays are useful to exclude isolated deficiencies of complement components. Sinopulmonary infections are generally not associated with complement deficiency. Anergy panels are used to evaluate cell-mediated immune function.
8. **The answer is A** [II.C.2 and II.G.1]. Allergic rhinitis symptoms that are present throughout the year (perennial rhinitis) suggest indoor allergens; the most common are dust mites and animal dander. This patient would benefit from allergy control measures in his bedroom, such as removing the stuffed animals and carpet. Tree pollen, weed pollen, and grasses are associated with seasonal allergies. Molds are associated with high-humidity indoor environments.
9. **The answer is B** [III.C.3]. Involvement of extensor surfaces and cheeks is characteristic of the infantile presentation of eczema. Common triggers include wool, foods, harsh chemicals, and extremes of temperature. Early childhood eczema typically involves the flexural surfaces, especially the elbows and knees. Urticaria is well-circumscribed, raised transient itchy areas of edema that may move. Drug allergy is usually related to pharmaceutical agents such as penicillins and nonsteroidal anti-inflammatory drugs. Urticaria, angioedema, and anaphylaxis are the major clinical manifestations.
10. **The answers are E, G, H, and D, respectively** [XI.B.1, XI.A, X.F, and X.C.2.b]. Shwachman–Diamond syndrome is an autosomal recessive condition characterized by decreased neutrophil activity and by cyclic neutropenia. Patients with Shwachman–Diamond syndrome have recurrent soft tissue infections as a result of the neutropenia, and also have pancreatic exocrine insufficiency with failure to thrive. Chronic granulomatous disease (CGD) refers to a group of disorders characterized by defective neutrophil oxidative metabolism resulting in severely impaired intracellular killing of catalase-positive bacteria and some fungal pathogens. CGD is predominantly X-linked. Patients with CGD have an increased susceptibility to infections of the lungs, liver, skin, lymph nodes, and skin, characteristically with abscess formation. Wiskott–Aldrich syndrome is an X-linked disorder characterized by combined immunodeficiency, eczema, and congenital thrombocytopenia (with small platelets). Patients typically present with recurrent infections with encapsulated organisms, thrombocytopenia, and eczema. Adenosine deaminase deficiency is a subtype of severe combined immunodeficiency disease (SCID) that is inherited in an autosomal recessive manner. SCID refers to a group of inherited disorders characterized by profoundly defective B-cell and T-cell function. Patients with adenosine deaminase deficiency usually present within the first few months of life with persistent lymphopenia, chronic diarrhea, failure to thrive, and infections with both common pathogens and opportunistic organisms (e.g., *Candida albicans, Pneumocystis jirovecii*).

CHAPTER 16

Rheumatology

Grant D. Syverson

I. Henoch–Schönlein Purpura (HSP)

A. **Definition.** A systemic **IgA-mediated vasculitis** that primarily involves the skin, joints, gastrointestinal (GI) tract, and kidneys.

B. **Epidemiology**
   1. HSP is primarily a disease of children (ages 3–15 years); the **peak incidence is at 4–6 years**.
   2. HSP is the **most common form of vasculitis of childhood**.
   3. **Males** are more likely to be affected.
   4. HSP occurs primarily in the fall, winter, and spring.

C. **Clinical features**
   1. **A viral syndrome or upper respiratory infection precedes** HSP in about half of patients, particularly in patients who have had a prior group A β-hemolytic streptococcal infection.
   2. Distinctive **skin, GI,** and **joint manifestations** follow the prodrome.
      a. **Skin manifestations**
         1. Classically, urticarial or erythematous maculopapular lesions progress to **petechiae and palpable purpuric lesions, concentrated on gravity-dependent areas (the buttocks and lower extremities)**.
         2. Children may also present with **edema** of hands, feet, scrotum, and scalp. Infants may present with a facial rash in addition to edema.
         3. GI and joint symptoms may precede the diagnostic rash by days or weeks in 25% of patients.
      b. **Joint manifestations** occur in **80%** of patients as arthralgia or arthritis. The **knees and ankles are most commonly involved**.
         1. Primarily involves large joints in the lower extremities and can be very painful.
         2. Swelling is periarticular but lacks effusions or increased warmth and does not cause chronic damage.
      c. **GI manifestations occur in about 50% of patients.**
         1. **Colicky abdominal pain** that may be severe
         2. **GI bleeding** (either occult blood or grossly bloody stool)
         3. Increased risk of **intussusception (most common GI complication of HSP)**
   3. **Renal manifestations** (see Chapter 11, section V.F.3)
      a. Presentations range widely, from mild hematuria and trace proteinuria to gross hematuria, nephrotic syndrome, chronic renal insufficiency, and end-stage renal disease (1% of cases).
      b. Onset of renal manifestations occurs within four weeks in most patients but can occur up to 6 months later.

D. **Diagnosis**
   1. **History and characteristic physical examination establish a clinical diagnosis**.
   2. Routine laboratory tests are neither specific nor diagnostic.
   3. Skin biopsies show leukocytoclastic vasculitis with IgA deposition.
   4. **Increased serum IgA** levels are present in 50% of patients.
   5. Circulating IgA immune complexes in serum and IgA deposition in skin and glomeruli are suggestive of the diagnosis.
   6. **Platelet counts are normal despite the presence of petechiae and purpura** (i.e., **the skin rash is a nonthrombocytopenic purpura**).

E. **Management.** Treatment is based on **relief of symptoms**, including use of analgesics and

hydration, and monitoring for complications.

1. **Steroids** may be effective for relief of abdominal pain and arthritis but do not impact the clinical course.
2. Patients should be followed up with **urinalysis and blood pressure monitoring** every 2 weeks for 1–2 months after presentation, then monthly for at least 6 months. **Hematuria, proteinuria, or hypertension should prompt referral to a nephrologist**.

F. **Prognosis**

1. Most patients recover within 4 weeks.
2. HSP **recurs at least once in one-third of patients**, usually within 3–4 months of presentation.
3. Long-term morbidity is dependent on the severity of renal disease.

II. Kawasaki Disease (KD)

A. **Definition.** An **acute febrile vasculitis of childhood**; this disease involves multiple organ systems, including the heart, skin, mucous membranes, GI tract, central nervous system (CNS), joints, and peripheral vascular bed.

B. **Epidemiology**
   1. KD is the **most common cause of acquired heart disease** in children in the United States.
   2. **Males** are slightly more commonly affected than females.
   3. Most common in **children of Asian ethnicity** but can occur in any ethnicity.
   4. The **mean age** at presentation is **18–24 months** (80–90% of cases occur in children younger than 5 years). It is uncommon in children younger than 6 months.

C. **Diagnostic criteria** (**Table 16-1**)
   1. **Temperature > 38.9°C (102°F) lasting ≥5 days**—most consistent manifestation of KD
   2. The patient must also have **four of the following five clinical manifestations**:
      a. **Bilateral conjunctivitis:** bulbar injection with limbic sparing and **without exudate**
      b. **Mucous membrane changes:** pharyngitis; strawberry tongue; or *most commonly*, **red, cracked, swollen lips**
      c. **Cervical adenopathy:** a unilateral nonsuppurative cervical lymph node ≥1.5 cm in diameter. This is the least consistent feature of KD.
      d. **Rash:** primarily on the trunk. The rash may assume many forms ("polymorphous"), including erythematous, maculopapular, morbilliform, or scarlatiniform. It often begins as perineal erythema and desquamation.
      e. **Changes in distal extremities**
         1. **Early** (first 7–10 days of illness): swelling and induration of the hands and feet with erythematous palms and soles
         2. **Later** (7–10 days after the start of fever): peeling around the nail beds of the distal extremities
      f. It is important that **the illness must not be explainable by any other disease process**. Known infectious conditions (including bacterial, viral, and rickettsial infections), rheumatologic conditions (including systemic juvenile idiopathic arthritis), and drug reactions must be excluded to make the diagnosis of KD.

D. **Other clinical features** (*not* diagnostic criteria)
   1. **Cardiovascular manifestations**
      a. **Coronary artery aneurysms** occur in **20%** of untreated patients, usually around days 7–14 (most commonly in the subacute phase of the disease).
      b. Low-grade myocarditis is common.
      c. Congestive heart failure
      d. Arrhythmias
      e. Aneurysms of the brachial arteries
   2. Urethritis (sterile pyuria), which can be missed by catheterization that bypasses the urethra to obtain urine directly from the bladder
   3. Aseptic meningitis
   4. **Hydrops of the gallbladder** may occur in 10% of patients and should be considered in patients with acute right upper quadrant abdominal pain.
   5. Arthritis (sterile) or arthralgias
   6. Anterior uveitis

E. **Time course of disease.** The clinical course is **triphasic** (see **Table 16-2**).
   1. Phase I: **Acute phase** (1–2 weeks)
   2. Phase II: **Subacute phase** (weeks to months)

3. Phase III: **Convalescent phase** (weeks to years)

F. **Laboratory findings.** *No laboratory tests are pathognomonic* for KD. Laboratory findings are not specific but include the following (**see Table 16-2**):
   1. Acute phase: (↑) erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Other common laboratory findings include elevations in white blood cell (WBC) count, transaminases (AST/ALT), sterile pyuria, and cerebrospinal fluid (CSF) pleocytosis. A normocytic, normochromic anemia is frequently observed, as is low serum albumin.
   2. Subacute phase: (↑) platelet count and a decreasing ESR and CRP
   3. Convalescent phase: Laboratory findings usually normalize within 6–8 weeks.

G. **Management.** Treatment includes anti-inflammatory therapy and assessment for coronary artery disease with serial echocardiography.
   1. **Intravenous immune globulin (IVIG). High-dose (2 g/kg) IVIG, in combination with aspirin (acetylsalicylic acid [ASA]).** Initiation within 10 days after the onset of fever substantially decreases the prevalence of coronary artery dilation and aneurysms detected 2 and 7 weeks later. A second dose of IVIG is typically given if fever returns 24–36 hours after initial treatment.
   2. **ASA**
      a. Acute phase: **high-dose ASA** for its **anti-inflammatory** effect
      b. Subacute phase: **low-dose ASA** for its **antiplatelet** effect
   3. **Steroids** are not the preferred first-line agent for the treatment of KD. Steroids may be useful, however, in some patients who are unresponsive to IVIG.
   4. **Tumor necrosis factor (TNF) inhibitors** are also not indicated as primary treatment for KD, but may have a role for patients who are unresponsive to IVIG.

H. **Incomplete or atypical KD**
   1. A subset of patients suspected of having KD **may not fulfill all of the clinical diagnostic criteria**. These patients have "incomplete" or "atypical" KD.
   2. Patients must still have at least 5 days of fever but otherwise have **only have 2–3 clinical features** from Table 16-1 and no alternative explanation for symptoms.
   3. **Laboratory and echocardiographic studies are used to make the diagnosis** in these children.
   4. Treatment is the same as for typical KD.

I. **Prognosis**
   1. If coronary artery disease is absent, mortality is rare. Recurrence is also rare.
   2. Even if coronary artery disease is present, the mortality is <1%, and aneurysms, especially those <8 mm, commonly regress over time.
   3. Long-term prognosis is unclear. It's possible that there may be an increased risk of atherosclerotic heart disease in adulthood.

Table 16-1
Diagnostic Criteria of Kawasaki Disease

I.	Fever for at least 5 days
	AND
II.	Four of the following features: Conjunctivitis Oropharyngeal changes Cervical adenopathy Rash Changes in distal extremities AND
III.	The illness cannot be explainable by any other disease process (i.e., exclusion of known infectious etiologic factors, drug reactions, and other rheumatologic conditions, such as juvenile idiopathic arthritis)

Table 16-2
Clinical Manifestations, Laboratory Findings, and Treatment of Kawasaki Disease

	Phase I	**Phase II**	**Phase III**
	Acute Phase	**Subacute Phase**	**Convalescent Phase**
Time Course	**1–2 Weeks**	**Weeks to Months**	**Weeks to Years**
Clinical manifestations	Fever	Defervescence and decreased inflammation	Gradual resolution of aneurysms
	Conjunctivitis		
	Oropharyngeal changes	Peeling from nail beds or distal extremities	
	Cervical adenopathy		
	Rash	**Coronary artery aneurysms**	
	Swollen hands		
Laboratory findings	(↑) ESR and CRP	ESR and CRP decreasing from acute phase(↑) **Platelet count**	Normalization of all laboratory findings
	(↑) WBC count		
	(↓) Hemoglobin		
	(↑) AST/ALT		
	(↓) Albumin		
	Sterile CSF pleocytosis		
	Sterile pyuria		
Treatment	High-dose IVIG	**Low-dose** aspirin	Continue low-dose aspirin only if aneurysms remain
	High-dose aspirin		

ESR = erythrocyte sedimentation rate; *CRP* = C-reactive protein; *WBC* = White blood cell count; *AST* = aspartate aminotransferase; *ALT* = alanine aminotransferase; *IVIG* = intravenous immune globulin; *CSF = cerebrospinal fluid*.

III. Juvenile Idiopathic Arthritis (JIA)

A. **Definition.** JIA is a disorder characterized by chronic joint inflammation in children, with or without extraarticular involvement.

B. **Epidemiology**

1. **JIA is the most common pediatric rheumatic disease with arthritis** as the distinguishing manifestation.
2. The mean age of onset is **1–3 years**; presentation before 6 months of age is unusual.
3. JIA most commonly occurs in **females,** with two exceptions. **Males are equally likely to have systemic-onset JIA,** and they are much **more likely to have late-onset human leukocyte antigen B27(HLA-B27)–related diseases**.

C. **Diagnosis** of JIA is based on history and clinical features. **Diagnostic criteria** are listed in **Table 16-3**.

D. **Classification.** The classification of JIA is determined on the basis of the number and types of joints involved, along with extraarticular manifestations *(***Table 16-4***)*. The categories of JIA include oligoarthritis, polyarthritis, systemic arthritis, enthesitis-related arthritis, and psoriatic arthritis. Regardless of type, all patients have arthritis during their clinical course.

E. **Clinical features** *(see* **Table 16-4****)**

1. **Oligoarticular JIA (≤ four joints involved)** accounts for 50% of cases. Patients usually present at 1–5 years of age with a female predominance. A good majority (65–85%) of patients have a **positive antinuclear antibody (ANA)**. These patients are at **high risk for developing chronic uveitis**, which is defined as inflammation of the iris and ciliary body. Uveitis must be monitored by regular slit-lamp evaluations.
    a. **Subtypes.** Subtypes of oligoarticular JIA are recognized on the basis of the presence and timing of joint involvement.
        1. **Persistent oligoarthritis** describes patients with one to four joints involved in the first 6 months of disease **who do not develop arthritis in additional joints**.
        2. **Extended oligoarthritis** describes patients with one to four joints involved during the first 6 months of disease who **then develop arthritis in greater than four joints**.
    b. **Articular involvement** may present with swelling of one or two joints, not necessarily symmetric. The most common joints involved are the knees and hips.
2. **Polyarticular JIA (five or more joints involved)** accounts for approximately 30–40% of cases, with systemic involvement and extraarticular features generally mild or absent.
    a. **Subtypes.** As in oligoarticular disease, polyarticular JIA can also be divided into two subtypes. Subtypes are based on the absence or presence of **serum rheumatoid factor (RF),** which is an IgM molecule directed against IgG. Both RF-negative (RF−) and RF-positive (RF+) polyarticular JIA affect **females** more frequently than males.
        1. **RF− disease** presents both early and late in childhood.
        2. **RF+ disease** presents in children older than 8 years and is generally **more severe than RF− disease,** with **higher risk of severe arthritis** and rheumatoid nodules.
    b. **Articular involvement** is characterized by a symmetric polyarthritis that typically involves both small joints (hands and feet) and large joints (knees, ankles, and hips).
3. **Systemic-onset JIA** accounts for 10–15% of cases. At presentation, severe systemic symptoms may overshadow symptoms of arthritis.
    a. **High spiking fevers** (temperature > 39°C [102.2°F]) occur most commonly in the late afternoon or evening and subsequently return quickly to baseline or subnormal

levels (Quotidian fever pattern). **Systemic JIA is typically included in the differential diagnosis of "fever of unknown origin."**

b. **Transient salmon-pink macular rash** is most commonly found on the trunk and proximal extremities, especially during febrile episodes. The rash is **evanescent** (occurs with fever spikes and then fades) and **nonpruritic**.

c. **Hepatosplenomegaly**

d. **Lymphadenopathy**

e. Other features include the following:

1. **Fatigue, anorexia, weight loss, and failure to thrive** are common.
2. **Serositis,** including pericarditis and pleuritis, is also common.
3. **CNS involvement,** including meningitis and encephalopathy, may occasionally be present.
4. **Myositis and tenosynovitis** can also be seen in addition to the arthritis.

F. **Laboratory findings.** Laboratory results are **nonspecific;** if present, they reflect the existence or extent of inflammation and are useful to evaluate for other disease processes.

1. **Anemia** is usually **microcytic and hypochromic,** consistent with anemia of chronic disease.
2. **Acute-phase reactants** are **elevated,** including ESR, CRP, and platelet count.
3. **Rheumatoid markers**

a. **RF** is negative in most patients with JIA. RF positivity is not diagnostic but can help determine prognosis for patients with polyarticular disease.

b. **ANA** is present in 65–85% of patients with oligoarticular JIA and in 50% of patients with polyarticular JIA. An ANA is not a diagnostic test for JIA but can help determine the risk of uveitis. *ANA is rare in children with systemic-onset JIA*.

G. **Management.** The goal of treatment is to decrease joint inflammation and preserve function.

1. **Control of inflammation**

a. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain and inflammation.

b. Immunomodulatory medications (e.g., glucocorticoids, methotrexate, sulfasalazine, TNF inhibitors) are commonly used for more severe symptoms.

2. **Mechanical and physical measures** include physical and occupational therapy.
3. **Surgery** (e.g., joint replacement, synovectomy) is generally reserved for patients who have recalcitrant joint contractures or destruction. Owing to advances in pharmacotherapy, surgery is becoming much less common.
4. **Psychosocial support**

H. **Prognosis.** The outlook is excellent with appropriate early diagnosis and treatment. However, the incidence of complications depends on the type and subtype of JIA.

Table 16-3
Diagnostic Criteria for Juvenile Idiopathic Arthritis

Age of onset ≤16 years of age
Arthritis in ≥one joint defined as follows:
Swelling or effusion OR
Limitation of motion, tenderness, increased warmth
Duration of disease ≥ 6 weeks
Exclusion of other causes of arthritis

Table 16-4
Distinguishing Features of the Subtypes of Juvenile Idiopathic Arthritis

		Frequency		

Subtype	Definition	(% of JIA)	Age of Onset	Sex Ratio
Oligoarticular	There are 2 subtypes of oligoarticular JIA: • Persistent oligoarticular arthritis: Never affects more than four joints • Extended oliogoarticular arthritis: Affects more than four joints after the first 6 months of disease	50%	Early childhood; peak at 2–4 years	Female > male
Polyarticular	There are 2 subtypes of polyarticular JIA: • RF–negative • RF–positive	30–40% for both subtypes	• RF-negative: Biphasic distribution; early peak 2–4 years and later peak at 6–12 years • RF-positive: Late childhood or adolescence	Female > male
Systemic onset	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented as daily ("Quotidian") for at least 3 days and accompanied by one or more of the following: (1) rash (evanescent), (2) lymphadenopathy, (3) hepatomegaly or splenomegaly, and (4) serositis	10–15%	Throughout childhood	Female = male
Psoriatic	Arthritis and psoriasis, or arthritis and at least two of the following: (1) dactylitis, (2) nail pitting, and (3) psoriasis in first-degree relative	2–11%	Biphasic distribution; early peak at 2–4 years and later peak at 9–11 years	Female > male
Enthesitis related	Arthritis or enthesitis with two or more of the following: (1) sacroiliac tenderness or lumbosacral pain, (2) presence of HLA-B27, (3) onset of arthritis in male >6 years of age, (4) acute anterior uveitis, and (5) family history in a first-degree relative of HLA-B27 associated disease	3–11%	Late childhood or adolescence	Male > female

RF = rheumatoid factor; *Enthesitis* = inflammation of tendinous insertions on bone; *HLA-B27* = human leukocyte antigen B27.

IV. Systemic Lupus Erythematosus (SLE)

A. **Definition.** This multisystem autoimmune disorder is characterized by widespread chronic inflammation and immune complex–mediated vasculitis.

B. **Epidemiology**
   1. There is a **female** predominance (female-to-male ratio is 8:1).
   2. **Age of onset** is rarely younger than 10 years and peaks in **adolescence**.
   3. SLE occurs most often in patients of **Asian, African, or Latino ethnicity**.

C. **Etiology.** The cause of SLE is **unknown,** but the disease may be triggered by drug reactions, excessive sun exposure, infections, or hormonal changes (e.g., menarche, menopause, pregnancy).

D. **Clinical features.** Signs and symptoms are variable and may involve multiple organ systems.
   1. **Constitutional symptoms** such as fever, weight loss, and fatigue are common.
   2. **CNS** involvement includes headache, encephalopathy, seizures, psychosis, and transverse myelitis.
   3. **Skin findings** may include a **malar rash** ("butterfly distribution" covering the nasal bridge and upper cheeks sparing the nasolabial folds) and **photosensitivity,** both common at presentation or during an illness flare. Other common skin findings include **alopecia** and **Raynaud phenomenon**.
   4. **Arthralgias and arthritis** are typically migratory and transient. SLE, unlike JIA, **rarely causes joint deformity or erosion**. Myositis may also occur.
   5. **GI involvement** may manifest as hepatosplenomegaly, splenic infarction, mesenteric thrombosis (secondary to vasculitis), and sterile peritonitis.
   6. **Cardiovascular involvement** is variable, with **pericarditis** as the most frequent manifestation. Congestive heart failure, arrhythmias, and sterile valvular vegetations **(Libman–Sacks endocarditis)** may also occur. **Neonates born to mothers with SLE** may have **congenital heart block** secondary to transplacental passage of maternal antibodies.
   7. **Pulmonary involvement** may include **pleuritis,** pulmonary hemorrhage, and interstitial fibrosis.
   8. **Renal involvement** is nearly **universal,** although lupus nephritis may be subclinical. Glomerulonephritis, nephrotic syndrome, hypertension, and subsequent renal failure are common.
   9. **Hematologic** manifestations typically include low WBC counts. In addition to leukopenia, anemia of chronic disease, immune-mediated thrombocytopenia, and Coombs-positive hemolytic anemia are also common findings.

E. **Diagnostic criteria for SLE** *(*Table 16-5**)**

F. **Laboratory findings**
   1. Elevated ESR
   2. Anemia (anemia of chronic disease or hemolytic anemia)
   3. Leukopenia
   4. Thrombocytopenia
   5. Urinalysis may show proteinuria depending on the extent of renal disease.
   6. **Rheumatologic markers**
      a. **ANA** is almost **universally elevated** (>99%) in SLE and is an **excellent screening test**. However, ANA is **nonspecific** for SLE and is found in many other diseases.
      b. **RF** is often elevated in SLE, but like ANA, is **nonspecific**.
      c. **Anti–double-stranded DNA (anti-dsDNA) antibodies** are much more **specific** (found only in SLE), and their **levels can be used as markers for active disease,** especially nephritis.

d. **Anti-Smith (anti-Sm) antibodies** are less prevalent in patients with SLE but, when present, are **very specific**. Unlike anti-dsDNA, anti-Sm antibody levels cannot be used as a measure of disease activity.

7. **Other findings**
   a. **Antiphospholipid antibodies** (e.g., positive lupus anticoagulant or anticardiolipin antibodies) present in patients with SLE **reflect an increased risk of thrombotic events**.
   b. **Decreased complement (C3 and C4)** is seen especially with active disease and represents immune complex–mediated complement activation.
   c. **Ro (SSA) and La (SSB) antibodies** are less strongly associated with SLE **(more specific for Sjögren syndrome)**. Babies born to mothers with these antibodies are at risk for neonatal lupus.

G. **Management.** Therapy is based on a multidisciplinary, team approach that attempts (1) to prevent or minimize inflammation and end-organ dysfunction, (2) to treat complications, and (3) to provide psychosocial and family support, as follows:

1. **Control of inflammation**
   a. **NSAIDs** are useful in the treatment of **minor** inflammatory symptoms, such as myalgias and arthralgias. Use should be carefully monitored owing to the risk of renal disease in SLE.
   b. **Immunosuppressive medications**
      1. **Glucocorticoids** are the **mainstay of therapy** for children with SLE. Depending on disease severity and extent, treatment ranges from low-dose oral to high-dose intravenously pulsed steroids.
      2. **Cyclophosphamide,** intravenously pulsed, is useful for children with severe clinical manifestations, including renal and CNS disease. Adverse effects of this cytotoxic agent include infertility and gonadal failure, secondary malignancies, and hemorrhagic cystitis.
      3. **Hydroxychloroquine** is useful for patients with mild disease and is often used as a maintenance therapy. Numerous studies have shown a beneficial effect on long-term disease activity and survival. Patients require ophthalmologic screening owing to the side-effect of potential vision damage with its use.
      4. **Other agents** include mycophenolate, rituximab, azathioprine, methotrexate, and cyclosporine. Mycophenolate, in particular, is being used more often as an alternative to cyclophosphamide to treat lupus nephritis.
2. **Treatment of complications**
   a. Patients with **thrombosis** and antiphospholipid antibodies should be anticoagulated with low–molecular weight heparin or warfarin.
   b. Patients with **renal failure** may require dialysis, fluid and electrolyte management, and ultimately renal transplant.
3. **Psychosocial and family support**

H. **Prognosis.** Before the advent of effective therapy, the outlook for patients with SLE was historically poor and uniformly fatal. However, with current treatment, the **survival rate is now 85–100%** at 5–10 years after initial diagnosis. The major causes of mortality are infection (because of immunosuppression), renal failure, and CNS complications.

TABLE 16-5
Diagnostic Criteria for Systemic Lupus Erythematosus*

Mnemonic "SOAP BRAIN MD"
Serositis (pleuritis or pericardial inflammation)
Oral or nasal mucocutaneous ulcerations

Arthritis, nonerosive
Photosensitivity
Blood cytopenias (leukopenia, hemolytic anemia, or thrombocytopenia)
Renal disease (hematuria, proteinuria, hypertension)
ANA-positive
Immunoserology abnormalities (antibodies to double-stranded DNA, Smith antigen, false-positive RPR or VDRL assays, or antiphospholipid antibodies)
Neurologic symptoms (encephalopathy, seizures, or psychosis)
Malar rash (butterfly rash)
Discoid lupus (red raised patches with scaling, can cause scarring)

*Four of eleven criteria provide a sensitivity and specificity of 96%.

RPR = rapid plasma reagin; *VDRL* = Venereal Disease Research Laboratories; *ANA* = antinuclear antibody.

V. Juvenile Dermatomyositis (JDM)

A. **Definition.** This inflammatory condition of children results in myopathy, progressive muscle weakness, and characteristic skin findings.

B. **Epidemiology**
   1. JDM is the **most common idiopathic inflammatory myopathy of childhood** (85% of all myopathies).
   2. Individuals are usually **5–10 years** of age. The mean age of onset is 6 years.
   3. **Females** are more likely to be affected.

C. **Clinical features**
   1. **Constitutional symptoms** are common and include fatigue, anorexia, malaise, low-grade fevers, and weight loss.
   2. **Characteristic cutaneous findings,** particularly over **sun-exposed areas,** include the following:
      a. **Periorbital violaceous heliotrope rash,** which may also cross the nasal bridge
      b. **Gottron papules,** in which the skin over the metacarpal and proximal interphalangeal joints (knuckles) may become erythematous and hypertrophic
   3. **Proximal muscle weakness** (mostly of the hip girdle and legs) is insidious in onset, is symmetric, and occurs weeks to months after the eruption of skin findings. It is the **primary manifestation** of JDM. **Gowers sign** may be positive (i.e., difficulty standing from the seated position, such that one has to use his or her arms to "climb" up the thighs for support).
   4. Other manifestations include
      a. **Neck flexor muscle weakness**
      b. **Calcinosis** (calcium deposition in muscle, fascia, and subcutaneous tissue), which occurs in approximately 40% of children
      c. **Nail bed capillary changes**
      d. **Constipation** from GI smooth muscle dysfunction
      e. **Dysphagia**
      f. **Cardiac involvement** with conduction abnormalities and dilated cardiomyopathy

D. **Diagnosis**
   1. **Classic clinical presentation** of proximal muscle weakness with associated characteristic rashes
   2. **Increased muscle enzymes** (creatine phosphokinase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and aldolase)
   3. **Magnetic resonance imaging (MRI)** shows diffuse muscle edema in proximal muscle groups and can be used to avoid more painful procedures, such as electromyography (EMG) and muscle biopsy.
   4. **Abnormal EMG** (used only when diagnosis is not certain)
   5. **Abnormal muscle biopsy** (used only when diagnosis is not certain)

E. **Complications**
   1. **Aspiration pneumonia** is a frequent complication resulting from a diminished gag reflex.
   2. **Intestinal perforation** may result from GI vasculitis.
   3. *Frequent fractures* may result from muscle weakness and *osteopenia* secondary to steroid therapy.

F. **Management**
   1. **Corticosteroids** are the **initial drugs of choice**.
   2. Other immunosuppressive agents, including methotrexate, IVIG, hydroxychloroquine,

cyclophosphamide, and cyclosporine are often used in combination with steroids to minimize adverse effects of long-term high dose corticosteroid use.

3. **Vitamin D and calcium supplementation** may be necessary to help treat osteopenia and decrease frequency of fractures.

G. **Prognosis**

1. **Prognosis is better in children** than in adults.
2. There is **no association with malignancy in pediatric dermatomyositis** (in contrast to adult disease, in which malignancy develops in 25% of patients).
3. Long-term survival is >95%. Morbidity is related to functional disability and calcinosis.

VI. Rheumatic Fever

A. **Definition.** Rheumatic fever is a *delayed, nonsuppurative, autoimmune complication occurring 2–4 weeks after an upper respiratory infection with group A β-hemolytic streptococcus* (GABHS) (*Streptococcus pyogenes*). It is characterized by inflammation of the heart, blood vessels, joints, CNS, and skin.

B. **Epidemiology**
   1. Rheumatic fever is now **rare in the United States** and Western Europe but was a worldwide problem during the 1960s. It remains a primary cause of cardiac death in the developing world in patients younger than 50 years.
   2. It is **most common in children 5–15 years of age,** reflecting the age group most susceptible to streptococcal throat infections.
   3. There is no gender predilection.
   4. The major risk factor is **pharyngitis** caused by certain strains of **GABHS**. *The streptococcal strains that cause streptococcal skin infection (i.e., impetigo) do not cause rheumatic fever*.

C. **Etiology.** The **cause of rheumatic fever is unknown,** but the disease appears to be autoimmune in nature and may represent "molecular mimicry," in which streptococcal antigens resemble autoantigens and trigger an autoimmune response.

D. **Clinical features.** These may be classified as "major" and "minor" features (*Jones criteria*).
   1. **Major features**
      a. **Cardiac involvement** is the **hallmark** and **most important complication** of rheumatic fever. The inflammatory process may involve all layers of the heart (pancarditis), including the epicardium, endocardium, myocardium, and pericardium.
         1. **Valvulitis** is frequent and typically causes insufficiency of the **left-sided valves** (mitral and aortic). *Mitral regurgitation* is the most common early valvular manifestation. It rarely affects the pulmonic or tricuspid valves.
         2. **Myocarditis** is usually manifested by **tachycardia out of proportion to the extent of the fever**. Other severe manifestations include cardiac dilatation and heart failure.
         3. Pericarditis and pericardial effusions are less common.
      b. **Arthritis** is classically **migratory, asymmetric,** and **exquisitely painful** and often the earliest manifestation of acute rheumatic fever. It occurs in 70% of patients and most commonly involves the elbows, knees, ankles, and wrists. **It does not result in chronic joint disease and responds quickly to NSAIDs and aspirin.**
      c. **Sydenham chorea** occurs later than the other rheumatic fever manifestations, often beginning subtly, months after GABHS pharyngitis. It reflects involvement of the basal ganglia and caudate nuclei. Chorea may start as hand clumsiness and progress to choreoathetoid movements with emotional lability.
      d. **Skin involvement**
         1. **Erythema marginatum** is an evanescent, nonpruritic rash that starts as pink to red macules, which may coalesce and spread centrifugally with central clearing over the trunk and proximal limbs.
         2. **Subcutaneous nodules,** although rarely seen, are associated with severe cardiac involvement. These small, mobile, and painless nodules occur on the bony prominences of the extensor surfaces of the extremities.
   2. **Minor features** include fever, arthralgias, leukocytosis, increased ESR, and prolonged PR interval on electrocardiogram.

E. **Diagnosis.** The **Jones criteria for rheumatic fever are shown in Table 16-6**. Diagnosis requires

evidence of recent streptococcal infection and either two major criteria or one major plus two minor criteria.

F. **Laboratory findings**
   1. Nonspecific inflammatory markers
      a. Elevated ESR and CRP
      b. Elevated WBC count
   2. Serologic markers
      a. **Antistreptolysin-O** titers are abnormally elevated in 70–80% of patients with rheumatic fever and are evidence of a recent GABHS infection.
      b. **Anti-DNase** antibodies may also be used to document GABHS infection.
   3. Echocardiography typically shows evidence of carditis, such as decreased ventricular function, valvular insufficiency, or pericardial effusion.

G. **Management**
   1. **Eradication of GABHS infection**
      a. Benzathine **penicillin** intramuscular injection (one dose) or
      b. Penicillin orally for 10 days
   2. **Control of inflammation**
      a. **NSAIDs** are useful for control of joint pain and swelling, but if given before definitive diagnosis, they may obscure the diagnosis by halting the development of migratory arthritis. Therefore, their use is **recommended only after the diagnosis of rheumatic fever is certain**.
      b. **Corticosteroids** are often used in patients with severe cardiac involvement, such as congestive heart failure and severe valvular dysfunction.
   3. **Supportive therapy**
      a. **Congestive heart failure** is treated with diuretics, dietary salt restriction, digoxin, and bed rest.
      b. **Sydenham chorea,** if severe, may be treated with haloperidol.
   4. **Long-term management** includes continuous antimicrobial prophylaxis to prevent recurrent episodes of rheumatic fever. Duration of prophylaxis depends on severity of heart disease.

H. **Prognosis**
   1. There are no chronic sequelae of the joint, skin, and CNS manifestations of rheumatic fever.
   2. Cardiac inflammation often leads to severe valvular dysfunction, which may require intervention immediately or many years after the event. Valvular insufficiency or stenosis is usually delayed (usually more than 3 years after rheumatic fever) and, if severe, may require valve replacement or valvuloplasty.

TABLE 16-6
The Jones Criteria for Diagnosis of Rheumatic Fever*

Major criteria
Migratory polyarthritis
Carditis
Sydenham chorea
Erythema marginatum
Subcutaneous nodules
Minor criteria
Fever
Arthralgia
Previous rheumatic fever
Leukocytosis
Elevated erythrocyte sedimentation rate

Elevated C-reactive protein
Prolonged PR interval on electrocardiogram

*The diagnosis requires evidence of previous streptococcal infection **and** either (1) two major criteria or (2) one major plus two minor criteria.

VII. Lyme Disease

A. **Definition.** This reactive inflammatory disorder of the skin, heart, CNS, and connective tissues is caused by spirochetal infection with ***Borrelia burgdorferi*** (in the United States) and transmitted via a tick bite.

B. **Epidemiology.** *High-risk areas* reflect the natural habitat of ticks of the *Ixodes* species, which are the vectors for Lyme disease transmission. These ticks are especially prevalent in woodlands and fields in the New England states and parts of the Pacific coast and Midwestern United States. Disease onset typically occurs during the summer months.

C. **Etiology**

1. **Vector.** In the United States, most human infections occur during feeding by an infected **deer tick,** *Ixodes scapularis.* Transmission from *Ixodes pacificus*, which is the tick most prevalent in the Western United States, is less common.
2. **Organism. *B. burgdorferi*** is passed into the bloodstream of the human host while the tick engorges itself with blood. The **infected tick must be attached for more than 36–48 hours** before the risk of *B. burgdorferi* transmission becomes substantial.

D. **Clinical features.** Clinical features are initially caused by the invasion of *B. burgdorferi* into local and distant tissues, and in later stages by a systemic inflammatory response against the spirochete. The untreated clinical course of Lyme disease is, therefore, divided into **two stages, early and late disease**. Early disease is further broken down into **early localized** and **early disseminated** disease.

1. **Early disease** (<4 months after transmission)
    a. **Early localized disease** can occur within days of transmission, resulting from local cutaneous invasion and subsequent inflammation.
        1. **Erythema migrans** is the classic rash of Lyme disease and is typically the first manifestation. It occurs in two-thirds of patients and is described as **annular and "targetlike"** with variable degrees of central clearing. Erythema migrans may be asymptomatic, pruritic, or painful and, if untreated, may expand (thus the term *migrans*) to more than 12 inches in diameter. It is the only manifestation that permits diagnosis without laboratory confirmation.
        2. **Constitutional symptoms** may begin to occur during this stage and include fever, headache, neck pain, myalgias, fatigue, arthralgias, and lymphadenopathy.
    b. **Early disseminated disease** typically occurs within 1–4 months after the tick bite. In addition to cutaneous findings, it is characterized by involvement of other organ systems.
        1. **Skin.** Up to 25% of children may develop **multiple secondary erythema migrans** lesions, which tend to be smaller than the initial lesion.
        2. **Constitutional symptoms** [see section VII.D.1.a.(2)] may initially appear and continue through this stage.
        3. **Neurologic**
            a. **Aseptic meningitis** may occur at this stage but is rare (1%).
            b. **Facial nerve palsy** is seen in approximately 3% of children. Lyme disease must therefore be considered in a child with unilateral or bilateral palsy of the seventh cranial nerve.
            c. **Encephalitis**
        4. **Carditis is rare** but usually presents as **heart block or myocarditis**.
2. **Late disease** (months after transmission) is the second stage and presents with arthritis as the most common manifestation. Arthritis typically is mono or oligoarticular and

involves the knee in >90% of cases.

E. **Diagnosis**
   1. **The diagnosis** is strongly suggested in the presence of epidemiologic risk factors and a classic erythema migrans rash.
   2. **Laboratory diagnosis** is **important in establishing a definitive diagnosis** because erythema migrans is not always present, and the clinical features and routine laboratory test results may be nonspecific. Testing should only be performed on patients with appropriate risk factors and symptoms.
      a. **Serologic testing** involves the **measurement of antibodies** to *B. burgdorferi* in the patient's serum and is the recommended laboratory approach. The US Centers for Disease Control and Prevention currently **recommends a two-step procedure**:
         1. **Enzyme-linked immunosorbent assay (ELISA),** which has a relatively high sensitivity. If negative, no further testing is indicated.
         2. **Western blot,** if the ELISA is positive or equivocal, to confirm the diagnosis. Patients require either five positive IgG bands or two positive IgM bands.
      b. **Other laboratory tests** (e.g., polymerase chain reaction, cultures from body fluids or tissue) are occasionally used, but their clinical utility is limited, offering no advantage over the recommended serologic method.

F. **Management** is aimed at eradicating *B. burgdorferi,* with the caveat that symptoms caused by systemic inflammation may not resolve immediately.
   1. **Early localized disease, or late disease with arthritis only,** is typically treated with doxycycline (for children ≥9 years of age), amoxicillin, or cefuroxime.
   2. **Carditis** and **meningitis** require intravenous ceftriaxone.

G. **Prognosis.** Children who are treated, even with arthritis or neurologic manifestations, have an excellent prognosis. Recurrent symptoms or chronic sequelae are rare.

VIII. Other Rheumatologic Conditions of Childhood

Disorders that are rare in children and adolescents are marked with an asterisk (*).

A. **Seronegative spondyloarthropathies.** This group of disorders involves inflammation of entheses (tendinous insertions into bones), joints, or axial skeleton and are characterized by the absence of RF, ANA, or other disease-specific serologic markers.
   1. **Reactive arthritis.** Inflammation of the joints triggered by an infection, typically an enteric or sexually transmitted pathogen. An example is the triad of arthritis, urethritis, and conjunctivitis (Reiter syndrome), which is most commonly triggered by *Chlamydia trachomatis.* The most common enteric pathogens which are associated with reactive arthritis include *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Clostridium difficile.*
   2. **Psoriatic arthritis (see also Table 16-4).** This arthritis of the small and large joints is seen in patients with or without psoriatic skin disease. It is also associated with dactylitis (digital swelling), nail pitting, and onycholysis. Diagnosis is based on the presence of arthritis and psoriasis. If psoriasis is absent, the diagnosis can also be established if there is a first- degree relative with psoriasis.
   3. **Ankylosing spondylitis.** This **male-predominant, HLA-B27**–related syndrome of arthritis affects the joints of the hips and sacroiliac joint. It is characterized by enthesitis.
   4. **Inflammatory bowel disease (IBD)–associated arthritis.** This arthritis is associated with ulcerative colitis or Crohn disease. It typically involves the large joints of the lower extremity and can wax and wane based on GI disease activity. Some patients with IBD and joint symptoms may be **HLA-B27 positive** and have involvement of the axial skeleton in a **pattern indistinguishable from ankylosing spondylitis**.

B. **Other vasculitides.** Like the previously described vasculitic diseases (e.g., KD, SLE, HSP), these disorders are characterized by constitutional symptoms and inflammation of blood vessels.
   1. **Takayasu arteritis.** This disease is a large-vessel vasculitis. The classic patient is an Asian adolescent or young adult female, with constitutional symptoms and **aneurysmal dilation or thrombosis of the aorta, carotid, or subclavian arteries**.
   2. ***Polyarteritis nodosa.** This vasculitis is characterized by aneurysms and thrombosis of the small- and medium-sized vessels (e.g., brachial, femoral, or mesenteric arteries).
   3. ***Granulomatosis with polyangiitis (**formerly known as Wegener granulomatosis). This vasculitis is characterized by necrotizing **granulomas** in multiple organs, most commonly the respiratory tract and kidneys. Classic clinical features include constitutional symptoms, severe **sinusitis, hemoptysis,** and **glomerulonephritis**. It is associated with PR3 antineutrophil cytoplasmic antibody, also known as the C-ANCA.

C. ***Sjögren syndrome.** This syndrome is defined by a classic triad of findings, including **sicca syndrome** (dry mouth and eyes), **high titers of autoantibodies** (usually ANA, RF, SSA, SSB), and **connective tissue disease**.

D. ***Scleroderma**
   1. **Systemic scleroderma.** This disorder is better termed **systemic sclerosis** because it is characterized by excessive fibrosis and subsequent dysfunction of multiple organ systems. This process affects the skin and vessels of the heart, kidneys, lungs, and GI tract. The cutaneous hallmark is **skin thickening with loss of dermal ridges,** resembling "tightened" skin.
   2. **CREST syndrome** refers to a form of scleroderma with less extensive involvement, manifesting with **c**alcinosis, **R**aynaud phenomenon, **e**sophageal involvement, **s**clerosis of the skin, and **t**elangiectasias.

Review Test

1. A 10-year-old girl presents for evaluation of fatigue, diminished appetite, and weakness. On physical examination, a periorbital violaceous heliotrope rash is evident. Which of the following statements is most accurate regarding the probable diagnosis?
   A. Children with this diagnosis typically present with distal muscle weakness with an ascending pattern.
   B. This patient has a 25% likelihood of developing a subsequent malignancy.
   C. Steroids are contraindicated.
   D. The clinical course may be complicated by calcium deposition in the muscle, fascia, and subcutaneous tissue.
   E. This patient's disease is more common in males than in females.
2. A 4-year-old boy presents to the emergency department for evaluation after 1 day of abdominal pain and a petechial rash on his bilateral thighs. He has no known history of prior bleeding or easy bruising but does have a 4-day history of upper respiratory tract infection (URI) symptoms and low-grade fevers. Physical examination is remarkable for a nontoxic, alert, and afebrile child. There is a petechial eruption on the lateral thighs, along with some edema of the hands and bilateral ankles. The abdomen is not distended, and bowel sounds are present. On examination, the abdomen is mildly tender to palpation in the periumbilical region without rebound tenderness. Laboratory studies reveal a white blood cell count of 14,000 cells/mm^3, hemoglobin of 11.8 g/dL, and platelet count of 260,000 platelets/μL. Which of the following treatments would be the most appropriate at this time?
   A. Intravenous immune globulin therapy for a presumed diagnosis of Kawasaki disease
   B. Intravenous immune globulin therapy for a presumed diagnosis of immune thrombocytopenic purpura
   C. Further evaluation by Child Protective Services for possible nonaccidental injury
   D. Conservative management for a presumed diagnosis of Henoch–Schönlein purpura
   E. Parenteral antibiotic therapy for a presumed diagnosis of meningococcemia pending blood culture results
3. A 3-year-old boy presents to the emergency department for evaluation of acute right upper quadrant abdominal pain. Further history reveals a 7-day history of fevers and sore throat. Physical examination reveals an irritable but consolable child with a temperature of 39.9°C (103.8°F). Other pertinent findings include bilateral nonpurulent conjunctivitis; red, cracked lips; swollen indurated fingers with erythematous palms; and an erythematous macular rash on the trunk. Which of the following is the most likely cause of the acute abdominal pain?
   A. Henoch–Schönlein purpura
   B. Hydrops of the gallbladder
   C. Intussusception
   D. Referred pain from arthritis involving the spine
   E. Constipation from gastrointestinal smooth muscle dysfunction
4. A 3-year-old girl is brought to your office by her parents, who report that she has had 2 months of intermittent high-spiking fevers with temperature up to 39°C (103°F), which occur nightly and return quickly to normal. The parents report that their daughter's activity and appetite are diminished. She is often reluctant to walk because of swelling of her ankles and knees. Six months ago her weight was at the 50th percentile, and now her weight is at the 25th percentile for age. On examination, you note a temperature of 39.2°C (102.6°F) and a salmon-colored maculopapular rash on the trunk. Diffuse lymphadenopathy is present, and the liver is palpable 4 cm below the right costal margin. Which of the following statements regarding this patient's likely diagnosis is most accurate?

A. Measuring the erythrocyte sedimentation rate will confirm the diagnosis.
B. Admission to the hospital and immediate treatment with intravenous immune globulin are necessary.
C. Antinuclear antibodies are likely to be positive.
D. The rash on the trunk is nonpruritic and is likely evanescent.
E. The patient has a 10% chance of developing severe chronic arthritis.

5. A 10-year-old boy develops a headache, fever, and rash approximately 2 weeks after camping with his family. The rash is annular and "targetlike" with central clearing. Which of the following is most accurate regarding the most likely diagnosis?
   A. This patient has a high likelihood of developing carditis.
   B. An infected tick must be attached to the skin for at least 36–48 hours before there is a significant risk of developing this condition.
   C. The prognosis for a child with this disease is poor, even with treatment.
   D. Treatment should be immediately initiated with an intravenous first-generation cephalosporin.
   E. Serologic testing for this condition is unreliable, and the diagnosis must be confirmed by culture of body fluids or tissue.
6. A 7-year-old boy with complaints of shortness of breath, nonpruritic rash, and very painful migratory arthritis presents to your clinic for evaluation. Two weeks ago, he had a sore throat and fever. On physical examination, a truncal macular rash is evident, and a grade 3/6 loud holosystolic murmur is audible at the apex and axilla. Which of the following statements is most accurate regarding this patient's likely diagnosis?
   A. Management may include corticosteroid therapy.
   B. Antistreptolysin-O titers would be expected to be abnormally high in 25% of patients with this condition.
   C. Laboratory evaluation is likely to demonstrate an elevated erythrocyte sedimentation rate and leukopenia.
   D. Chorea is also likely to be found on examination of this patient.
   E. Development of chronic and debilitating arthritis is likely.
7. A 12-year-old boy presents with severe arthritis of the hips and sacroiliac joints. Laboratory studies reveal that the patient is human leukocyte antigen B27 (HLA-B27) positive. Which of the following is the most likely diagnosis?
   A. Early-onset oligoarticular juvenile idiopathic arthritis (JIA)
   B. Juvenile ankylosing spondylitis
   C. Rheumatoid factor–negative polyarticular JIA
   D. Rheumatoid factor–positive polyarticular JIA
   E. Systemic-onset JIA
8. A 3-year-old girl is referred to you for evaluation of fever. Her fever has lasted 6 days, and her parents have noticed eye redness, a truncal rash, and swollen lips. Your physical examination confirms these findings, along with an enlarged left cervical lymph node measuring 3 cm in diameter. On the basis of your findings, you suspect Kawasaki disease. Which of the following findings on physical examination or laboratory analysis would best correlate at this time with the finding of coronary artery aneurysms on echocardiogram?
   A. Her current signs of fever, truncal rash, and swollen lips
   B. Elevated erythrocyte sedimentation rate
   C. Elevated platelet count of 840,000 platelets/μL
   D. Cervical adenopathy
   E. Laboratory evidence of aseptic meningitis

The response options for statements 9–14 are the same. You will be required to select one answer

for each statement in the following set.

A. Henoch–Schönlein purpura
B. Psoriatic arthritis
C. Systemic-onset juvenile idiopathic arthritis
D. Reactive arthritis
E. Inflammatory bowel disease-associated arthritis
F. Systemic lupus erythematosus
G. Kawasaki disease
H. Dermatomyositis
I. Oligoarticular juvenile idiopathic arthritis
J. Rheumatic fever
K. Lyme disease

For each patient, select the most likely diagnosis.

1. An human leukocyte antigen B27 (HLA-B27)–positive 14-year-old boy with abdominal pain and chronic diarrhea.
2. A 6-year-old boy with erythematous and hypertrophic papules over the metacarpal and proximal interphalangeal joints and "dark rings" around the eyes.
3. A sexually active 16-year-old boy with arthritis and conjunctivitis.
4. A 3-year-old boy with fever, bilateral knee swelling, and a "salmon-colored" rash on the trunk and proximal extremities.
5. A 14-year-old girl with arthritis, alopecia, leukopenia, and "a bad sunburn" on her face.
6. A 5-year-old girl with arthritis, abdominal pain, and a petechial eruption on her buttocks.

Answers and Explanations

1. **The answer is D** [V.C]. The constellation of clinical signs and symptoms that include fatigue, muscle weakness, and a heliotrope rash in a girl between 5 and 10 years of age is suggestive of dermatomyositis. Calcinosis, or calcium deposition, in muscle, fascia, and subcutaneous tissue occurs in up to 40% of children with this disorder. Dermatomyositis typically presents with proximal muscle weakness, characterized by a positive Gowers sign (difficulty standing from the sitting position and, as a result, having to "climb" up the thighs for support). Females are twice as likely as males to develop dermatomyositis. In childhood dermatomyositis, unlike in adult dermatomyositis, there is no association with malignancy. Steroids are the mainstay of therapy.
2. **The answer is D** [I.A, I.C.1–2, and I.E] Henoch–Schönlein purpura is an IgA-mediated vasculitis that involves the skin, joints, gastrointestinal tract, and kidneys. Despite the presence of petechiae, the platelet count is normal (i.e., a nonthrombocytopenic purpura). Steroids are indicated for patients who present with severe abdominal pain, poorly controlled joint pain, or nephritis. The diagnosis of Kawasaki disease is unlikely given the absence of fever for a minimum of 5 days and the absence of at least four of the five diagnostic criteria. The patient's normal platelet count is inconsistent with the diagnosis of immune thrombocytopenic purpura. Although nonaccidental trauma must always be considered, there is no other bruising of concern on examination, and the clinical presentation is most consistent with the diagnosis of Henoch–Schönlein purpura. The diagnosis of meningococcemia is also unlikely because this patient is nontoxic, alert, and afebrile.
3. **The answer is B** [II.C and II.D.4]. This patient meets the diagnostic criteria for Kawasaki disease based on the duration of fever and the presence of four of the five diagnostic criteria, including conjunctivitis, oropharyngeal changes, a truncal rash, and swelling of the distal extremities. Approximately 10% of patients with Kawasaki disease may develop hydrops of the gallbladder, which presents with acute right upper quadrant pain. Sore throat, conjunctivitis, and red cracked lips are not associated with constipation, arthritis, or intussusception. Dermatomyositis may present with constipation from smooth muscle dysfunction and constitutional symptoms, but abdominal pain is not a feature of the disorder. Although edema of the hands and abdominal pain can be seen in Henoch–Schönlein purpura, fevers and mucous membrane findings are not usually present.
4. **The answer is D** [III.E.3]. This patient has features consistent with systemic-onset juvenile idiopathic arthritis (JIA). Intermittent high-spiking fevers, joint pain and swelling, lymphadenopathy, and hepatosplenomegaly are common features. The classic rash of systemic-onset JIA is described as salmon-colored and maculopapular, located on the trunk and proximal extremities. It is nonpruritic and evanescent (comes and goes) and tends to be more prominent during febrile episodes. Diagnosis is on the basis of characteristic clinical features and does not rely on specific laboratory tests. Although the erythrocyte sedimentation rate is often elevated, it is nonspecific because it is also elevated in many other inflammatory conditions, such as infectious disorders, some malignancies, and other rheumatologic conditions. Moderate to severe symptoms can be treated with anti-inflammatory (e.g., aspirin) or immunomodulatory (e.g., glucocorticoids) medications, but intravenous immune globulin is not recommended for use in JIA. Children with systemic-onset JIA have a 50% chance of having a severe, erosive arthritis. Antinuclear antibodies (ANA) in patients with systemic-onset JIA are negative, in contrast to most patients with early-onset oligoarticular JIA and 50% of patients with polyarticular JIA in whom ANA is positive.
5. **The answer is B** [VII.C.2, VII.D.1–2, and VII.F.1]. The scenario of constitutional symptoms in the face of a classic rash suggestive of erythema migrans, shortly after a camping trip,

supports the diagnosis of Lyme disease. To transmit Lyme disease, an infected tick must be attached to the skin for at least 36-48 hours. Early in the disease, patients may present with fever, headache, myalgias, arthralgias, and lymphadenopathy, along with an annular, or "targetlike," skin eruption with central clearing. Treatment of early disease includes oral doxycycline for children ≥8 years of age, oral cefuroxime or oral amoxicillin. Subsequent neurologic complications are not common but may include aseptic meningitis, facial cranial nerve palsy, and encephalitis. Cardiac complications are quite rare and may include heart block and myocarditis. The prognosis for a child with any stage of Lyme disease, if treated, is excellent. Arthritis, the hallmark of late disease, occurs months after the initial clinical presentation. Serologic testing (enzyme-linked immunosorbent assay and Western blot analysis) is recommended for confirmation of disease.

6. **The answer is A** [VI.A, VI.B.4, VI.D, VI.E, VI.G, and Table 16-6]. This patient's clinical presentation should raise suspicion for acute rheumatic fever. The diagnosis of acute rheumatic fever requires evidence of previous group A β-hemolytic streptococcal infection, in addition to either two major Jones criteria or one major and one minor Jones criteria. The major Jones criteria include erythema marginatum, carditis, migratory polyarthritis, subcutaneous nodules, and Sydenham chorea. Unlike the other major criteria, the onset of chorea is usually several months after the other manifestations. Minor Jones criteria include fever, arthralgias, elevated erythrocyte sedimentation rate, and leukocytosis (not leukopenia). The great majority of patients (70–80%) with acute rheumatic fever have elevated antistreptolysin-O titers. Acute management includes eradication of streptococcal infection with penicillin and control of inflammation with nonsteroidal anti-inflammatory agents or corticosteroids. This patient's shortness of breath may be caused by congestive heart failure or a pericardial effusion. There are usually no chronic joint sequelae from acute rheumatic fever.
7. **The answer is B** [III.D and Table 16-4]. Unlike all other types and subtypes of juvenile idiopathic arthritis (JIA), juvenile ankylosing spondyloarthritis is male predominant and almost always presents in children older than 8 years. Typically, patients with ankylosing spondylitis are human leukocyte antigen B27 (HLA-B27) positive and have involvement of the hips and sacroiliac joints. In contrast, patients with early-onset oligoarticular JIA are usually female, present between 1 and 5 years of age, have a high risk of developing chronic uveitis, and do not have involvement of the sacroiliac joints. Patients with polyarticular JIA (whether rheumatoid factor–positive or –negative) are also usually female and have involvement of multiple large and small joints but not typically the sacroiliac joints. Patients with systemic-onset JIA may be either male or female. Other presenting features of systemic-onset JIA include fever, a characteristic transient skin rash (salmon-colored), hepatosplenomegaly, and lymphadenopathy.
8. **The answer is C** [II.C–F]. Coronary artery aneurysms in Kawasaki disease are more likely to occur during the subacute phase of the disease, which begins 1–2 weeks after the onset of fever. The subacute phase is also characterized by decreasing erythrocyte sedimentation rate (ESR) and by marked thrombocytosis. High-spiking fevers, rash, swollen lips, cervical adenopathy, edema of the distal extremities, and elevations of the ESR and C-reactive protein are all characteristic of the acute phase of Kawasaki disease. Aseptic meningitis is a well-described complication of Kawasaki disease, but there is no known increased incidence of aneurysm formation in patients with aseptic meningitis.
9. **The answers are E, H, D, C, F, and A, respectively** [VIII.A.4, V.C.2, VIII.A.1, III.E.3, IV.C–E, Table 16-5, and I.C]. Abdominal pain and chronic diarrhea may be caused by inflammatory bowel disease. Arthritis may be associated with either ulcerative colitis or Crohn disease. Some patients with inflammatory bowel disease are also human leukocyte antigen B27 (HLA-B27) positive and have involvement of the axial skeleton, which is clinically indistinguishable from ankylosing spondylitis. The diagnosis of dermatomyositis should be suspected in a child

with proximal muscle weakness, a violaceous heliotrope rash around the eyes, and erythematous, hypertrophic papules over the knuckles (Gottron papules). Reactive arthritis is triggered by an enteric or sexually transmitted pathogen (classically, *Chlamydia trachomatis*). Reactive arthritis can present with arthritis, conjunctivitis, and urethritis. The diagnosis of systemic-onset juvenile idiopathic arthritis should be considered in a child presenting with fever of unknown origin, an evanescent salmon-colored rash, arthritis, organomegaly, and polyserositis. Systemic lupus erythematosus may be diagnosed when four of eleven diagnostic criteria are fulfilled, including photosensitivity and a malar rash. Adolescent females might also present with alopecia or Raynaud phenomenon when their disease is active. Henoch–Schönlein purpura is a systemic IgA-mediated vasculitis that involves the skin, joints, gastrointestinal tract, and kidneys. It commonly presents with a nonthrombocytopenic purpuric or petechial eruption on the buttocks or thighs with abdominal pain, arthritis, and glomerulonephritis.

CHAPTER 17

Orthopedics

Ryan J. Coller, Robert M. Bernstein

I. Upper Extremity

A. **Brachial plexus (C5–T1) injury** most commonly occurs as a result of **birth trauma** from excessive traction on the neonate's head, neck, or arm, which stretches the nerves of the brachial plexus.
   1. **Erb palsy** is an upper brachial plexus injury involving the **C5 and C6 nerve roots.** It is the **most common brachial plexus injury** and most often involves the right arm as the result of shoulder dystocia, macrosomia, or forceps delivery. **Clinical features** include a **flaccid arm and an asymmetric Moro reflex.** (See Chapter 2, Table 2-2 for a description of the Moro reflex.) Eventually, the arm is held in internal rotation with the elbow extended, forearm pronated, and the wrist held in flexion. This positioning is often described as the **"waiter's tip."**
   2. **Klumpke palsy** is less common and is the result of a lower brachial plexus injury caused by upward traction on the arm. It involves the **C7 and C8 nerve roots. Clinical features** include a **claw hand** because of loss of intrinsic function and a decreased ability to extend the elbow and flex the wrist. **Horner syndrome** (ipsilateral ptosis, miosis, and anhydrosis) may be present if the sympathetic fibers of the first thoracic nerve have also been damaged.
   3. **Diagnosis** is based on the history and physical examination, but typically also includes a plain radiograph of the shoulder to evaluate for an associated clavicular fracture. Electromyography (EMG) and nerve conduction studies may be considered if no recovery has occurred within 6 months.
   4. **Management.** Treatment includes observation and range-of-motion physical therapy to prevent contractures. Improvement is often noted within 48 hours. Approximately 80% of patients fully recover. Surgery may be required if there is no improvement within 3–9 months.

B. **Nursemaid's elbow** is a **subluxation of the annular ligament over the radial head.** The usual mechanism of injury is an upward force on the arm, such as **pulling a toddler upward** by the hand or wrist to help the child stand or clear an obstacle. The radial head in children younger than 6 years has a cylindrical shape, allowing it to slip out of the annular ligament, which normally keeps it in place.
   1. **Clinical features**
      a. Sudden onset of pain, which is difficult to localize
      b. The **elbow is held flexed** and no swelling is present. The child is unwilling to use the affected arm, but hand function is normal.
   2. **Diagnosis** is usually based on the clinical presentation. No radiograph is needed if the episode was witnessed. Unwitnessed injury should not be assumed to be nursemaid's elbow, and radiographs should be obtained.
   3. **Management.** Treatment of the subluxation is to reduce it by **simultaneously flexing the elbow and supinating the hand.** Spontaneous movement of the arm confirms successful reduction. Postreduction radiographs are not needed.
   4. **Prognosis is excellent.** Usually, the child will start to use the arm within 15 minutes of the reduction, but use of the arm may occasionally be delayed for up to 24 hours. Subluxation may recur.

C. **Anterior shoulder dislocation** is the **most common type of shoulder dislocation.** It occurs with excessive external rotation, abduction, and extension of the shoulder, as it may occur in gymnastics or wrestling.
   1. **Diagnosis** is on the basis of physical examination (the arm being held in external rotation and an inability to touch the contralateral shoulder) and radiographs (especially an

axillary view) of the glenohumeral joint to visualize the dislocation and exclude fractures.

2. **Management.** Treatment is immobilization after closed reduction. **Recurrence of dislocation approaches 90%** in the adolescent population.

II. Spine

A. **Disorders of the cervical spine**

1. **Torticollis** is defined as the tilting of the head to one side. It may be either congenital or acquired.
    a. **Congenital muscular torticollis** is very **common** and is usually the result of uterine constraint or birth trauma, either of which causes contracture of the ipsilateral sternocleidomastoid muscle. Rare causes of congenital torticollis include cervical spine deformities, for example Klippel–Feil syndrome [see section II.A.3].
        1. **Clinical features**
            a. The **head is tilted toward the affected side** and the **chin is rotated away** from the affected side. This is typically present by 1 month of age.
            b. Limited range of motion with passive lateral neck flexion or chin rotation may be present.
            c. Soft tissue mass or tightness may be palpable within the sternocleidomastoid muscle, possibly representing a hematoma or fibrosis. This usually **resolves by 2–6 months** of age.
            d. Asymmetric head shape (**plagiocephaly,** see Chapter 1, section II.B.2.e) may develop in untreated torticollis.
        2. **Diagnosis** is on the basis of physical examination. Radiographs of the cervical spine may identify abnormalities of the cervical spine and should be obtained in anyone presenting late or failing to improve with physical therapy. Strabismus, nystagmus, and abnormal back or neurologic examination should prompt evaluation for conditions other than congenital muscular torticollis.
        3. **Management.** Treatment includes stretching exercises with physical therapy to relieve the muscle contracture.
        4. **Complications** include skull deformity and facial asymmetry (plagiocephaly) if torticollis is not treated promptly.
        5. **Prognosis** after 6 months of diligent muscle stretching is **complete resolution in 90%**, with higher success rates when therapy is started earlier in life.
    b. **Acquired torticollis** arises later in childhood and is much less common than congenital torticollis. **Lack of plagiocephaly** can help distinguish acquired from congenital torticollis. Etiologies are typically from ophthalmologic, central nervous system, musculoskeletal, infectious, or traumatic causes, and they may include strabismus and refractive errors, posterior fossa tumors, syringomyelia, atlantoaxial subluxation [see section II.A.2], cervical adenitis, retropharyngeal abscess, cervical discitis, osteomyelitis, trauma, gastroesophageal reflux disease (Sandifer syndrome), and dystonic drug reactions.
2. **Atlantoaxial instability** is caused by an unstable joint and is characterized by **excessive mobility and potential for dislocation.** It occurs most commonly between the first and second cervical vertebrae and less commonly between the occiput and the first cervical vertebrae. Down syndrome (see Chapter 5, section IV.B.1), skeletal dysplasias (Chapter 5, section IV.H.), and Klippel–Feil syndrome [see section II.A.3] are associated with atlantoaxial instability.
    a. **Clinical features.** Physical examination is usually normal, and **patients are often asymptomatic. With the abovementioned syndromes, a high index of suspicion is important** because spinal cord injury may occur with dislocation or significant instability. Early neurologic signs include neck pain, loss of motor skills, or loss of bowel/bladder control. Significant instability requires surgical stabilization.

b. **Diagnosis** is made by observing excessive movement at the C1 and C2 junction on lateral cervical spine radiographs in the neutral positions followed by flexion–extension radiographs.
c. **Management** includes fusion of C1 and C2 if instability is severe. No contact sports, tumbling, or trampolines are allowed if there is any sign of instability.
d. **Complications** include paralysis or even death if the instability is not detected before injury.

3. **Klippel–Feil syndrome** is defined as *congenital fusion of the cervical vertebrae.* The triad is **low-set hairline, short neck, and limited neck motion.** Associated abnormalities may include congenital torticollis, genitourinary anomalies, congenital heart disease, hearing loss, and congenital failure of scapula to descend to its proper location.

B. **Scoliosis** is a **fixed lateral curvature of the spine of greater than or equal to 10°.** This disorder occurs equally in males and females, but adolescent females require treatment eight times more frequently.

1. **Etiology**
a. Most cases of scoliosis (80%) are **idiopathic.** A positive family history is common.
b. Improper spine development, including failure of vertebral formation or abnormal fusion, leads to **congenital scoliosis.**
c. Other types of scoliosis are **neuromuscular** (associated with cerebral palsy) or **syndromic** (associated with skeletal dysplasias and connective tissue disorders). Leg length discrepancy can mimic scoliosis.

2. **Clinical features. Scoliosis is typically asymptomatic.** Asymmetry of the shoulder height, scapular position, and the waistline may be present. As the patient bends forward, a hump, representing rib or transverse process rotation of the curved spine, may be seen (forward bending test; Figure 17-1). Curves are right thoracic 90% of the time. **Pain or left-sided curves are signs of underlying disorders,** and should prompt investigation for nonidiopathic causes.

3. **Diagnosis** is on the basis of clinical findings and radiologic confirmation. Standing posterior–anterior (PA) films of the spine confirm the curvature and are used to calculate the **Cobb angle** (Figure 17-2). The Cobb angle, which measures the degree of scoliosis, is measured by drawing a line along the superior aspect of the most angulated vertebrae at the top of the curvature, and drawing another line along the inferior aspect of the lowest most angulated vertebrae of the curvature. The angle at the intersection of these lines is the Cobb angle. A lateral radiograph is helpful to rule out kyphosis, spondylolisthesis, and congenital anomalies of the spine.

4. **Management.** Treatment options include observation, bracing, and surgery, and management decisions are based on the magnitude of the curve and the remaining growth potential. **Bracing prevents progression** of the curvature; therefore, bracing is not likely helpful after skeletal growth is completed. **Progression of scoliosis generally occurs only during growth.** It is important to remember that almost all growth in females ceases within 6 months of menarche. **Two years postmenarche is considered skeletally mature.** Surgery is required for very severe curves or to stop curves that progress in spite of bracing. If a thoracic curve reaches **50°**, **there is always progression**, even after skeletal maturity. **Table 17-1** summarizes management approaches based on skeletal maturity and the degree of curvature.

5. **Complications.** Severe thoracic curves (>70°) can be associated with restrictive or obstructive lung disease.

C. **Kyphosis (roundback)** is defined as **anterior–posterior (AP) curvature of the thoracic spine.** Fixed kyphosis beyond 50° is considered pathologic.

1. Flexibility in the rounded area should be assessed by having the patient extend his or her

back while prone. Most adolescents with kyphosis have **flexible kyphosis,** in which they can voluntarily correct the rounded area. This is called "postural roundback," and it is managed with physical therapy and postural exercises.

2. **Scheuermann kyphosis** is a **rigid kyphosis greater than 50°**, in which at least **three consecutive vertebrae are wedged.** End plate changes and disk space narrowing are noted on radiographs. It develops in otherwise healthy adolescents and is managed with referral to physical therapy and orthopedics.

D. **Back pain.** *Any complaint of back pain that interferes with play should be further evaluated.* The differential diagnosis is extensive and includes congenital or traumatic musculoskeletal problems such as fractures; infections such as osteomyelitis or pyelonephritis; neoplasms; and rheumatologic conditions. See *Table 17-2*. Some common causes include the following:

1. **Back strain** is muscular soreness from overuse or poor body mechanics. **Back strain is the most common cause of back pain in children.**
   a. **Clinical features.** Diffuse muscular pain is present without neurologic deficits. Physical examination is normal.
   b. **Management.** Treatment includes rest, stretching, and analgesics.
2. **Spondylolysis** is a **stress fracture in the pars interarticularis** (i.e., the bone that connects the superior and inferior articular facets of a vertebral body) usually secondary to **repetitive hyperextension of the spine** as occurs in gymnastics, tennis, and diving. It typically involves the lumbar region, particularly L5. Pain is localized and **increases with hyperextension.**
   a. **Diagnosis** is on the basis of AP, lateral, and oblique views of the lumbar spine. However, because spondylolysis is a stress fracture, plain films may not detect the fracture. Magnetic resonance imaging (MRI), bone scan, or a single photon-emission computed tomographic (SPECT) scan may be used for diagnosis if the fracture is acute.
   b. **Management.** Treatment includes rest and analgesics for pain. Bracing for immobilization may be necessary if pain persists. Surgery is rarely required.
   c. **Complications** include spondylolisthesis, which is discussed below.
3. **Spondylolisthesis** occurs when the **vertebral body involved in the spondylolysis slips anteriorly** (i.e., subluxation of the vertebra). The subluxated vertebra can impinge on nerve roots. Diagnosis and treatment is the same as for spondylolysis. Indications for surgery include nerve impingement, persistent pain, or progression of the subluxation beyond 50% of the vertebral width.
4. **Discitis** is defined as **infection** (***Staphylococcus aureus*** is the most commonly identified organism) **or inflammation** (idiopathic, traumatic, or rheumatologic) **of the intervertebral disk.**
   a. **Clinical features.** Discitis typically begins with signs and symptoms of an upper respiratory illness or minor trauma, followed by back pain with **tenderness over the involved disk.** Fever is sometimes present. Children refuse to bend forward, and young children may refuse to walk.
   b. **Diagnosis.** Erythrocyte sedimentation rate (ESR) is typically elevated. MRI or bone scan confirms the diagnosis.
   c. **Management.** Antistaphylococcal antibiotics are given to patients who are suspected to have infection. Treatment also includes bed rest and analgesics.
5. **Herniated intervertebral disk** is much more common in adults, but may occur in adolescents. The lumbar region is most commonly affected. Unlike in adults, herniation in adolescents is caused by repetitive activity and rarely by trauma. Initial treatment includes nonsteroidal anti-inflammatory drugs (NSAIDs) and rest. Epidural steroids may be considered. Surgery to remove the disk is necessary only if symptoms persist or if the

neurologic examination is abnormal.

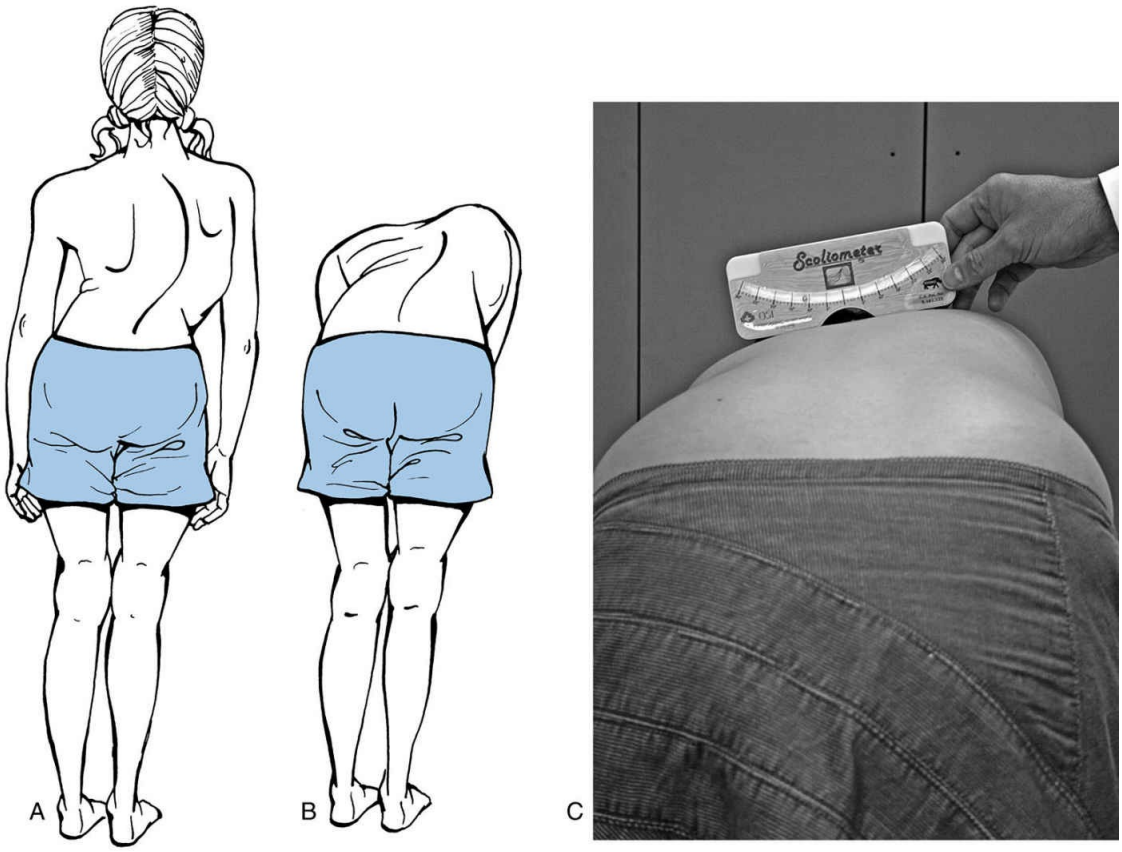

FIGURE 17.1 Scoliosis. **A.** Curve is visible when standing. **B.** Rib hump is visible when the child performs forward bending test. **C.** Scoliometer is used to quantify the degree of curvature on the forward bend test.

(C) Reprinted with permission from Weinstein SL, Flynn JM. *Lovell and Winter's Pediatric Orthopaedics*. 7th Ed. Philadelphia: Lippincott Williams & Wilkins, 2013.

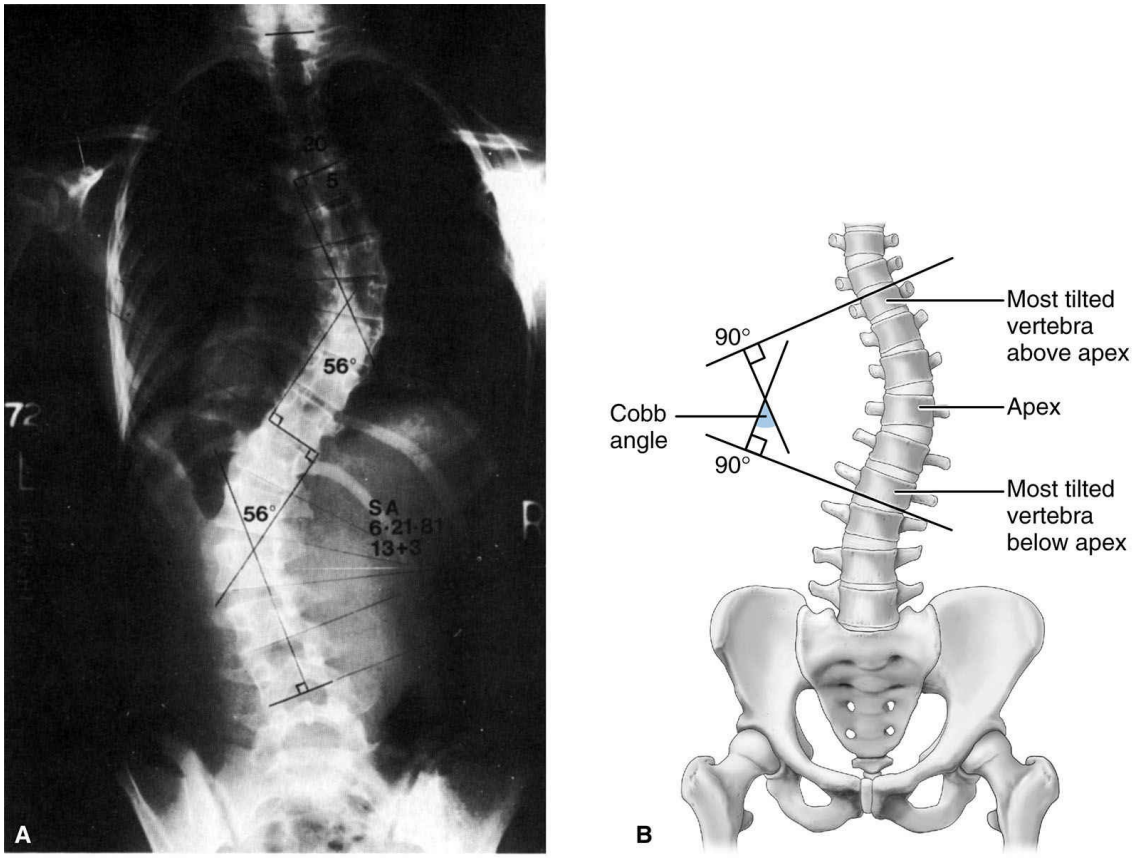

FIGURE 17.2 Cobb angle measurement noted on radiograph (A) and figure (B).

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Table 17-1
Management of Adolescent Idiopathic Scoliosis

Scoliosis Curvature	Skeletally Immature	Skeletally Mature
	Before or During Growth	**Growth Completed**
10°–25°	• Follow-up scoliosis films 6 months after diagnosis	• No treatment required
	• ≥7° progression—refer to orthopedic surgeon	
25°–40°	• Bracing indicated	• No treatment required
>40°	• Surgery may be indicated	• Surgery may be indicated if scoliosis > 50°

Table 17-2
Common Causes of Back Pain in Children and Distinguishing Features

	Back Strain	Spondylolysis	Spondylolisthesis	Discitis
Key features	Most common cause of back pain	Repetitive hyperextension of the spine	Complication of spondylolysis	*Staphyloccocus aureus* is most common
Etiology	Overuse or poor body mechanics	Stress fracture in pars interarticularis	Anterior subluxation of the vertebral body after	Infection or inflammation of

			spondylolysis	intervertebral disk	
Diagnosis	History and physicalNormal examination with possible tenderness of paraspinal muscles	Localized painWorse with hyperextensionAP, lateral, oblique radiographs of lumbar spine confirm diagnosis	Same as spondylolysis	Tenderness over involved disc	
					Refusal to bend forward
					Elevated ESRBone scan/MRI confirm diagnosis
Management	Rest, stretching, and analgesics	Rest, analgesicsBracing to immobilize if pain is severe	Same as spondylolysisSurgery if signs of nerve impingement or subluxation >50% of vertebral width	Antistaphylococcal antibiotics	
				Rest, analgesics	

AP = anteroposterior; *ESR* = erythrocyte sedimentation rate; *MRI* = magnetic resonance imaging.

III. Hip

A. **Developmental dysplasia of the hip (DDH)** occurs when the acetabulum is shallow or poorly formed, leading to the **subluxation or dislocation of the head of the femur.** The spectrum of disease severity ranges from hip joint laxity to frankly dislocated hips. DDH was formerly termed congenital hip dysplasia; however, this name was abandoned to reflect the spectrum of findings possible, including a normal examination at birth with progression to dislocation later in life.

1. **Epidemiology**
    a. DDH is more common in **girls** than in boys.
    b. **Risk factors include female sex, firstborn, breech presentation, and family history of DDH.**
2. **Clinical features.** DDH is **asymptomatic** in infants. Physical examination may show the following findings:
    a. **Positive Barlow maneuver.** (The Barlow maneuver attempts to **dislocate a dislocatable hip.**) With the hips at 90° flexion, the thumb is placed on the medial side of the thigh and the middle finger on the greater trochanter, and gentle pressure is applied posteriorly and laterally to dislocate the hip. The hip is then gently abducted, and a "clunk" is felt as the hip relocates.
    b. **Positive Ortolani maneuver.** (The Ortolani maneuver attempts to **reduce a dislocated hip.**) In the same position described above, the hip is abducted with pressure gently applied upward with the middle finger to slide the head of the femur back into the acetabulum. In a positive Ortolani maneuver, the hip can be felt slipping into the acetabulum as it is being reduced. An Ortolani-positive hip is one in which the hip is dislocated but can be reduced.
    c. **Galeazzi sign,** which assesses asymmetry of the apparent femoral length. The examination is performed by placing the hips in flexion at 90° with the feet flat on the table, heels apposed to the buttocks, while the infant is supine. If the hip is dislocated, the affected femur, and therefore knee, appears shorter compared with the normal limb. If both hips are dislocated, Galeazzi sign will not be positive as the knees will be at the same height.
    d. **Asymmetric abduction of the hips and asymmetric thigh or buttock folds. Ortolani and Barlow maneuvers are not useful after about 4 months of age** because the hip stabilizes in either the dislocated or reduced position. After this age, decreased ability to abduct the affected hip, asymmetric thigh or buttock folds, or Galeazzi sign is more useful in the diagnosis of DDH.
3. **Diagnosis.** Physical examination alone may be the basis of diagnosis. However, imaging is helpful if the examination is equivocal or the patient is at high risk, such as an infant who was breech in utero or children with positive family histories.
    a. **Ultrasound** is used to assess for DDH in young infants because the femoral head does not ossify until 4–6 months of age.
    b. **AP radiographs** of the pelvis may be used to assess for DDH if the infant is older than 6 months.
4. **Management.** Treatment depends on the age of the patient at the time of diagnosis. The **earlier the diagnosis, the less likely surgical intervention will be necessary.**
    a. The **Pavlik harness** holds the head of the femur against the acetabulum to stimulate formation of the normal cup shape of the acetabulum. It is typically used for 2–3 months if the diagnosis is made by 6 weeks of age. It is successful in 90–95% of cases.

b. **Surgery** may be required if the diagnosis is made beyond 6 weeks of age, if the hips are bilaterally dislocated, if the hips are not reducible on physical examination, or if the Pavlik harness fails to stabilize the hip. Surgery may involve closed or open reduction of the hip. After surgery, the infant is in a cast for 2–3 months.

5. **Complications**
   a. **Avascular necrosis of the femoral head**
   b. **Limb length discrepancy, limp, and osteoarthritis** if DDH is not treated

B. **Limp** is a common symptom during childhood. The differential diagnosis is extensive and is listed in **Table 17-3.** The more common causes include the following:

1. **Septic arthritis** is a bacterial infection of the joint, which can be caused by hematogenous spread (most common), contiguous spread, or direct inoculation. **Septic arthritis of the hip is an orthopedic emergency.**
   a. **Epidemiology**
      1. The peak age is 1–3 years.
      2. The **hip is most commonly affected in younger children,** whereas the knee is more commonly affected in older children.
   b. ***S. aureus, Streptococcus pneumoniae,*** and ***Streptococcus pyogenes*** are the most common organisms. Relevant Gram-negative organisms include *Neisseria gonorrhoeae* in neonates and adolescents and *Kingella kingae* in children younger than 3 years.
   c. **Clinical features**
      1. **Fever and irritability** are common.
      2. **Limp, refusal to walk, and pain with movement of the joint** may occur. Attempts to move the joint result in significant pain. If the hip is affected, it is usually held in **flexion, abduction, and external rotation** to relieve the pressure within the joint capsule.
      3. **Erythema, swelling, and asymmetry of soft tissue folds** may be present.
   d. **Diagnosis**
      1. **Laboratory studies** include an **elevated white blood cell (WBC) count, ESR, and C-reactive protein (CRP).**
         a. Blood culture is positive in 30–50% of cases.
         b. Analysis of the synovial fluid for cell count, Gram stain, and culture is important. **Synovial fluid with a WBC count > 50,000–100,000 cells/mm^3** with neutrophilic predominance is suggestive of septic arthritis. Culture of synovial fluid is positive in only 60% of cases. Unless the child is toxic-appearing, cultures should be obtained before administering antibiotics.
      2. **Imaging** complements physical examination and laboratory findings.
         a. Ultrasound is the best imaging screen and demonstrates fluid in the joint capsule.
         b. Plain radiographs may reveal a widened joint space and may exclude other diagnoses in the differential (e.g., fracture) but are often normal.
   e. **Management**
      1. **Surgical decompression** is necessary to avoid avascular necrosis and to obtain synovial fluid for analysis.
      2. **Empiric intravenous antibiotics** to cover Gram-positive organisms, including consideration for methicillin-resistant *S. aureus*, should be started ***after*** blood and joint cultures are obtained. Duration of antibiotic treatment is 4–6 weeks.
   f. **Complications.** The femoral head is vulnerable to ischemic injury. Ischemia may lead to **avascular necrosis and cartilaginous damage.**
2. **Transient synovitis** (also known as **toxic synovitis**) is a common self-limited, irritation of

the hip joint. It may be a postinfectious inflammatory reaction. A viral prodrome (upper respiratory infection or diarrheal illness) often precedes transient synovitis. Transient synovitis is a **diagnosis of exclusion,** and it is extremely important to rule out septic arthritis, especially if a patient is ill-appearing, given the potentially disabling consequences of missed septic arthritis (Table 17-4).

a. **Epidemiology**
    1. **Transient synovitis is the most common cause of a painful limp in toddlers.**
    2. Its peak age of presentation is **2–7 years.**
    3. It is more common in **males.**
b. **Clinical features**
    1. **Low-grade fever, limp,** and mild irritability may be present. Patients usually appear relatively well.
    2. **Hip pain** may be acute or insidious in onset. Although patients may be more willing to move their legs than patients with septic arthritis, they may also hold their hip in a flexed, abducted, and externally rotated position, similar to the position seen in septic arthritis.
c. **Diagnosis** is often on the basis of the history and physical examination.
    1. The WBC count and ESR are normal or only slightly elevated.
    2. There may be an effusion in the hip, and if fluid is present with clinical concern for the possibility of septic arthritis, it should be aspirated and analyzed to rule out septic arthritis. Synovial fluid WBC counts may be elevated above the normal reference range, but are less than that seen in septic arthritis (see Table 17-4).
d. **Management.** Treatment includes NSAIDs, rest, and observation.
e. **Prognosis** is excellent. Pain usually improves within 3 days with analgesics and rest. Complete resolution of symptoms usually occurs by 3 weeks. Recurrence is unusual unless vigorous activities are resumed too soon.

3. **Legg–Calvé–Perthes** (Perthes) **disease** is **idiopathic avascular necrosis of the femoral head.**
    a. **Epidemiology**
        1. The disease is more common in Caucasians and Asians.
        2. The disease is more common in **boys** and has a male-to-female ratio of 4:1.
        3. Patients are typically active, thin boys who are small for their age.
        4. The disease most commonly affects children between **4 and 8 years of age.**
    b. **Clinical features.** Children have a slightly painful limp with **decreased internal rotation and abduction of the hip.** This can be assessed on examination by logrolling the leg internally. Pain may be referred to the knee and to the groin.
    c. **Diagnosis** is on the basis of AP and frog-leg lateral radiographs of the pelvis, which show increased density in the affected femoral head, or a crescentic subchondral fracture in the femoral head, termed the **"crescent sign."**
    d. **Management.** Treatment involves containment or ensuring that the femoral head is positioned within the acetabulum to facilitate its remolding and reossifying.
        1. **Physical therapy** and **restriction of vigorous exercise** are effective. If pain persists, analgesia, traction, casting, or crutches may be used.
        2. **Surgery** is indicated if there is more than 50% involvement of the femoral head, or if there is subluxation of the femoral head out of the acetabulum.
    e. **Prognosis** is best in younger patients. If children develop the disease when they are younger than 9 years, complete resolution within 3 years is common. The majority of patients who develop the disease at age 9 years or older go on to develop osteoarthritis in the affected hip as adults.

4. **Slipped capital femoral epiphysis (SCFE)** is slipping of the femoral head off the femoral neck.
    a. **Epidemiology**
        1. Age of onset is usually during peak linear growth in adolescence.
        2. The male-to-female ratio is 2–3:1.
        3. The typical patient is an **obese adolescent male.**
    b. **Clinical features.** Patients have a **painful limp with pain in the groin, hip, or knee.** The degree of pain varies from severe (acute slip) to mild (chronic slip). **Internal rotation, flexion, and abduction are usually reduced in the affected hip.** SCFE is bilateral in 30% of cases, and patients with **hypothyroidism** are especially more likely to develop bilateral disease. Diagnosis of SCFE outside the typical age range, or in patients who are thin or have short stature, should prompt consideration of endocrine, renal, or genetic disorders.
    c. **Diagnosis.** AP and frog-leg lateral radiographs of the pelvis confirm the slipped epiphysis. A line drawn flanking the superior edge of the femoral neck (**Klein line**) crosses 10–20% of the epiphysis in a normal hip on AP pelvis films. However, in SCFE, the Klein line may not cross the epiphysis at all.
    d. **Management.** Treatment involves pinning the epiphysis to prevent further slippage. The femoral head is not placed back into a normal position with the femoral neck because the force required may cause avascular necrosis.
    e. **Complications**
        1. **Avascular necrosis** and collapse or deformity of the femoral head
        2. **Chondrolysis** (degeneration of articular cartilage of the hip)
        3. **Limb length discrepancy,** which may cause limp and pain
        4. **Osteoarthritis**
5. **Osteomyelitis** is an infection of the bone.
    a. **Epidemiology**
        1. The peak ages of onset are less than 1 year and between 9 and 11 years.
        2. The male-to-female ratio is 2:1.
    b. **Etiology**
        1. ***S. aureus*** and ***S. pyogenes*** are the most common organisms. ***Salmonella*** should be considered in patients with **sickle cell anemia.** ***Pseudomonas aeruginosa*** infection of a bone in the foot can occur if a child has a puncture wound passing through his or her sneaker into the foot.
        2. Although contiguous spread and direct inoculation can cause osteomyelitis, children most commonly acquire infection by **hematogenous seeding.**
        3. **The causative organism is not isolated in up to 30–50% of cases.**
    c. **Clinical features**
        1. **Fever** and irritability
        2. **Bone pain, erythema, swelling,** and induration, which may develop in the area over the osteomyelitis
        3. **Painful limp**
    d. **Diagnosis**
        1. **Laboratory studies** include an **elevated WBC count, ESR, and CRP.**
            a. Blood culture is positive in 50% of cases.
            b. Blood culture in combination with a culture of the aspirated bone may identify the organism in 70% of cases. Unless the child is toxic-appearing, cultures should be obtained before administering antibiotics.
        2. **Imaging.** Although a plain radiograph may not show bone changes early, soft tissue swelling (displacement of fat planes) can often be detected. **Bone scan**

or MRI can detect osteomyelitis a few days after the onset of symptoms. After 10–14 days of infection, a plain radiograph begins to reveal **elevation of the periosteum**, suggesting osteomyelitis.

e. **Management**

1. Antibiotics should be given for 4–6 weeks, although the length of treatment varies depending on the organism and patient response. Unless the patient is septic, antibiotics should be held until blood cultures are obtained and the bone has been aspirated for culture.
2. Improving symptoms and decreasing ESR/CRP generally indicate response to intravenous antibiotics, at which time oral antibiotics can be used to complete the antibiotic course.
3. Surgery is necessary to drain and debride a subperiosteal abscess if fever and swelling persist despite 48 hours of intravenous antibiotics.

f. **Complications**

1. **Spread of infection** may occur, either by contiguous spread infecting a joint or distant seeding of other organs.
2. **Chronic osteomyelitis** results from a nidus of residual infection, such as a **sequestrum** (i.e., focus of necrotic bone) or an **involucrum** (i.e., formation of new bone or fibrosis surrounding the necrotic, infected bone). Symptoms of chronic osteomyelitis are usually insidious, so the diagnosis is often delayed and complications are common. Both surgery and antibiotics are needed.
3. **Pathologic fracture** at the site of the infection may occur as a result of healing and remodeling of bone, bone necrosis, or a sequestrum. Activity should be restricted during antibiotic therapy to prevent a fracture, especially if the diagnosis of osteomyelitis was initially delayed.
4. **Angular deformity or limb length discrepancy** may occur if the growth plate is involved in the infection.

Table 17-3
Differential Diagnosis of a Painful Limp

Mnemonic: "The Joint STARTSSSS HOTT"	Other Causes of Limp
S Septic arthritis	**D** Developmental hip dysplasia
T Transient synovitis	**D** Discitis
A Acute rheumatic fever	**L** Legg–Calvé–Perthes
R Rheumatoid arthritis	**L** Limb length discrepancy
T Trauma Fracture Strain or sprain	**L** Lyme disease
S Sickle cell disease Pain crisis (vaso-occlusive crisis) Osteomyelitis	
S Systemic lupus erythematosus	
S Steroid use (chronic)	
S Slipped capital femoral epiphysis (SCFE)	
H Henoch–Schönlein purpura	
O Osteomyelitis	
T Tuberculosis	
T Tumor Osteosarcoma Leukemia	

Table 17-4
Septic Arthritis Versus Transient Synovitis

	Septic Arthritis	**Transient Synovitis**
Organisms	*Staphylococcus aureus*	Typically sterile inflammationPossibly postviral
	Streptococcus pyogenes	
	Streptococcus pneumoniae	
Clinical features	Peak 1–3 years	Peak 2–7 years
Acute	Acute or subacute	
Ill-appearing	Well-appearing	
Fever	Mild viral prodrome	
Limp	Limp	
Refusal to bear weight	Refusal to bear weight	
Flexion, abduction, external rotation of the hip	Flexion, abduction, external rotation of the hip	
Typical joints involved	Hip, knee, ankle	Hip
Laboratory findings	Elevated ESR (>40 mm/hour)	Mildly elevated ESR
Elevated CRP (>2 mg/dL)	Mildly elevated CRP	
Elevated WBC	Mildly elevated WBC	
Blood culture positive 30–50%	Blood culture negative	
All laboratory results may be normal		
Joint aspirate	>50,000–100,000 cells/mm^3	<50,000 cell/mm^3
Gram stain may have organisms	Gram stain without organisms	
Treatment	Surgical decompression	NSAIDs
Intravenous antibiotics	Rest	

ESR = erythrocyte sedimentation rate; *CRP* = C-reactive protein; *WBC* = white blood cell; *NSAIDs* = nonsteroidal anti-inflammatory drugs.

IV. Lower Extremity

A. **Torsional abnormalities**

1. **In-toeing** ("pigeon-toe"), a common parental concern, **is typically normal** and corrects with growth (see Table 17-5). The following are the most common causes of in-toeing:
    a. **Metatarsus adductus** is **medial curvature of the mid-foot** (metatarsals).
        1. **Epidemiology and etiology**
            a. Metatarsus adductus occurs in children younger than 1 year.
            b. It is usually caused by intrauterine "packaging" or "molding."
        2. **Clinical features** include a C-shaped or kidney bean-shaped foot that can be straightened to varying degrees by gentle manipulation. Dorsiflexion is normal, but if the ankle cannot dorsiflex, clubfoot should be considered.
        3. **Diagnosis** is by physical examination. Radiographs are not needed.
        4. **Management**
            a. **Flexible foot that can overcorrect** with passive motion needs observation only.
            b. **Flexible foot that can correct with passive motion, but not overcorrect,** may benefit from gentle stretching of the foot.
            c. **Stiff foot that cannot be straightened** warrants evaluation by a pediatric orthopedic specialist. Casting of the foot for 3–6 weeks may be necessary.
        5. **Prognosis** is excellent. Resolution occurs in almost all patients by 1 year of age.
    b. **Talipes equinovarus (clubfoot)** is a fixed inversion and equinus position of the foot with minimal flexibility. Bilateral involvement occurs in 50% of cases.
        1. **Epidemiology**
            a. Incidence is 1 in 1000; it is increased to 6 in 1000 in Pacific Islanders.
            b. The male-to-female ratio is 2:1.
        2. **Etiology** is multifactorial, but genetics is thought to play a strong role because of the increased incidence of clubfoot within families. Talipes equinovarus is usually isolated but can have associations with DDH, myelomeningocele, myotonic dystrophy, trisomy 18, and some skeletal dysplasias. It is not an in utero packaging problem.
        3. **Clinical features.** The ankle is held in plantar flexion and inversion. The forefoot is curved medially (metatarsus adductus). The deformity is rigid with very little range of motion in the ankle.
        4. **Diagnosis** is generally on the basis of physical examination.
        5. **Management.** Treatment involves casting within the first few weeks of life. Achilles tendon release is often required. If the deformity is severe or if there is no improvement after 3 months of casting, surgical correction may be necessary.
        6. **Prognosis** is good, with 50–80% of patients improving with casting alone.
    c. **Internal tibial torsion** is a medial rotation of the tibia, causing the foot to point inward.
        1. **Epidemiology and etiology**
            a. Internal tibial torsion is the **most common cause of in-toeing in children younger than 3 years.**
            b. It is caused by in utero positioning.
        2. **Clinical features** include a **foot that points medially when the knee is flexed to 90°.** The patella faces forward. Bilateral torsion is more common, but

unilateral torsion also occurs. Torsion is present at birth but is often **noted between 1 and 3 years of age** when the child starts to stand. The **thigh–foot angle** is determined laying the patient prone, flexing the knee to 90° with the plantar surface of the foot parallel to the ceiling (Figure 17-3). The angle between the line along the length of the femur and the line from the heel through the third web space of the foot is assessed. A normal angle is 10°–15° of external rotation.

3. **Management** involves observation only.
4. **Prognosis** is excellent with improvement by 3 years of age and resolution by 5 years of age.

d. **Femoral anteversion** (or medial femoral torsion) is an inward rotation of the femur.

1. **Epidemiology.** Femoral anteversion is the **most common cause of in-toeing in children older than 3 years.** The female-to-male ratio is 2:1.
2. **Clinical features**
   a. **Feet and patella point medially.**
   b. **Hips are able to internally rotate more than normal.** External rotation is more limited than normal.
   c. Child prefers to **sit in a "W" position** (opposite of sitting crossed-legged on the floor).
3. **Management** is observation only.
4. **Prognosis** is excellent with resolution by 8 years of age.

2. **Angulation of the knee.** Children go through developmentally normal periods of genu varum and genu valgum. Identifying a deviation from the expected trajectory is most important.

a. **Physiologic bowed legs (genu varum)** is symmetric bowing of the legs in children younger than 2 years. **Bowed legs are developmentally normal until about 2 years of age**, when the legs begin to naturally straighten.

1. **Clinical features**
   a. **"Cowboy" stance.** When the child stands erect with the feet together, the knees bow laterally and the patella point forward.
   b. **Normal gait,** with the body weight held in midline throughout the gait cycle. If the weight seems to shift from side to side, then **Blount disease** may be considered [see section IV.A.2.b].
2. **Diagnosis** is on the basis of physical examination. Genu varum is present at birth but is usually not noticed until the child begins to walk. A standing AP radiograph of the lower extremities is indicated only if bowing is unilateral, severe, painful, or persists after 2 years of age to assess for pathologic bowing as may occur with rickets, growth plate injury, Blount disease, or skeletal dysplasias.
3. **Management** is observation. Progression of bowing may be monitored by measuring the intercondylar distance when the patient stands erect with the feet together. Bracing or corrective shoes are not necessary.
4. **Prognosis** is excellent with resolution by 2 years of age.

b. **Blount disease (progressive tibia vara)** is a progressive angulation at the proximal tibia.

1. **Epidemiology and etiology**
   a. Risk factors may include obesity and early walking.
   b. Incidence of the disease is increased with African American race/ethnicity.
   c. The disease is thought to be a result of overload injury to the medial

tibial growth plate, causing inhibited growth only on the medial side.

2. **Clinical features**
    a. **Angulation just below the knee**
    b. **Lateral thrust with gait** (i.e., the shifting of weight away from midline while walking)
3. **Diagnosis.** Blount disease should be **suspected in any child with progressive bowing, unilateral bowing, or persistent bowing after 2 years of age.** Diagnosis is on the basis of a standing AP radiograph of the lower extremities.
4. **Management**
    a. **Bracing** may be attempted if the bowing is mild and if the patient is 2–3 years of age.
    b. **Osteotomy** may be performed if there is no improvement when the patient is approaching 4 years of age, if there is recurrence of angulation, or if the deformity is very severe.
5. **Prognosis**
    a. **Osteoarthritis** is common if angulation is not corrected.
    b. **Recurrence of angulation** is common in obese children if treatment is started after 4 years of age, or if the epiphysis is fragmented from injury.

c. **Knock-knees (genu valgum)** is idiopathic angulation of the knees toward the midline.

1. **Epidemiology and etiology**
    a. **Developmentally normal between 3–5 years of age**
    b. Most cases are physiologic as a result of overcorrection of normal genu varum.
2. **Clinical features**
    a. **Separation of the ankles** when standing erect with knees together
    b. **Swinging of legs laterally with walking or running**
3. **Diagnosis** is on the basis of physical examination.
4. **Management** is **observation** for the majority of patients. Surgical intervention is indicated only if genu valgum persists beyond 10 years of age or causes knee pain.
5. **Prognosis** is excellent as the condition spontaneously resolves in the majority of patients.

B. **Osgood–Schlatter disease** is an inflammation or microfracture of the tibial tuberosity caused by overuse injury.

1. **Epidemiology.** Osgood–Schlatter disease is the most common **apophysitis.** Apophysitis is inflammation at the site of tendon insertion onto bone.
    a. Age of onset is most commonly 10–17 years.
    b. Osgood–Schlatter disease usually occurs in children who participate in sports involving **repetitive jumping or cutting**, such as basketball or soccer. The disease is more common in boys.
2. **Clinical features** include **swelling of the tibial tuberosity** and knee pain with **point tenderness over the tibial tubercle.** Pain occurs with extension of the knee against resistance. The pain worsens with running, jumping, and kneeling.
3. **Diagnosis** is on the basis of history and physical examination. Radiographs are not necessary.
4. **Management** includes ice, NSAIDs, stretching, and strengthening of the quadriceps and hamstrings.

C. **Sever disease (calcaneal apophysitis),** caused by overuse, is inflammation at the site of Achilles tendon insertion on the posterior calcaneus.

1. **Epidemiology.** Sever disease is one of the most common causes of heel pain. Similar to Osgood–Schlatter, Sever disease usually occurs in children participating in sports with repetitive jumping or cutting and **repetitive heel striking**, such as soccer, gymnastics, basketball, and track.
2. **Clinical features** include **heel pain with an insidious onset.** Physical examination demonstrates pain with **calcaneal compression.** Symptoms are exacerbated by wearing footwear without adequate heel support.
3. **Diagnosis** is on the basis of history and physical examination. Radiographs are not necessary.
4. **Management** includes ice, NSAIDs, stretching, use of heel cups and strengthening of the Achilles tendon. Rarely, a walking cast may be required in severe cases.

D. **Patellofemoral pain syndrome (formerly patellar chondromalacia)** is increased contact pressure between the patella and the femur, causing knee pain.
1. **Epidemiology.** Patellofemoral pain syndrome is **common in adolescent girls.**
2. **Clinical features**
   a. **Anterior knee pain** is directly under or around the patella.
   b. Pain is worse with activity or with walking up and down stairs. It is relieved with rest, although pain may be noted after prolonged periods of knee flexion (e.g., during movies or air travel).
3. **Diagnosis** is on the basis of history and physical examination.
4. **Management** includes stretching and strengthening of the medial quadriceps.

E. **Growing pains** are idiopathic bilateral leg pains that occur in the late afternoon or evening but **do not interfere with play during the day. Pain is not due to growth but rather is an overuse syndrome.**
1. **Epidemiology.** Growing pains are **very common** and occur in **children 4–12 years** of age, although this should be considered a diagnosis of exclusion.
2. **Clinical features.** Children may awaken at night crying in pain; however, the physical examination is normal.
3. **Management.** Treatment includes analgesics and reassurance.

Table 17-5
Typical Causes of In-toeing in Children

	Metatarsus Adductus	**Tibial Torsion**	**Femoral Anteversion**
Typical age	<1 year	1–3 years	>3 years
Etiology	Medial curvature of the foot	Internal rotation of the tibia	Internal rotation of the femur
Physical examination	C-shaped foot	Patella faces forward	Patella points medially
Flexible (passively straightened) or stiff	Thigh–foot angle abnormal	Increased internal hip rotation	
		"W" sitting position	

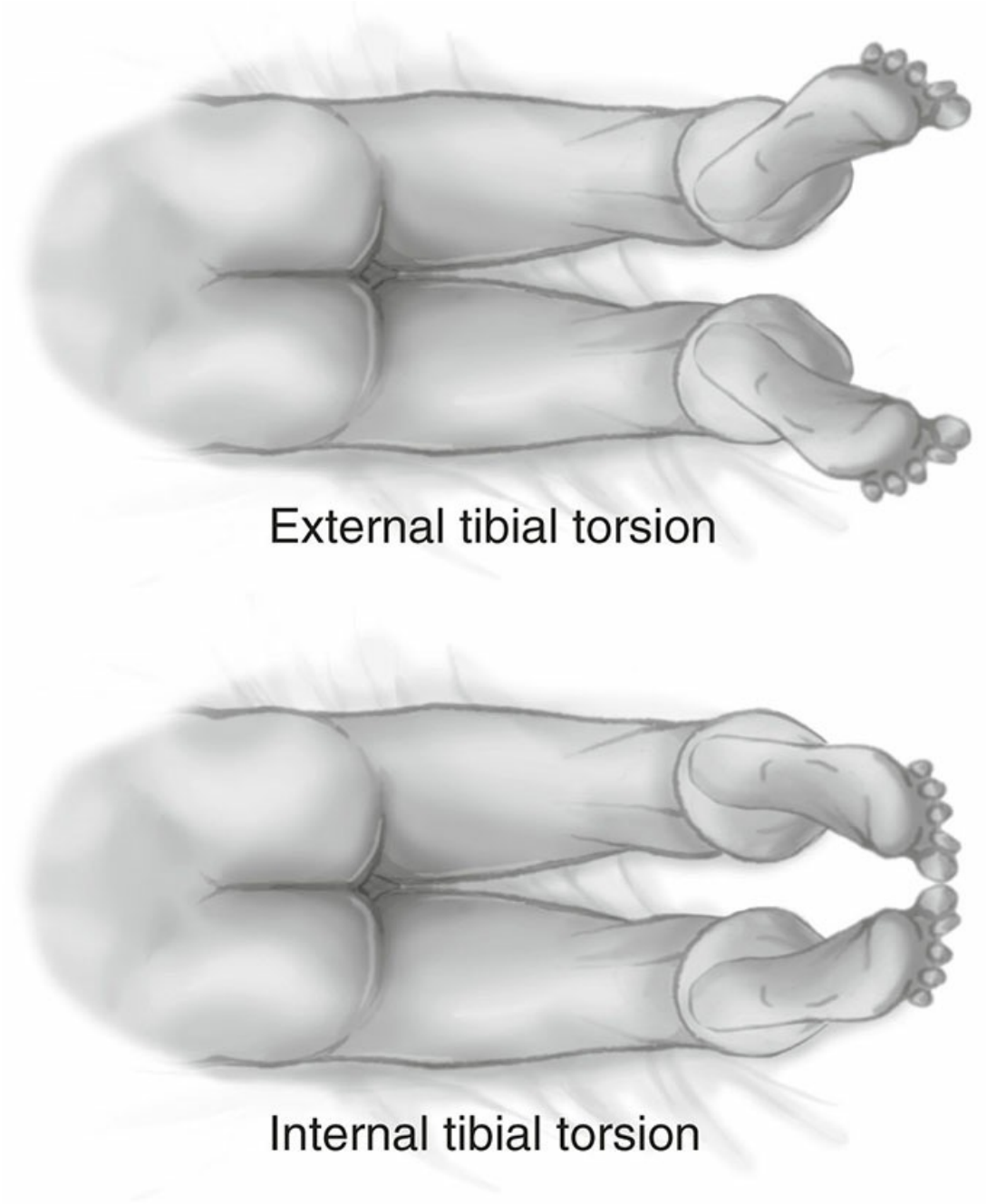

FIGURE 17.3 Determining the thigh–foot angle.

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V. Common Fractures

A. **Describing fractures** is critical because it may dictate the management of a fracture.
   1. **Open or closed fracture** describes whether a break in the skin overlies a fracture. In a closed fracture, the skin is intact. In an open fracture, the skin is broken and antibiotics are required because of the risks of local infection and osteomyelitis.
   2. **Spatial relationship of the fractured ends** describes the orientation of the fractured ends.
      a. **Nondisplaced or nonangulated** describes fracture ends that are well approximated and in normal position.
      b. **Displaced** describes fractured ends that are shifted.
      c. **Angulated** describes fractured ends that form an angle.
      d. **Overriding** describes a fracture whose ends override without cortical contact.
   3. **Types of fractures (Figure 17-4)**
      a. **Compression fracture (torus or buckle fracture)** occurs if the soft bony cortex buckles under a compressive force. This type of fracture commonly occurs in the metaphysis and requires only splinting for 3–4 weeks.
      b. **Incomplete fracture (greenstick fracture)** occurs if only one side of the cortex is fractured with the other side intact. The intact side is the site of compression injury and may be bent, whereas the fractured side receives the tension and fractures. Because angulation can increase even within a cast, reduction may include fracturing the other side of the cortex.
      c. **Complete fractures**
         1. **Transverse** describes a fracture that is horizontal across the bone.
         2. **Oblique** describes a diagonal fracture across the bone.
         3. **Spiral** describes an oblique fracture encircling the bone. Spiral fractures may occur with twisting injury.
         4. **Comminuted** describes a fracture that is composed of multiple fracture fragments.
      d. **Any fracture can be a sign of child abuse**—there is no fracture that is pathognomonic for abuse.
   4. **Location of the fracture**
      a. **Epiphyseal** fracture involves the end of the bone.
      b. **Physeal** fracture involves the growth plate. The **Salter–Harris classification** describes fractures involving the physis. **Table 17-6** contains a mnemonic to help remember the classification, and **Figure 17-5** illustrates this classification. The Salter–Harris classification may be an important prognostic factor in determining subsequent growth of the limb. For example, subsequent bone growth is affected in some **type II–III** Salter–Harris fractures and all **type IV–V** Salter–Harris fractures.
      c. **Metaphyseal** fracture involves the ends of the central shaft (i.e., between the epiphysis and diaphysis).
      d. **Diaphyseal** fracture involves the central shaft of the bone.

B. **Clavicular fractures** are **common fractures in childhood** and are usually caused by falling onto the shoulder. **Birth injury** is the major cause of clavicular fractures in neonates.
   1. **Clinical features**
      a. **Infants** may be **asymptomatic** or may present with an **asymmetric Moro reflex or pseudoparalysis** (refusal to move extremity because of pain). Crepitus may be felt over the fracture.
      b. Children typically hold the affected limb with the opposite hand, and the child's head is often tilted toward the affected side. Point tenderness and deformity may be

noted over the fracture.

2. **Diagnosis** is on the basis of plain radiographs showing the fracture. Most fractures caused by trauma involve the middle and lateral aspects of the clavicle.
3. **Management.** Treatment includes placement in a sling for 4–6 weeks to assist in immobilizing the limb. Neonates with clavicle fractures often do not require any treatment.
4. **Complications.** Injury to nerves and vessels is rare. However, brachial plexus injuries can coexist with clavicular fractures in neonates as a result of birth injury.

C. **Supracondylar fracture of the humerus** occurs when a child falls onto an outstretched arm or elbow. Children younger than 10 years are mostly at risk for this type of fracture because the mechanical force of the impact is transmitted to the supracondylar area. **A supracondylar fracture is an orthopedic emergency if the fracture is displaced and angulated, because of the risk of neurovascular injury and compartment syndrome.**

1. **Clinical features**
   a. **Point tenderness, swelling, and deformity of the elbow** may be seen.
   b. It is important to assess the pulse, sensation, and movement of the fingers to **detect neurovascular injury.** If the fractured fragment is angulated or displaced, it can cause injury by stretching the radial or median nerves or the brachial artery.
   c. **Pain with passive extension of the fingers is suggestive of compartment syndrome.**
2. **Diagnosis** is on the basis of AP and lateral radiographs. A triangular fat pad shadow posterior to the humerus may be observed if an occult fracture is present (i.e., **"posterior fat pad sign"**).
3. **Management.** Passive movement of the elbow (i.e., when the examiner moves the arm) may increase the risk of further neurovascular injury. Therefore, **if a supracondylar fracture is suspected, never passively move the arm.**
   a. **Nondisplaced and nonangulated fractures** require casting.
   b. **Displaced or angulated fractures** require surgical reduction and pinning.
4. **Complications**
   a. **Compartment syndrome** occurs when the pressure within the anterior fascial compartment is greater than 30–45 mm Hg, leading to ischemic injury and Volkmann contracture (flexion deformity of the fingers and the wrist). The **"5 P's" of compartment syndrome** (pallor, pulselessness, paralysis, pain, and paresthesias) are late signs. A more sensitive indication of impending compartment syndrome is **pain with passive extension of the fingers.**
   b. Injury to the **radial, median, or ulnar nerve** may cause temporary palsy but usually resolves.
   c. **Cubitus varus** is a decreased or absent carrying angle as a result of poor positioning of the distal fragment. This is a permanent complication.

D. **Forearm fractures**

1. **Common types of forearm fractures**
   a. **Distal radius fracture** is the most common upper extremity fracture in children.
   b. **Monteggia fracture** is a fracture of the proximal ulna with dislocation of the radial head.
   c. **Galeazzi fracture** is a fracture of the radius with distal radioulnar joint dislocation.
2. **Diagnosis** is on the basis of AP and lateral radiographs of the forearm.
3. **Management.** Treatment includes open or closed reduction and splinting. A cast replaces the splint in 4–7 days after the swelling has resolved. Forearm fractures heal within 6–8 weeks.

E. **Femur fractures** require a great deal of mechanical force. Therefore, it is important to assess

for other injuries in the joint above and below the fracture.

1. **Clinical features** include erythema, swelling, deformities, and point tenderness.
2. **Diagnosis** is on the basis of AP and lateral radiographs that include the joint above and below the area of injury.
3. **Management.** Treatment depends on the age of the patient as well as other factors. It may include using a Pavlik harness in neonates, spica casting in young children, traction, or surgical stabilization.

F. **Toddler's fracture** is a **spiral fracture of the tibia.** This type of fracture may occur after very mild or no identified trauma. The fibula remains intact.

1. **Epidemiology.** Toddler's fractures usually occur between 9 months and 3 years of age. Typically, they occur when a child trips and falls while running or playing.
2. **Clinical features.** The child refuses to bear weight but is willing to crawl. Erythema, swelling, and mild point tenderness may be found over the distal tibia on examination.
3. **Diagnosis.** Oblique views of the tibia may show the fracture line, although sometimes plain radiographs do not visualize the fracture.
4. **Management.** Treatment involves a long leg cast for 3–4 weeks.

G. **Fractures typical of child abuse.** Any fracture before walking age should raise the concern for abuse. (See also Chapter 20, section VI.B.2.d.) A **"skeletal survey"** (radiographic studies of all bones) is the screening tool used to assess for current and previous bony injuries. A "baby-gram" is not an adequate skeletal survey. The following fractures should make the clinician suspect abuse:

1. **Metaphyseal fractures (corner or bucket handle fractures)**
2. **Posterior or first rib fractures**
3. **Multiple fractures at various ages of healing**
4. **Complex skull fractures**
5. **Scapular, sternal, and vertebral spinous process fractures**
6. Any fracture whose **mechanism does not fit the history provided or the child's developmental abilities** (e.g., fracture of the lower extremities in a nonambulatory child)

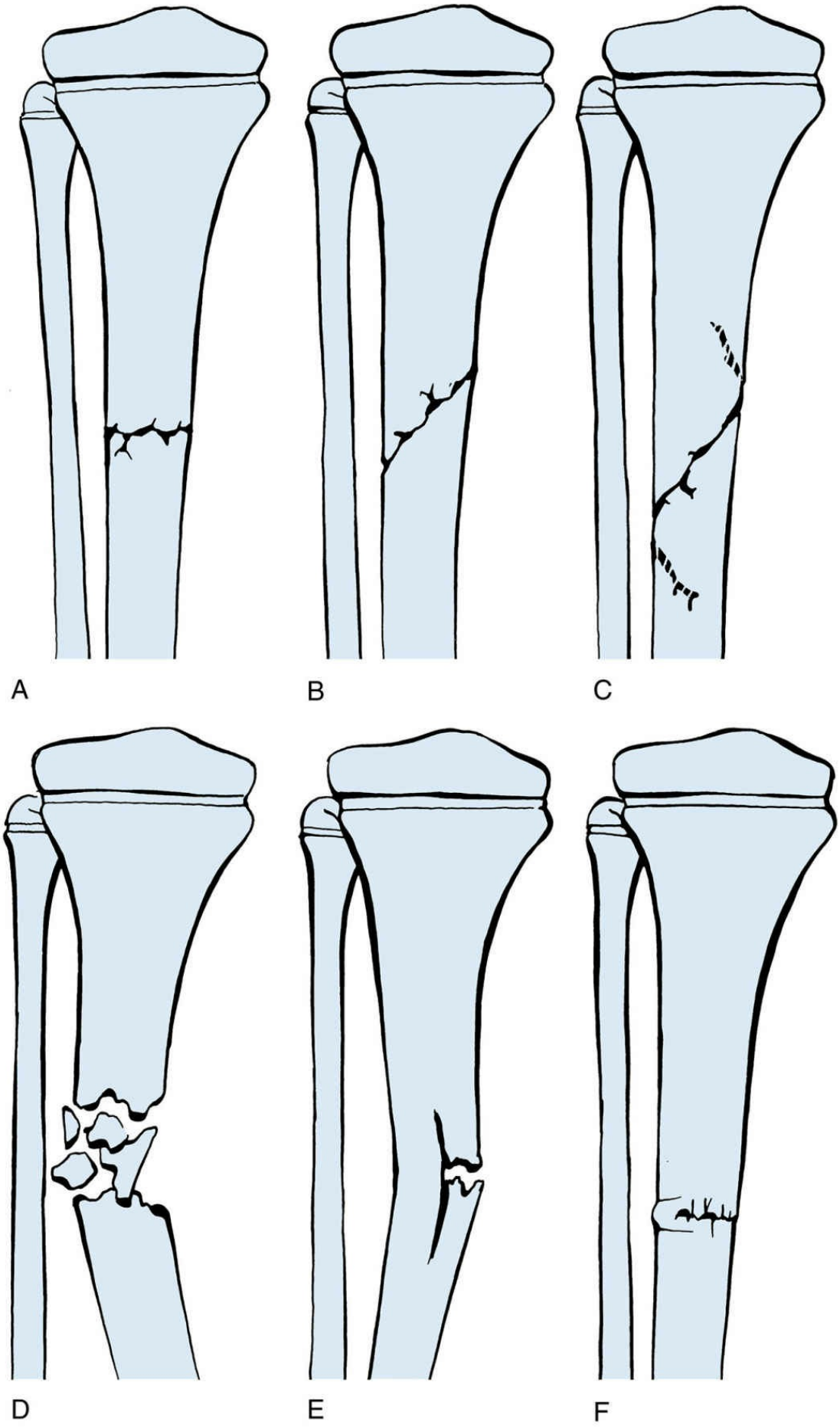
A
B
C
D
E
F

FIGURE 17.4 Common types of fractures. **A.** Transverse. **B.** Oblique. **C.** Spiral. **D.** Comminuted. **E.** Greenstick. **F.** Buckle.

Table 17-6
Salter–Harris Classification

Type	Acronym	Description of Fracture
I	S	***S*ame:** Fracture is within the physis
II	A	***A*bove:** Fracture is in the physis and above into the metaphysis
III	L	***L*ow:** Fracture is in the physis and below into the epiphysis
IV	T	***T*hrough and through:** Fracture is in the physis through both the metaphysis and the epiphysis
V	R	**C*r*ush:** Crushing of the physis

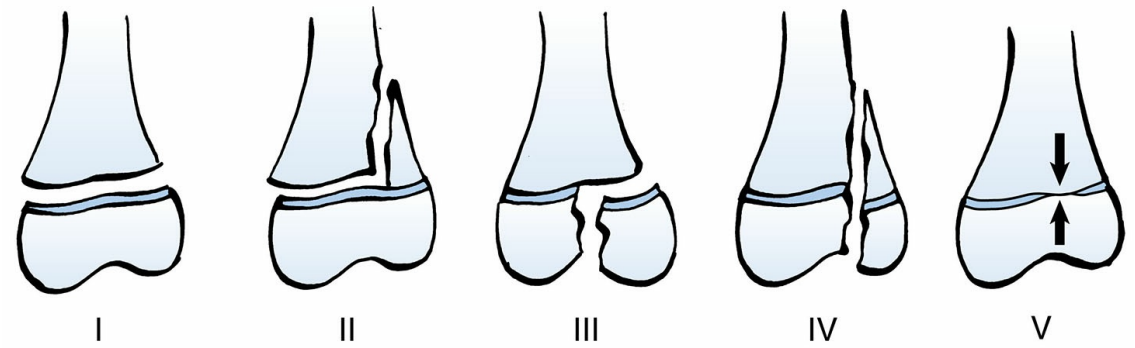

FIGURE 17.5 Salter–Harris classification of fractures. Type I is a fracture within the physis. Type II is a fracture within the physis and into the metaphysis. Type III is a fracture within the physis and into the epiphysis. Type IV is a fracture through the metaphysis, physis, and epiphysis. Type V is a crush fracture of the physis.

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Review Test

1. A healthy, developmentally normal 15-month-old boy is brought to the emergency department because he is irritable and refuses to walk after falling down on carpet this afternoon. His parents report that he was running when he fell, but the fall did not seem to be very forceful. A radiograph of the right tibia reveals a nondisplaced spiral fracture. The fibula is intact. Which of the following is most appropriate in the management of this patient?
   A. Casting only
   B. Immediately filing a report with Child Protective Services for suspected abuse
   C. Consulting orthopedics for operative management of the fracture
   D. Ordering a skeletal survey and awaiting the results before calling Child Protective Services
   E. Beginning intravenous antibiotics
2. A 15-year-old girl comes to your office complaining of knee pain. She is in the high school basketball team, and she began having knee pain after 4 weeks of preseason training. On examination, she has mild tenderness and swelling over her left anterior tibial tuberosity. The examination is otherwise normal. Which of the following is the most appropriate set in this patient's management?
   A. Casting for suspected fracture
   B. Radiograph of the knee to confirm patellofemoral syndrome
   C. Hip ultrasound for possible transient synovitis
   D. Explanation to the patient that these are growing pains and do not require treatment
   E. Muscle stretching and pain control
3. The parents of a 6-month-old boy are concerned because his feet "turn in." They noticed his "pigeon toes" when he was a few months old. On examination, the infant's mid-foot curves inward but can be straightened beyond the midline by gentle manipulation. Which of the following is the most appropriate treatment?
   A. Reassurance only
   B. Referral for corrective orthotic shoes
   C. Prescription of special shoes that are connected by a bar to point the toes outward
   D. Referral for casting
   E. Referral to pediatric orthopedic surgery for operative repair
4. A 15-month-old boy is brought to the emergency department because of a 1-day history of high fever with temperature up to 39.4°C (103°F) and refusal to walk. He previously was able to walk without difficulty. No known trauma has occurred. On examination, the child is fussy but consolable, and manipulation of his left hip elicits moderate discomfort. Range of motion in the left hip, however, is normal. Laboratory studies reveal a white blood cell count of 28,000 cells/mm^3 and an erythrocyte sedimentation rate of 42 mm/hour. Which of the following is the next most appropriate management step?
   A. Order an ultrasound of the hip.
   B. Order magnetic resonance imaging of the hip.
   C. Admit the patient to the hospital and immediately begin intravenous antibiotics.
   D. Order plain radiographs of the spine and pelvis.
   E. Discharge the patient to the home with reassurance and close follow-up.
5. A 15-year-old girl is brought to your office because the school nurse noticed possible scoliosis on a screening examination. She is a previously healthy girl. Menarche occurred at 13 years of age. On examination, when she stands upright, the iliac crests appear level, but there is an obvious curvature of the back and the left shoulder is 1.5 cm lower than the right shoulder. When she bends forward at the waist, there is a rib hump in the right thoracic region. You

order a standing spine radiograph, which reveals scoliosis with a Cobb angle of 30°. Which of the following is the most appropriate treatment at this point?

A. Referral for surgery
B. Referral for bracing
C. Referral for shoe orthotics
D. Referral for physical therapy for anticipated back pain associated with scoliosis
E. Reassurance that her curve will not worsen significantly because the majority of her growth has concluded

6. An 8-year-old boy is brought to the emergency department after being hit by a car after he ran into the street. Lower extremity radiographs reveal a physeal fracture of the proximal tibia that extends into the medial metaphysis. Which of the following is the Salter–Harris type of this fracture?

A. Type I
B. Type II
C. Type III
D. Type IV
E. Type V

7. A 7-year-old girl is jumping up and down on a bed when she falls onto her outstretched right hand. She has severe elbow pain and is brought to the emergency department. On examination, she is crying and holding her right arm at her side. Because of the mechanism of injury, you suspect a supracondylar fracture. A radiograph confirms your suspected diagnosis and demonstrates a displaced and angulated supracondylar fracture. Which of the following statements regarding her fracture is correct?

A. Pain with passive flexion of the fingers is an early sign that she may have compartment syndrome.
B. Passive movement of the right elbow should be performed by the examiner to assess for neurovascular involvement.
C. Even though the fracture is displaced, casting within the emergency department with outpatient orthopedic follow-up is an appropriate management step for this type of fracture.
D. Child Protective Services should be consulted because this fracture is unusual in a child of her age and is suggestive of child abuse.
E. Orthopedics should be contacted immediately because this is an orthopedic emergency.

8. A 12-year-old obese boy is brought to your office for pain in the right hip and thigh during the past 24 hours. He is also limping. Six months ago, he was diagnosed with slipped capital femoral epiphysis (SCFE) of the left hip and underwent surgical repair. You suspect he may have SCFE involving the right hip. Which of the following tests would be appropriate to assess for other pathology associated with bilateral SCFE?

A. Antinuclear antibody
B. Rheumatoid factor
C. Thyroid studies
D. Calcium level
E. Magnesium level

9. During a 2-week health maintenance evaluation, you notice that a 15-day-old male infant seems to favor looking to the right side only. On examination, range of motion in the neck is also diminished, and there is stiffness of the left sternocleidomastoid muscle. Within the body of the muscle, you appreciate a soft 1 × 2-cm mass. Which of the following statements regarding the most likely diagnosis is correct?

A. The symptoms are most likely caused by a congenital cervical spine abnormality.
B. Urgent ophthalmologic referral should be placed for possible lack of vision in the left eye

given the patient's right gaze preference.

C. Plagiocephaly is a potential complication.
D. Neurosurgical consultation should be obtained to rule out atlantoaxial instability.
E. Otolaryngology consultation should be obtained to biopsy the mass within the sternocleidomastoid muscle.

10. A 17-year-old boy is evaluated in the emergency department after falling down an embankment while hiking. His left mid-thigh is swollen and tender with deep lacerations. Lower extremity radiographs reveal a left femur that is fractured at the middle portion of the shaft, with the ends overlapping side by side, without angulation. Which of the following best describes this fracture?

A. Closed, nondisplaced, nonangulated, transverse, diaphyseal fracture of the femur
B. Closed, overriding, angulated, transverse, diaphyseal fracture of the femur
C. Open, displaced, angulated, transverse, diaphyseal fracture of the femur
D. Open, nondisplaced, nonangulated, transverse, diaphyseal fracture of the femur
E. Open, overriding, nonangulated, transverse, diaphyseal fracture of the femur

Answers and Explanations

1. **The answer is A** [V.F]. The patient's age, the mechanism of injury, and the radiographic findings are classic characteristics of a toddler's fracture. A toddler's fracture is a spiral fracture of the tibia without concomitant fracture of the fibula. It occurs after little or no trauma. Casting only is appropriate for a nondisplaced toddler's fracture. Although it is always necessary to be vigilant for child abuse, a toddler's fracture alone in an ambulatory child should not raise suspicion of abuse, and therefore neither a skeletal survey nor immediate referral to Child Protective Services is indicated. Operative management is not needed in a nondisplaced spiral fracture. This toddler's fracture is not an open fracture and therefore antibiotics are not required.
2. **The answer is E** [IV.B]. This patient has swelling and tenderness over the tibial tuberosity, which is consistent with Osgood–Schlatter disease. Osgood–Schlatter disease is an overuse injury that is characterized by inflammation or microfracture of the tibial tuberosity. It is the most common apophysitis (i.e., inflammation at the site of tendon insertion onto bone) in childhood. Treatment includes quadriceps and hamstring stretching/strengthening, ice, and pain control with nonsteroidal anti-inflammatory drugs. A fracture is unlikely because the patient has the ability to ambulate, and therefore casting is unnecessary. Patellofemoral syndrome is a misalignment of the patella that results in pain around the patella or directly under the knee. The tibial tuberosity is not involved. Transient synovitis is unlikely because of the absence of hip pain. It is also uncommon during adolescence. Growing pains occur in younger children, not in adolescents. Growing pains occur mainly at night and do not interfere with daily activities.
3. **The answer is A** [IV.A.1.a]. This child has metatarsus adductus, which is a medial curvature of the mid-foot usually caused by intrauterine constraint. In a child whose foot can be manipulated beyond straight (beyond midline), no intervention is necessary and reassurance alone is sufficient. In contrast, a child with a flexible curved foot that cannot be straightened beyond a straight position would benefit from exercises to stretch the foot. Neither corrective shoes nor shoes with a bar are indicated for metatarsus adductus. Casting is reserved for feet that do not correct with manipulation. Surgical repair is not indicated for metatarsus adductus.
4. **The answer is A** [III.B.1.c.(2) and III.B.1.d–e]. Although transient synovitis is a consideration because this boy is nontoxic and is able to move his hip without severe pain, the presence of high fever, along with an abnormal erythrocyte sedimentation rate and white blood cell count, mandates evaluation for septic arthritis. The most appropriate next test is an ultrasound to assess for fluid in the joint. If fluid is present, it must be aspirated and analyzed. Magnetic resonance imaging can also detect joint fluid, but it is expensive and time-consuming and often requires sedation in a young child to help decrease motion artifact. Intravenous antibiotics and admission to the hospital are required for the treatment of septic arthritis, but antibiotics should be started after cultures are obtained so that the infecting organism can be identified. A plain radiograph of the pelvis may show a widened joint space but is often normal in septic arthritis. Reassurance without further evaluation would risk missing the diagnosis of septic arthritis, which can potentially lead to avascular necrosis.
5. **The answer is E** [II.B.3–4 and Table 17-1]. Because the growth spurt in females precedes menarche, almost all growth ceases within 6 months after the onset of menstrual cycles. Menarche occurred 2 years before evaluation of this patient, and therefore no treatment for scoliosis is necessary because growth has likely concluded. Surgery is indicated after the growth spurt if the Cobb angle is >50°. Scoliosis alone should cause no pain unless the curve is very great. Bracing is not indicated because it only prevents progression of scoliosis during the

growth period. Neither shoe orthotics nor physical therapy is useful in scoliosis.

6. **The answer is B** [V.A.4.b, Table 17-6, and Figure 17-5]. A physeal fracture that extends into the metaphysis is a Salter–Harris II fracture. A type I fracture is within the physis. A type III fracture is in the physis and extends into the epiphysis. A type IV fracture is in the physis and through both the metaphysis and epiphysis. A type V fracture describes a crushing of the physis.
7. **The answer is E** [V.C]. A supracondylar fracture occurs most commonly in a child younger than 10 years who falls on an elbow or on an outstretched hand. The displaced and angulated supracondylar fracture in this patient is an orthopedic emergency because of the risks of compartment syndrome and neurovascular injury. Pain with passive extension (not flexion) of the digits of the hand is a sensitive indicator of compartment syndrome. Passive movement of the elbow (examiner moves the extremity) can result in neurovascular injury and should not be performed if a supracondylar fracture is suspected. A fracture that is displaced will very likely require surgical reduction and pinning, rather than casting alone. Abuse should always be considered in any childhood injury. However, a supracondylar fracture is a typical fracture in a child of this age, and this injury fits with the purported mechanism.
8. **The answer is C** [III.B.4.b]. Slipped capital femoral epiphysis (SCFE) is a slipping of the femoral head off the femoral neck. It is most common in males and is associated with obesity. Thirty percent of patients have bilateral involvement, and patients with hypothyroidism are especially at risk for bilateral disease. Therefore, it would be appropriate to obtain thyroid studies. Systemic lupus erythematosus and juvenile idiopathic arthritis can cause hip pain, but they are not associated with bilateral SCFE; thus, neither antinuclear antibody nor rheumatoid factor would be helpful. Neither calcium nor magnesium abnormalities play a role in SCFE.
9. **The answer is C** [II.A.1.a]. This patient most likely has congenital muscular torticollis, a tilting of the head to one side as a result of intrauterine constraint or birth trauma. Congenital torticollis is commonly associated with asymmetry of the head and face (plagiocephaly). The treatment of congenital torticollis, including head positioning during sleep and physical therapy, should be started as soon as the diagnosis is made to prevent this complication. A congenital cervical spine abnormality (e.g., Klippel–Feil syndrome) may cause congenital torticollis, but this is uncommon. Vision problems should always be considered in a child with a gaze abnormality, but the presence of a stiff neck muscle makes it unlikely that a problem with vision is the cause of the torticollis. Atlantoaxial instability is an unstable joint high in the cervical spine and does not manifest as congenital torticollis. The mass within the sternocleidomastoid muscle represents bleeding or fibrosis within the muscle body and does not require biopsy by otolaryngology. It will likely disappear by 2–6 months of age.
10. **The answer is E** [V.A]. An accurate description of a fracture is important when determining a need for surgical intervention or consultation with an orthopedic specialist. A description should include whether there is a break in the skin (open versus closed), the spatial relation of the fractured ends (displaced versus angulated), the type of fracture, and the location of the fracture. In this patient, the fracture has resulted in a break in the skin (open fracture), and the ends of the fracture override (overriding ends). The fracture is nonangulated and cuts all the way across the bone (transverse) in the mid-thigh (diaphyseal fracture).

CHAPTER 18

Ophthalmology

Omondi L. Nyong'o

I. Ocular Examination and Vision Screening

A. The **purpose** of ocular examination and vision screening is **early detection and treatment** of pediatric ocular disease. **Delay in diagnosis may result in irreversible vision loss** and even death.

B. **Vision screening principles** can be remembered using the **acronym I-ARM PLUS** (**I**nspection, **A**cuity assessment, **R**ed reflex testing, **M**otility assessment).

1. **Inspection** includes evaluation for pupil and eyelid symmetry, head turn or head tilt (i.e., torticollis), and conjunctival injection.
2. **Acuity assessment**
   a. Neonates and infants: evaluation of eye fixation, tracking of light or objects, and pupillary responses
   b. Children: use of eye charts or cards
3. **Red reflex assessment,** in which a direct ophthalmoscope is directed at the patient's eyes from a distance of 2–3 feet **(Bruckner test)**, is the **single best screening examination** for infants and children. **Table 18-1** presents information about the differential diagnosis of an abnormal red reflex.
4. **Motility assessment and eye alignment.** Motility assessment of each eye involves having the child follow a target in all directions. At the same time, alignment is assessed by evaluating for the symmetry of light reflecting off both corneas (**Hirschberg test**).
5. **Plus. Instrument-based objective vision screening with devices that measure the focusing and alignment of eyes in preverbal children**

Table 18-1
Differential Diagnosis of an Abnormal Red Reflex

Disorder	Red Reflex Finding
Cataract	Dark, dull, or white reflex
Vitreous hemorrhage	Dark or dull reflex
Retinoblastoma	Yellow or white reflex
Anisometropia	Unequal red reflex
Strabismus	Brighter red reflex in deviated eye
	Corneal light reflex will be uncentered
Glaucoma	Dull reflex

II. Normal Visual Development and Amblyopia

A. **Visual development**
   1. **Visual acuity is poor at birth,** in the range of 20/200, as a result of physiologic immaturity of the visual cortex responsible for visual processing.
   2. **Visual acuity** rapidly **improves during the first 3–4 months of life,** as a clear in-focus retinal image stimulates functional and structural development of the visual centers of the brain.
   3. **Normal visual development** is dependent on both of the following:
      a. **Proper eye alignment**
      b. **Equal visual stimulation of each retina** with clearly focused images
   4. **Abnormal visual development** results from the following:
      a. **Improper eye alignment,** such as uncorrected strabismus [see section IX]
      b. Any pathologic condition that **blocks retinal stimulation,** such as a congenital cataract [see section VIII.A]
   5. **Visual development is most critical during the first 3–4 months of life.** Any pathologic condition that disrupts alignment or retinal stimulation during this period may result in poor vision as a result of amblyopia [see section II.B].
   6. **Binocular vision** requires the integration of sufficiently clear and equal monocular retinal images from both eyes into a single, three-dimensional perception (binocular, sensory fusion). Binocular cortical connections are present at birth. However, appropriate visual input from each eye is necessary to refine and maintain these binocular neural connections.
   7. **Normal depth perception (stereopsis),** similar to normal visual development, may be impaired because of the following:
      a. **Improper eye alignment**
      b. Any pathologic condition that **unilaterally blurs the retinal image,** such as a congenital cataract

B. **Amblyopia**
   1. **Definition.** Amblyopia is *subnormal visual acuity caused by abnormal visual development early in life.*
   2. **Epidemiology.** Amblyopia is the **most common cause of decreased vision during childhood** and occurs in approximately 2–4% of the general population.
   3. **Etiology.** Any pathologic condition that causes abnormal retinal stimulation can cause amblyopia.
      a. **Eye misalignment (strabismus:** see section IX*).* If a child has a strong preference for one eye and constant suppression of the nonpreferred eye, amblyopia will develop in the nonpreferred eye.
      b. **Any pathologic condition that causes a blurred visual image.** Opacification of the lens (cataract), severe uncorrected refractive error, significant differences in refractive errors between the eyes (anisometropia), and vitreous opacities (hemorrhage) all lead to poor visual stimulation, and therefore abnormal visual development.
   4. **Clinical features. Severity of amblyopia** depends on when the abnormal stimulus began, the length of exposure to the abnormal stimulus, and the severity of the blurred image.
      a. The earlier the onset, the longer the duration of the abnormal stimulus, and the more blurry the image, the **more severe the vision loss.**
      b. Children are **most susceptible to amblyopia** during the **first 3–4 months of life,** the

period of critical visual development.

5. **Diagnosis**
    a. In infants and preverbal children, the bilateral red reflex test [see section I.B.3] is the best screening test.
    b. In older children, formal acuity testing is the best screening test.
6. **Management. Early detection and early intervention are critical** to the treatment of amblyopia.
    a. **A clear retinal image** should be ensured by correcting any refractive errors with eyeglasses or by surgically removing any visually significant lens opacities.
    b. Either depriving the normal eye of clear vision through occlusion or causing blurriness by an eye drop forces the use of the amblyopic eye.
    c. **The earlier the intervention, the better the prognosis.**

III. Conjunctivitis and Red Eye

Conjunctivitis is a nonspecific finding that refers to conjunctival inflammation. It may be the result of infectious or noninfectious causes. The causes of conjunctivitis vary with the age of the patient.

A. **Neonatal conjunctivitis (ophthalmia neonatorum)**
   1. **Definition.** Conjunctivitis occurring during the **first month of life**
   2. **Etiology.** Causes of neonatal conjunctivitis may include infections or chemical irritation.
      a. **Infection** is **acquired from the vaginal canal during birth** or from hand-to-eye contamination from infected individuals. Infectious agents include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and herpes simplex virus.
      b. **Chemical conjunctivitis.** Chemical irritation (chemical conjunctivitis) results from drops or ointment that are topically instilled into a newborn's eyes as prophylaxis against *N. gonorrhoeae.* Chemical conjunctivitis is most often secondary to **1% silver nitrate.** Other medications used to prevent *N. gonorrhoeae*, such as 1% tetracycline and 0.5% erythromycin, tend to be less irritating to the conjunctiva.
         1. **Chemical conjunctivitis is the most common cause** of red, watery eyes in the **first 24 hours of life.**
         2. This **self-limited** condition lasts for less than 24 hours.
   3. **Clinical features, diagnosis, and management are found in Table 18-2.**
   4. **Differential diagnosis** of a red, teary eye in newborns also includes the following:
      a. **Congenital glaucoma** [see section VI], which is characterized by tearing, an enlarged globe, and corneal edema
      b. **Dacryocystitis** (infection of the nasolacrimal sac)
      c. **Endophthalmitis** (infection within the vitreous and aqueous fluid), a rare but devastating infection that often results in blindness

B. **Red eye in older infants and children**
   1. **Etiology.** The differential diagnosis of red eye in infants and children is extensive *(***Figure 18-1***)*. The most common causes include **viral, bacterial, and allergic conjunctivitis,** as well as **blepharitis** (eyelid inflammation).
   2. **Evaluation**
      a. **History,** which often establishes the cause
         1. **Infectious causes** are suggested by history of contact with others who have conjunctivitis.
         2. **Allergic conjunctivitis** is suggested by severe itchiness and is usually seasonal.
         3. **Conjunctivitis associated with contact lens use** may be secondary to **allergy** to the contact lens solution, to a **corneal abrasion,** or to a **vision-threatening bacterial corneal ulcer.**
         4. **Unilateral conjunctivitis** may be associated with a **foreign body, corneal ulcer, or herpes simplex keratitis.**
      b. **Ocular examination (I-ARM** acronym; see section I.B*)*
      c. **Fluorescein staining** of the corneal epithelium is performed to evaluate for an abrasion of the corneal tissue. Positive staining is most commonly associated with **trauma,** but may also be associated with a **bacterial corneal ulcer** or with **herpes simplex keratitis.**
   3. **Specific causes of conjunctivitis.** The **distinguishing clinical features** of the common causes of pediatric red eye are presented in **Table 18-3.**
      a. **Bacterial conjunctivitis**
         1. **Etiology.** Causes most commonly include **nontypeable *Haemophilus***

***influenzae, Streptococcus pneumoniae, Moraxella catarrhalis,* and *Staphylococcus aureus*.**

2. **Clinical features.** Purulent discharge, conjunctival erythema, and lid swelling are usually present. Bilateral involvement is common. Some patients have associated otitis media.
3. **Diagnosis. History and clinical presentation are the basis of diagnosis.**
    a. Conjunctival cultures and Gram stain are not performed routinely for mild to moderate infections, and patients are usually treated empirically.
    b. However, **conjunctival cultures** and **Gram stain** should be obtained in **severe** cases.
4. **Management**
    a. **Topical antibiotics** are effective and include bacitracin, sulfacetamide, polymyxin B and trimethoprim sulfate, gentamicin, tobramycin, ofloxacin, and erythromycin.
    b. Indications for referral to an ophthalmologist include severe eye involvement, conjunctivitis associated with contact lens use, suspected corneal ulcer, or lack of improvement with topical antibiotics.

b. **Viral conjunctivitis**

1. **Pharyngoconjunctival fever** is characterized by an upper respiratory infection that includes pharyngitis, fever, and **bilateral conjunctivitis.**
    a. **Etiology.** The cause is **adenovirus,** types 3 and 7.
    b. **Clinical features**
        1. **Symptoms and signs: severe watery conjunctival discharge,** hyperemic conjunctiva, chemosis (conjunctival edema), preauricular lymphadenopathy, and typically a foreign body sensation caused by corneal involvement
        2. **Highly contagious** and lasts for 2–3 weeks
    c. **Management.** Treatment is supportive and includes cool compresses and topical nonsteroidal anti-inflammatory drug (NSAID) drops. Antibiotics may be necessary if bacterial superinfection occurs.
2. **Epidemic keratoconjunctivitis** is clinically similar to pharyngoconjunctival fever, but symptoms are confined to the eyes.
    a. **Etiology.** The cause is **adenovirus,** types 8, 19, and 37.
    b. **Clinical features**
        1. **Symptoms and signs: petechial conjunctival hemorrhage,** preauricular lymphadenopathy, and a **pseudomembrane** along the conjunctiva
        2. **Photophobia** from corneal inflammation **(keratitis)** caused by a hypersensitivity reaction to the virus (occurs in **one-third** of patients)
        3. **Lack of fever or pharyngitis**
        4. **Highly contagious**
    c. **Management.** Treatment is **supportive,** including cool compresses and topical NSAID drops. Children with corneal involvement should be referred to an ophthalmologist.
3. **Primary ocular herpes simplex virus**
    a. **Etiology.** The cause is **herpes simplex virus type 1 (HSV-1)** and typically represents the initial exposure to HSV-1 virus.
    b. **Clinical features**
        1. **Skin eruption** with **multiple vesicular lesions**

2. **Corneal ulcer** (rare)

c. **Diagnosis.** History, clinical presentation, and positive viral culture or direct fluorescent antibody staining of vesicular fluid are the basis of diagnosis.

d. **Management**

1. **Systemic or topical acyclovir** may speed recovery if administered within 1–2 days of onset.
2. **Topical antibiotics** applied to the skin may *prevent* **secondary bacterial infection.**

c. **Allergic conjunctivitis**

1. **Epidemiology.** Allergic conjunctivitis is most typically seasonal, often accompanying seasonal allergic rhinitis. It affects 10% of the population.
2. **Etiology.** The cause is a **type 1 hypersensitivity reaction.**
3. **Clinical features.** Marked itching and watery discharge are present.
4. **Diagnosis.** History and clinical presentation are the basis of diagnosis.
5. **Management**
   a. **Removal** of environmental allergens
   b. **Topical mast cell–stabilizing drops,** such as **cromolyn**
   c. **Topical antihistamines**

d. **Hemorrhagic conjunctivitis** is a dramatic presentation of pediatric red eye in which the child presents with both conjunctivitis and subconjunctival hemorrhage. Causes include infection with ***H. influenzae*, adenovirus, and picornavirus.**

e. **Blepharitis**

1. **Definition.** Blepharitis is **eyelid inflammation.**
2. **Epidemiology.** Blepharitis is one of the most common causes of red eye.
3. **Etiology.** The usual cause is ***S. aureus*** infection.
4. **Clinical features.** Burning, **crusting, and scales** at the eyelash base; thickened and hyperemic eyelid margins; broken or absent eyelashes; and a history of awakening in the morning with eyelashes stuck together are characteristic.
5. **Diagnosis.** History and clinical presentation are the basis of diagnosis.
6. **Management.** Treatment includes **eyelid hygiene,** in which eyelids are scrubbed twice daily with baby shampoo. Topical erythromycin ointment may also be applied.

Table 18-2
Etiology, Clinical Features, Diagnosis, and Management of Neonatal Conjunctivitis

Etiology	Onset and Clinical Features	Conjunctival Studies	Management
Chemical	**Within first 24 hours**	Negative Gram stain	No treatment necessary
Watery discharge	Few PMNs		
Neisseria gonorrhoeae	**2–4 days of life**	Gram-negative intracellular diplococci	Intravenous cefotaxime and topical erythromycin
Purulent discharge			
Eyelid swelling	Positive gonococcal culture	Treat parents	
Can lead to corneal ulcer			
Chlamydia trachomatis	**4–10 days of life**	Cytoplasmic inclusion bodiesPositive DFA or culture	**Oral** erythromycin
Serous or purulent discharge	Treat parents		
Variable lid swelling			

Herpes simplex virus	**6 days–2 weeks of life**Usually **unilateralSerous** discharge	Multinucleated giant cells on Gram stain	Intravenous acyclovir and topical trifluorothymidine
Positive HSV culture			

PMNs = polymorphonuclear neutrophils; *DFA* = direct fluorescent antibody assay; *HSV* = herpes simplex virus.

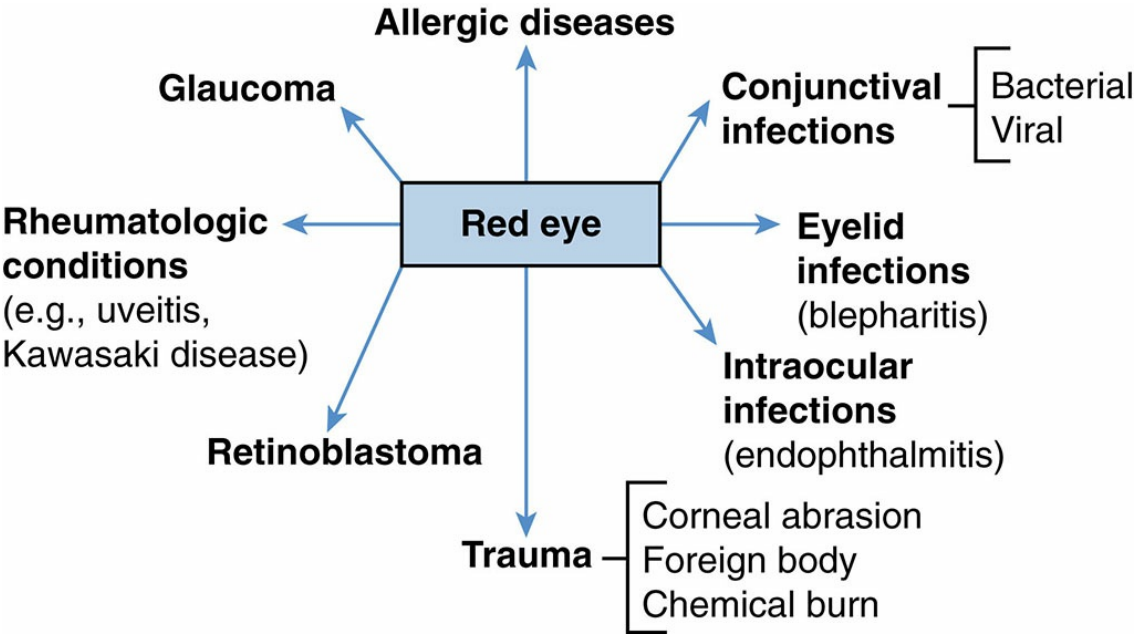

FIGURE 18.1 Differential diagnosis of red eye in older infants and children.

Table 18-3
Distinguishing Clinical Features of Conjunctivitis

Clinical Feature	Bacterial	Viral	Allergic	Blepharitis
Discharge	Purulent	Watery	Watery or mucoid	Minimal
Itching	Minimal	Minimal	Severe	Minimal (irritation rather than itching)
Preauricular lymphadenopathy	Absent	Common	Absent	Absent
Laboratory findings	Bacteria and PMNs on Gram stain	No bacteria on Gram stain	Eosinophils on conjunctival scraping	Positive culture for *Staphylococcus aureus*

PMNs = polymorphonuclear neutrophils.

IV. Abnormal Tearing

A. **Nasolacrimal duct (NLD) obstruction**
   1. **Definition.** NLD obstruction is *failure of complete canalization of the lacrimal system* that results in obstruction to tear outflow. Obstruction typically occurs distally at **Hasner valve.**
   2. **Epidemiology.** NLD occurs in 1–5% of children.
   3. **Etiology.** The cause of incomplete canalization is unknown.
   4. **Clinical features**
      a. **Watery eye** with increased tear lake (meniscus of tears upon the lower eyelid margin that spill over onto the cheek and eyelid)
      b. **Matted eyelashes**
      c. **Mucus** in the medial canthal area
      d. **Bilateral** involvement in **one-third** of patients
   5. **Management**
      a. **Observation** only is needed for most children.
         1. **Over 80%** of cases *resolve spontaneously within* **9–12 months.**
         2. **Nasolacrimal massage** may help open the distal obstruction.
         3. **Topical antibiotics** are administered if infection is present.
      b. **NLD probing,** in which a small steel wire is passed through the nasolacrimal system through Hasner valve into the nose, will cure NLD obstruction in most cases. It is typically performed between 6 and 12 months of age.

B. **Amniotocele (dacryocele)**
   1. **Definition.** Amniotocele is swelling of the nasolacrimal sac.
   2. **Etiology.** The cause is accumulation of fluid as a result of NLD obstruction.
   3. **Clinical features**
      a. **Bluish swelling** in the medial canthal area may be apparent and represents fluid sequestered within the distended nasolacrimal sac.
      b. **Infection** may occur, manifesting as warmth, erythema, tenderness, and increased induration.
   4. **Management**
      a. **Local massage,** if there is no evidence of infection
      b. **Intravenous antibiotics** and **urgent NLD probing** if infection is present

V. Ocular Trauma

A. **Retinal hemorrhages**
   1. **Etiology**
      a. Retinal hemorrhages are **highly suggestive of child abuse.** (Physical characteristics of child abuse are described further in Chapter 20, section VI.)
      b. **Nonabuse causes** of retinal hemorrhages include birth trauma, leukemia, increased intracranial pressure, malignant hypertension, bacterial endocarditis, immune thrombocytopenic purpura, and rarely, cardiopulmonary resuscitation.
   2. **Clinical features.** Retinal hemorrhages appear as hemorrhagic dots and blots, or hemorrhage within the preretinal vitreous on a dilated funduscopic examination.

B. **Corneal abrasion**
   1. **Definition.** Corneal abrasion is damage to, and loss of, corneal epithelium.
   2. **Etiology.** The cause is trauma, including injury from contact lens use.
   3. **Clinical features**
      a. **Severe pain,** tearing, and photophobia
      b. **Foreign body sensation**
   4. **Diagnosis.** Identification of the abrasion on **fluorescein staining** of the cornea is the basis of diagnosis.
   5. **Management. Complete healing usually occurs within 24–48 hours.**
      a. Placement of a protective shield or patch for 24–48 hours may be recommended in severe cases.
      b. **Instillation of a topical antibiotic** prevents bacterial superinfection.
      c. **Ophthalmologic consultation** to evaluate for a bacterial corneal ulcer is necessary if the abrasion is associated with contact lens use.

C. **Hyphema**
   1. **Definition.** Hyphema is **blood within the anterior chamber.**
   2. **Etiology**
      a. **Blunt trauma** is the **most frequent cause.** Blunt trauma compresses the globe, and when the globe subsequently re-expands, the iris vasculature tears, resulting in bleeding.
      b. **Nontraumatic causes** include iris neovascularization (associated with diabetes mellitus, intraocular tumors, and retinal vascular diseases), clotting disorders, and iris tumors (e.g., melanoma, juvenile xanthogranuloma).
   3. **Clinical features**
      a. **Impaired vision.** As blood settles, a **blood-aqueous** fluid level may be seen. A large hyphema may obscure the pupil and iris, thereby impairing vision.
      b. **Complications**
         1. **Rebleeding 3–5 days** after initial injury can occur due to repeat trauma or an underlying bleeding diathesis, or as the clot retracts.
         2. **Glaucoma**
         3. **Staining of the cornea with blood**
         4. **Optic nerve damage** in children with sickle cell disease
   4. **Management.** Treatment includes ophthalmologic consultation, pain control, prevention of vomiting (which may cause a sudden increase in intraocular pressure) and bed rest for at least 5 days.

D. **Orbital floor fracture ("blow-out" fracture)**
   1. **Etiology. Blunt trauma** to the eye or orbital rim fractures the orbital floor, which is normally thin and easy to fracture.

2. **Clinical features**
    a. **Orbital fat** and the **inferior rectus muscle** can become entrapped within the fracture, leading to **diplopia** as a result of restricted vertical eye movement, to **strabismus,** and to **enophthalmos** (backward displacement of the globe into the orbit).
    b. **Numbness of the cheek and upper teeth** below the orbital fracture may occur as a result of **infraorbital nerve injury.**
3. **Management**
    a. **Empiric oral antibiotics** are administered to prevent infectious contamination of the orbit from organisms from the maxillary sinus.
    b. **Surgical repair** is indicated if diplopia persists 2–4 weeks after injury or if enophthalmos is significant.

VI. Congenital Glaucoma

A. **Definition.** Congenital glaucoma is **increased intraocular pressure occurring at or soon after birth.**
   1. **Normal intraocular pressure** in infants is **10–15 mm Hg.** Infants with **congenital glaucoma** have intraocular pressures **exceeding 30 mm Hg.**
   2. **Congenital glaucoma** is very different from adult glaucoma.
      a. **Adult glaucoma** is characterized by increased intraocular pressure that damages the optic nerve but does not change the size of the eye.
      b. **Congenital glaucoma** not only results in optic nerve injury but also expands the size of the eye, because the eye wall is much more elastic during infancy. Congenital glaucoma results in corneal edema, corneal clouding, and amblyopia.

B. **Etiology**
   1. **Outflow of aqueous humor is reduced** because of maldevelopment of the trabecular meshwork.
   2. Most cases are inherited in an **autosomal dominant** fashion.
   3. Other causes include infection (e.g., congenital rubella syndrome), ocular abnormalities (e.g., aniridia [absence of the iris]), or genetic syndromes, (e.g., Sturge–Weber syndrome, neurofibromatosis, Marfan syndrome).

C. **Clinical features**
   1. **Ocular enlargement, tearing,** photophobia, **enlarged cornea, corneal clouding,** and a **dull red reflex** are common.
   2. **Bilateral** involvement is present in **70% of patients.**
   3. Glaucoma may be initially **misdiagnosed as NLD obstruction** because of the presence of tearing, but is distinguished by the presence of a normal red reflex in patients with NLD obstruction.

D. **Management**
   1. **Surgery** to open outflow channels is **almost always required.**
   2. Topical or systemic medications, such as β-adrenergic and carbonic anhydrase inhibitors, may help to lower intraocular pressure.

E. **Prognosis.** Congenital glaucoma, if not detected and treated surgically early, leads to blindness.

VII. Retinopathy of Prematurity (ROP)

A. **Definition.** ROP is the **proliferation of vessels** in the immature retina, seen in premature infants exposed to oxygen.

B. **Etiology**

1. The **precise cause** of ROP is **unknown;** however, vascular endothelial growth factors are posited to be involved**. High concentrations of oxygen play a major role** in the development of ROP.
2. **Other risk factors** include low birth weight (<1500 g), young gestational age, blood transfusions, respiratory distress syndrome (surfactant deficiency syndrome), and intracranial hemorrhage.

C. **Late complications.** Myopia, astigmatism, amblyopia, strabismus, and blindness may develop.

D. **Management**

1. **Ophthalmologic** examinations are performed every 1–2 weeks in patients with ROP to monitor for normal maturation of retinal vessels.
2. **If disease is severe, retinal cryotherapy and laser therapy** may be effective to prevent blindness.

E. **Screening and prevention**

1. **Early detection is essential.**
2. **Minimizing** the **amount of oxygen delivered** and effective treatment of respiratory distress syndrome (see Chapter 4, section VI) are the two most important factors for prevention of ROP.
3. Infants born at a gestational age of 28 weeks or less or with a birth weight of less than 1500 g should have a **dilated ophthalmoscopic examination** at 4–6 weeks of age.

VIII. Leukocoria

Leukocoria is a white pupil and refers to an opacity at or behind the pupil. It may be caused by a cataract, by an opacity within the vitreous, or by retinal disease, such as retinoblastoma.

A. **Congenital cataract**
   1. **Definition.** Congenital cataract is a crystalline opacity of the lens present at birth.
   2. **Etiology.** The **majority of cataracts are idiopathic.** Other causes include the following:
      a. **Genetic syndromes**, such as Down, Noonan, Marfan, Alport, and Smith–Lemli–Opitz syndromes
      b. **Nonsyndromic genetic inheritance**
      c. **Metabolic derangements**, such as hypoglycemia, **galactosemia,** and diabetes mellitus
      d. **Intrauterine infections,** such as cytomegalovirus and rubella
      e. **Trauma**
   3. **Management.** Treatment includes evaluation for underlying disease and **early surgery to prevent amblyopia.**
   4. **Prognosis.** Congenital cataracts treated within the first weeks of life have a good prognosis, whereas surgery performed after 2–3 months of age is associated with poor visual outcome.

B. **Retinoblastoma**
   1. **Definition.** Retinoblastoma is a **malignant tumor** of the retina.
   2. **Epidemiology**
      a. Retinoblastoma is the **most common ocular malignancy in childhood.**
      b. **The average age at presentation is 13–18 months. More than 90% of cases are diagnosed before 5 years of age,** which makes retinoblastoma a tumor of toddlers and preschool children.
   3. **Etiology**
      a. **Mutation or deletion** of a growth suppressor gene on **both alleles on the long arm of chromosome 13.** Because the development of retinoblastoma requires two deletions or mutations (one on each allele), the cause has been termed the "two-hit" model.
      b. **Mutations** may be **sporadic** or inherited in an **autosomal recessive** fashion.
   4. **Clinical features**
      a. **Leukocoria** and **strabismus** are the **two most common presenting signs.** Often a careful history will elicit that an observing parent has noticed the leukocoria.
      b. Glaucoma, vitreous hemorrhage, retinal detachment, and hyphema are less common presenting signs.
      c. **Calcification within the tumor,** identified on imaging studies of the eye, is a **hallmark** of retinoblastoma.
   5. **Diagnosis.** Visual inspection with an ophthalmoscope is the basis of diagnosis. Ocular ultrasound or computed tomographic scan of the orbit can further evaluate the tumor and assess for tumor extension.
   6. **Management**
      a. **Early diagnosis is critical. Retinoblastoma should be suspected in any child with leukocoria.**
      b. **Large tumors** involving the macula have a poor prognosis and are generally treated by removal of the entire eye (i.e., enucleation).
      c. **Smaller tumors** may be treated with external beam radiation; however, radiation may induce formation of secondary tumors.

   d. **Very small peripheral tumors** may be treated with cryotherapy or laser photocoagulation.
   e. Systemic and local intraretinal arterial **chemotherapy** are additional treatments.
7. **Prognosis.** Outcome is excellent if retinoblastoma is identified early. The **cure rate** is 90% if the tumor does not extend beyond the sclera or into the orbit. Retinoblastoma is uniformly lethal if untreated.

IX. Strabismus

A. **Definition.** Strabismus is **misalignment** of the eyes.
   1. **Esotropia** refers to the eye turned nasally.
   2. **Exotropia** refers to the eye turned laterally.
   3. **Vertical** strabismus refers to the eye turned up or down.
   4. **Pseudostrabismus** is a prominence of the epicanthal folds that results in the **false appearance of strabismus,** even though the eyes are actually appropriately aligned.

B. **Etiology.** The cause of most childhood strabismus is usually **unknown.** However, brain tumors, farsightedness (hypermetropia), or neurologic processes causing paresis of cranial nerves III, IV, or VI may also cause strabismus.

C. **Clinical features**
   1. **If strabismus occurs before 5–7 years of age,** the child suppresses the image in the deviated eye. If this suppression is prolonged, amblyopia may result.
   2. **If strabismus occurs later than 5–7 years of age** (i.e., **acquired strabismus**), the mature visual system is unable to suppress the image in the deviated eye, and **diplopia** results.
   3. **Acquired strabismus, decreased eye movement, ptosis, decreased vision, and abnormal red reflex are all red flags that suggest a dangerous underlying cause,** such as a tumor or neurologic process.

D. **Management.** Treatment depends on the underlying cause.
   1. Ocular patching or use of eye drops to cause blurring to the normal eye to prevent amblyopia is important.
   2. Strabismus associated with farsightedness is initially treated with corrective lenses.
   3. Surgery is often required to correct any misalignment that does not respond to patching or glasses.

Review Test

1. A 1-month-old male infant is brought to the office for a routine health maintenance visit. The infant has been feeding well, and the parents have no concerns. Physical examination is unremarkable except for a lens opacity in the right eye. Which of the following statements regarding this finding is most correct?
   A. Because of this infant's age, he is not susceptible to amblyopia.
   B. Immediate referral for cataract surgery is indicated.
   C. The opacity was probably not present at birth but has developed after birth.
   D. Surgery can be safely delayed until 6 months of age.
   E. Red reflex testing is normal and does not identify this finding.
2. A 3-year-old girl with a normal past medical history presents with a 5-day history of bilateral mucoid conjunctival discharge and conjunctival hyperemia. The girl is rubbing her eyes, and her mother believes that her daughter's eyes are very itchy. Which of the following statements regarding the most likely diagnosis is correct?
   A. The girl's symptoms are secondary to a type 2 hypersensitivity reaction.
   B. Topical antihistamines would be effective.
   C. *Staphylococcus aureus* is the likely pathogen.
   D. Coexisting rhinitis would be unusual.
   E. Topical polymyxin B and trimethoprim sulfate is an effective treatment.
3. A 14-year-old boy who wears contact lenses presents with conjunctival hyperemia and severe photophobia of the right eye. Which of the following statements regarding his diagnosis and management is most correct?
   A. Immediate ophthalmologic evaluation is necessary.
   B. Viral conjunctivitis is likely and supportive care should be provided.
   C. Eosinophils are seen on conjunctival scraping.
   D. Fluorescein staining is normal.
   E. Topical erythromycin should be prescribed and the patient should follow up if no improvement is seen in 1 week.
4. A 5-year-old boy presents with a history of fever, bilateral watery conjunctival discharge, sore throat, and a foreign body sensation in his eyes. Physical examination is notable for bilateral conjunctival hyperemia with watery discharge and bilateral preauricular lymphadenopathy. Which of the following statements regarding the most likely diagnosis is correct?
   A. Topical nonsteroidal anti-inflammatory drugs are contraindicated in the management of this illness.
   B. Corneal involvement is unlikely.
   C. Cool compresses should be used.
   D. Bilateral eye involvement is uncommon.
   E. This highly contagious illness is most often caused by *Staphylococcus aureus.*
5. A 2-year-old child is brought to the office with a 3-month history of "uneven eyes." Physical examination shows right eye exotropia and leukocoria. Computed tomography of the orbit reveals a large retinoblastoma that involves the macula. Which of the following statements regarding the diagnosis is most correct?
   A. This tumor occurs sporadically and is not inherited.
   B. Computed tomography reveals calcifications within the tumor.
   C. Strabismus is uncommon at presentation.
   D. Radiation therapy is effective and has few complications.
   E. The age at diagnosis is unusual.
6. A 10-year-old girl is brought to the emergency department after sustaining a baseball injury to

the right eye. Which of the following signs or symptoms is most consistent with the suspected diagnosis of a fracture of the orbital floor?

A. Glaucoma
B. Exophthalmos
C. Diplopia
D. Numbness of the lower teeth and chin
E. Hyphema

The response options for statements 7–10 are the same. You will be required to select one answer for each statement in the set.

A. Chemical conjunctivitis
B. Conjunctivitis caused by *Neisseria gonorrhoeae*
C. Conjunctivitis caused by *Chlamydia trachomatis*
D. Conjunctivitis caused by herpes simplex virus

For each patient, select the most likely diagnosis.

1. A 7-day-old male infant with purulent conjunctival discharge and mild lid swelling.
2. A 12-hour-old male infant with bilateral watery conjunctival discharge.
3. A 10-day-old female infant with unilateral serous conjunctival discharge and multinucleated giant cells on Gram stain.
4. A 2-day-old female infant with purulent eye discharge and eyelid swelling.

Answers and Explanations

1. **The answer is B** [VIII.A and I.A]. Presentation with a lens opacity is consistent with a congenital cataract, a potentially very serious opacity of the lens. Immediate referral to a pediatric ophthalmologist is warranted. Surgery should occur within the first several weeks of life to ensure a good prognosis. If an opacity is not removed promptly in a young infant, the retina and nervous connections are not appropriately stimulated, and amblyopia (poor vision caused by abnormal retinal stimulation) may develop. Children are most susceptible to amblyopia during the first 3–4 months of life. Congenital cataracts are present at birth. The majority of cataracts are idiopathic, although known causes include trauma, metabolic abnormalities like galactosemia, genetic syndromes, and nonsyndromic genetic inheritance. The Bruckner test, which is used in the assessment of the bilateral red reflex, is usually abnormal in the presence of a cataract.
2. **The answer is B** [III.B.2.a.(2) and III.B.3.c]. Itching is the hallmark of allergic conjunctivitis, the likely cause of this patient's symptoms. Symptoms and signs of allergic conjunctivitis also include conjunctival erythema and watery or mucoid discharge. Management includes topical antihistamines, topical mast cell stabilizers, and environmental modification (removing from the environment any known or suspected allergens such as stuffed animals, pets, or carpet). Allergic conjunctivitis is a type 1 hypersensitivity reaction and is commonly seasonal. Uncomplicated allergic conjunctivitis is not associated with bacterial infection. Other signs and symptoms of allergy are commonly found, including allergic rhinitis. Topical antibiotics are ineffective for allergic conjunctivitis.
3. **The answer is A** [III.B.2.a.(3) and V.B.5.c]. Conjunctivitis associated with contact lens use suggests three major possibilities, including an allergy to the contact lens solution, a corneal abrasion, or a bacterial corneal ulcer, which can be vision-threatening. A possible corneal ulcer requires urgent ophthalmologic consultation. Viral conjunctivitis is unlikely because of the acuity of the presentation, the unilateral findings, and severe photophobia. Eosinophils on conjunctival scraping are found in allergic conjunctivitis. A corneal ulcer usually appears on fluorescein staining. Because a corneal ulcer is a possibility, prescribing antibiotics with follow-up in a week would risk missing the early diagnosis of this serious condition.
4. **The answer is C** [III.B.3.b.(1)]. This patient's signs and symptoms are consistent with pharyngoconjunctival fever, a highly contagious illness that lasts for 2–3 weeks and is best managed with supportive care, including topical nonsteroidal anti-inflammatory drugs and cool compresses. Corneal involvement does occur and usually manifests as a foreign body sensation within the eye. Pharyngoconjunctival fever is commonly bilateral. It is a highly contagious illness caused by infection with adenovirus. The presence of preauricular adenopathy and watery discharge is inconsistent with bacterial conjunctivitis.
5. **The answer is B** [VIII.B]. Retinoblastoma is diagnosed on the basis of visual inspection and imaging studies, such as computed tomography or ocular ultrasound. Calcification within the tumor is a hallmark of retinoblastoma. Retinoblastoma is inherited sporadically or in an autosomal recessive fashion. The two most common presenting features are leukocoria (white light reflex) and strabismus. Management of large tumors often includes enucleation, although small retinoblastomas may be managed with external beam radiation. The side effects of radiation therapy include induction of secondary tumors. The majority of children with retinoblastoma are younger than 5 years.
6. **The answer is C** [V.D.2]. Orbital floor fracture, or a "blow-out" fracture, is generally secondary to blunt trauma to the orbit and can lead to entrapment of orbital fat and the inferior rectus muscle within the fracture. Glaucoma is typically not a complication of an orbital floor fracture. Entrapment leads to enophthalmos (i.e., retracted globe), restricted

vertical movement of the eye, and strabismus with resultant double vision (diplopia). Because the infraorbital nerve may be injured, numbness of the cheek and upper teeth may result. Hyphema, or blood within the anterior chamber, also occurs secondary to blunt trauma. Hyphema should certainly increase your index of suspicion for other injuries associated with blunt trauma, but hyphemas frequently occur without concurrent injuries to the orbital floor.

7. **The correct answers are C, A, D, and B, respectively** [III.A.1–3 and Table 18-2]. Neonatal conjunctivitis is defined as conjunctivitis occurring within the first month of life. *Chlamydia trachomatis* causes serous or purulent conjunctivitis with variable lid swelling in infants between 4 and 10 days of age (question 7). Conjunctivitis within the first 24 hours (question 8) is characteristic of chemical irritation from neonatal prophylactic drops or ointment, such as 1% silver nitrate. Herpes simplex virus presents with vesicles, corneal ulcers, and multinucleated giant cells on Gram stain of conjunctival cells (question 9). *Neisseria gonorrhoeae* causes purulent, rapid onset conjunctivitis with lid swelling in infants between 2 and 4 days of age (question 10).

CHAPTER 19

Dermatology

Amy E. Gilliam, Lloyd J. Brown

I. General Concepts

A. **Skin examination** should be conducted in good light and should be complete, including evaluation of the scalp, hair, nails, eyes, mouth, palms, and soles. Examination should be both visual and tactile.

B. **Description** of skin disease requires identification of primary lesions and any secondary characteristics. Configuration and distribution of lesions should also be noted.

1. **Primary lesions**
    a. **Macules** are <10 mm in size, **flat**, and nonpalpable, and represent a cutaneous color change. A **patch** is a large macule (≥10 mm).
    b. **Papules** are **epidermal or superficial dermal** lesions <10 mm in size that are elevated **above the skin surface.** A **plaque** describes large or coalesced papules (≥10 mm).
    c. **Nodules** are **dermal lesions** that are <10 mm in size and generally **below the skin surface,** although they may have an epidermal component that rises above the skin surface. A **tumor** is a large nodule (≥10 mm).
    d. **Vesicles** are fluid-filled papules. A **bulla** is a large vesicle.
    e. **Pustules** are purulent-filled papules.
    f. **Cysts** are nodules filled with expressible material.
    g. **Wheals** are cutaneous elevations caused by dermal edema.
2. **Secondary characteristics** include the following:
    a. **Scale:** desquamation of the stratum corneum
    b. **Crust:** dried exudate and debris
    c. **Pigmentary changes**
    d. **Excoriations:** linear erosions into the epidermis caused by fingernail scratches
    e. **Scars:** thickened fibrotic dermis
    f. **Ulcers:** absence of epidermis and some of the dermis
    g. **Atrophy:** thinning of the epidermis or dermis
    h. **Fissures:** linear cracks into the dermis
3. **Configuration and distribution**
    a. **Configuration of lesions** may be described as **linear, annular** (i.e., ring shaped), **arcuate** (i.e., in half-circles), **serpiginous** (i.e., with a wavy or serpentine border), **reticulated** (i.e., netlike), **grouped,** or **discrete** (i.e., distinct and separate).
    b. **Distributions** include generalized, flexural, acral (hands, feet, buttocks), dermatomal (confined to a dermatome), or other specific locations. Some skin lesions are **blaschkoid**, meaning they follow the lines of Blaschko, which are the lines of cutaneous development in utero.

C. **Diagnostic procedures**

1. **Woods light** can highlight pigmentary changes and some dermatophytes.
2. **Scrapings**
    a. **Fungus.** Ten percent potassium hydroxide (KOH) can be added to a scraping of a scale or exudate to identify fungal hyphae.
    b. **Scabies.** Examination under a microscope of a scraping of an unscratched lesion or burrow for mites, eggs, or feces may be diagnostic of scabies.
    c. **Herpes simplex virus** (HSV). The base of a vesicle can be scraped for laboratory identification of the herpes virus.
3. **Cultures** may be obtained for bacteria, virus, fungus, and yeast.
4. **Invasive techniques**
    a. **Incision and drainage** may be performed for diagnosis, to obtain cultures, or for

therapy.

b. **Biopsy**
    1. **Shave or tangential** biopsy for epidermal and superficial dermal lesions
    2. **Punch** biopsy for epidermal, dermal, and superficial subcutaneous lesions
    3. **Excisional** biopsy for complete lesion removal

5. **Immunofluorescent staining** of biopsied skin lesions may be useful in diagnosis of autoimmune and/or vasculitic disorders.

D. **Management**

1. **General concepts**
    a. **Absorption** of topical agents through the skin of infants and small children is greater than in adults owing to the increased body surface area to weight ratio that children have as compared with adults. This is especially true for premature infants in whom there is also greater absorption through the skin owing to a thinner stratum corneum.
    b. **Therapeutic efficacy** of a topical agent is related to both the active ingredient and the **vehicle** (e.g., cream, lotion, ointment).
2. **Hydration of the skin is critical.** Dry, irritated skin is a poor barrier and easily damaged. Moisturizers include the following:
    a. **Ointments** contain little or no water and have **maximal water-retaining properties,** making them useful for very dry skin.
    b. **Creams** contain 20–50% water and are useful for skin of average dryness.
    c. **Lotions** contain more water than creams and are useful for minimally dry skin or for large surface areas.
    d. **Solutions** and **alcohol-based gels** are most useful for hair-bearing areas (e.g., scalp).
3. **Thickened skin** (hyperkeratosis) responds well to treatment with **keratolytics,** such as salicylic acid, urea, α-hydroxy acids, and retinoic acid.
4. **Destructive therapies** (e.g., for warts, molluscum contagiosum) include high-dose salicylic acid, cantharidin, podophyllin, 5-fluorouracil, cryotherapy, electrotherapy, and laser therapy.
5. **Anti-infective agents** include topical antibiotics, antifungals, antivirals, and antiparasitic agents.
6. **Anti-inflammatory agents**
    a. **Topical corticosteroids** are categorized on the basis of their vehicle and potency. Effectiveness and potential side effects mirror steroid potency. **The weakest steroid that will achieve the treatment goal should be used first.** In general, only low-potency corticosteroids should be used on the face or groin because the epidermis is thinner in these areas, resulting in an increased risk of side effects.
        1. **Systemic side effects.** Systemic steroid levels can be achieved if very potent steroids are used on damaged or thin skin for long periods of time. Rare side effects may include **adrenal suppression,** depressed growth, cataracts, glaucoma, and Cushing syndrome (see also Chapter 6, section IV.E.2).
        2. **Local side effects** are **more common** and are also more likely to occur after long-term use of topical corticosteroids.
            a. **Acne** (acne rosacea and steroid acne)
            b. **Hirsutism**
            c. **Folliculitis**
            d. **Striae** (especially in the axilla or groin)
            e. **Hyper- or hypopigmentation**
            f. **Skin atrophy**

g. **Ecchymoses and telangiectasias**
h. **Tachyphylaxis** (insensitivity to the medication)

b. **Other topical anti-inflammatory agents**
    1. **Tacrolimus ointment and pimecrolimus cream** are topical calcineurin inhibitors/immunomodulators used to treat atopic dermatitis, psoriasis, and other inflammatory skin conditions.
    2. **One to five percent sulfur,** formulated with other medications, for acne
    3. **Tar,** used for eczema and psoriasis
    4. **Antibiotics,** used for anti-inflammatory properties to treat acne and perioral dermatitis.

II. Newborn Skin Diseases

See Chapter 4, section I.K.

III. Inflammatory Disorders

A. **Contact dermatitis**
   1. **Definition.** Contact dermatitis is inflammation of the epidermis and superficial dermis secondary to direct contact with the skin by a sensitizing substance.
   2. **Categories**
      a. **Allergic contact dermatitis**
         1. **Etiology.** Allergic contact dermatitis occurs as a direct **T-cell–mediated** response to an exogenous applied allergen. There must be an initial sensitization and then a rechallenge (which may be very small and is not dose-dependent) to elicit a reaction. **Common causes** include poison ivy, oak, or sumac; nickel found in jewelry, belt buckles, or snaps; topical lotions or creams; and perfumes or soaps.
         2. **Clinical features.** Erythematous pruritic papules and vesicles occur in the area that came into contact with the allergen.
         3. **Management.** Treatment involves topical corticosteroids and avoidance of the offending allergen.
      b. **Primary irritant contact dermatitis**
         1. **Etiology.** Primary irritant contact dermatitis is caused by caustic substances that irritate the skin, rather than an allergic reaction. **No prior sensitization is required.** The reaction is dose-dependent. The **most common form is diaper dermatitis,** a multifactorial disorder caused by prolonged contact with urine and fecal matter, friction, maceration, and proteases contained in the feces and urine. *Secondary infection with Candida albicans may occur.*
         2. **Clinical features** of diaper dermatitis include erythema with papules on the skin that is exposed to the diaper surface, including the upper thighs, buttocks, and genitourinary area **without involvement of the inguinal creases.** Involvement of the inguinal creases, more-intense confluent erythema, and satellite lesions all suggest candidal superinfection.
         3. **Management** of diaper dermatitis includes protecting the skin from urine and stool; application of skin moisturizers, barrier creams, and ointments (e.g., zinc oxide); and frequent diaper changes. Low-potency corticosteroids may be used for severe inflammation. Candidal infection may be treated with topical antifungal medication (e.g., nystatin, clotrimazole).

B. **Atopic dermatitis** (see Chapter 15, section III)

C. **Seborrheic dermatitis**
   1. **Epidemiology.** Seborrheic dermatitis predominantly affects two age groups, infants and adolescents.
   2. **Etiology.** The cause is **unknown** but is thought to be a hypersensitivity reaction to a saprophytic yeast (*Pityrosporum ovale*) that lives in areas that overproduce sebum.
   3. **Clinical features.** Erythema with overlying "greasy" thick yellow-white scale and sometimes crusting in areas with high numbers of **sebaceous glands,** such as the scalp, face (including the eyebrows, nose, and beard area), chest, and groin
      a. **Infants** may have dermatitis limited to the scalp, termed seborrheic capitis or **cradle cap.** Involvement of the face, upper chest, and flexor creases of the extremities may also occur.
      b. **Adolescents** may have dermatitis in the nasolabial folds, pinnae, and scalp.
   4. **Management**
      a. **Low-potency topical corticosteroids**

b. **Sulfur-, zinc-, or salicylic acid–based** shampoos may be used, followed by light scrubbing with a brush to remove crusts. Loose scales may also be removed with mineral oil.
c. **Topical antiyeast medications** (e.g., clotrimazole) **or shampoos** (containing zinc pyrithione or ketoconazole) are used to eradicate *Pityrosporum ovale.*

D. **Pityriasis rosea**
1. **Epidemiology.** Pityriasis rosea is uncommon before 5 years of age but is extremely common during late childhood and adolescence.
2. **Etiology.** The cause is unknown, although it is thought to be an immune response to a virus.
3. **Clinical features**
a. **Papulosquamous** skin lesions that begin with a solitary, large 2- to 5-cm scaly, erythematous lesion (**herald patch**) that is usually located on the trunk or extremities. The herald patch is present for 1–30 days.
b. Approximately 1–2 weeks after the appearance of the herald patch, similar smaller **oval pink scaling macules and papules** erupt for approximately 3–6 weeks on the trunk and extremities, following skin lines in a "**christmas tree**" distribution on the trunk.
c. Lesions are pruritic in 50% of cases.
4. **Management.** Treatment may include topical or systemic antihistamines as well as topical corticosteroids or immunomodulators to help treat pruritus. Exposure to ultraviolet light may shorten the disease course.

E. **Psoriasis**
1. **Epidemiology.** Psoriasis occurs in 3% of children in the United States. Although it is more common in adults, 30% of patients develop signs and symptoms during childhood.
2. **Etiology.** Childhood-onset psoriasis is often a **genetic condition.** It is caused by immune dysregulation, causing epidermal proliferation and skin inflammation.
3. **Clinical features**
a. Distribution of skin lesions and severity are variable. If severe, psoriasis may be disfiguring.
b. Lesions are characterized by erythematous **scaling papules and plaques** often found on the scalp (nongreasy scale without hair loss), ears, elbows, knees, lumbosacral area, and groin. Lesions often have a classic **silvery scale.**
c. Lesions often demonstrate the **Koebner phenomenon** in which new lesions develop at sites of skin trauma.
d. **Nail involvement is common** and may include pits, distal thickening, lifting of the nail bed, and nail destruction.
e. Arthritis during childhood is uncommon.
4. **Management.** Treatment may include moderate- or high-potency topical corticosteroids, topical calcineruin inhibitors, ultraviolet light therapy, vitamin D analogues, topical salicylic acid, tar, retinoids, and anthralin (downregulates epidermal growth factor).

F. **Miliaria rubra (heat rash)**
1. **Etiology.** Heat rash is caused by **disrupted sweat ducts** near the upper dermis (often caused by occlusion or friction) that result in sweat being released onto the skin. The sweat on the skin produces an inflammatory response. Therefore, the more sweat produced and the more occlusion, the more likely heat rash will develop.
2. **Clinical features.** Small erythematous pruritic papules or vesicles occur in areas of occlusion or in areas that have been rubbed, such as the inguinal region, axilla, chest, and neck.
3. **Management.** Treatment is avoidance of occlusive clothing to decrease sweating.

Medications are unnecessary.

IV. Hypersensitivity Disorders

A. **Urticaria** (see Chapter 15, section VI)

B. **Serum sicknesslike reaction** may initially mimic urticaria, but it tends to produce skin lesions with a more annular (ring-shaped) appearance with a dusky or bruised-looking central component. It is associated with systemic signs and symptoms including fever, arthralgias, adenopathy, and evidence of organ injury. Viral triggers and medications, such as cephalosporins, are common causes.

C. **Erythema multiforme (EM) and Stevens–Johnson syndrome (SJS)**

1. **Definition.** EM is a hypersensitivity reaction to many potential stimuli, including drugs, viruses, bacteria, fungi, protozoa, and systemic disease.
2. **Categories.** There are two major categories of EM: **EM minor** and **EM major. SJS** is now considered to be a separate entity from EM. The **classic skin lesion** present in both EM and SJS is a **target lesion,** which is a **fixed,** *dull red, oval macule with a dusky center* that may contain a papule or vesicle. **Table 19-1** summarizes the **causes, clinical features, management, and prognosis** of EM and SJS.

D. **Toxic epidermal necrolysis** is a **severe reaction to medications** (e.g., anticonvulsants, antibiotics, anti-inflammatory drugs) that results in **widespread epidermal necrosis.** Clinical features include sloughing of the epidermis (usually >30% skin loss) and severe mucous membrane involvement. Target lesions are usually not seen. **Nikolsky sign** (skin peels away with lateral pressure) is often present. Mortality is high (10–30%) as a result of the high incidence of complications due to sepsis, dehydration, and electrolyte abnormalities.

Table 19-1
Characteristic Features of the Types of Erythema Multiforme and Stevens–Johnson Syndrome

	Erythema Multiforme Minor	Erythema Multiforme Major	Stevens–Johnson Syndrome
Major cause	**Herpes simplex virus**	***Mycoplasma pneumoniae;* Medications**	**Medications**
Skin findings	Symmetric target lesions; acral distribution	Typical symmetric target lesions; acral and truncal distribution	Widespread **atypical, asymmetric** target lesions, blisters, and necrosis
Mucous membrane findings	Occurs in 25%; *only one* surface involved (often mouth)	*At least two* mucosal surfaces involved (often mouth and eyes)	*At least two* mucosal surfaces involved (often mouth and eyes)
Systemic findings	Prodrome of low-grade fever, arthralgias, myalgias	Prodrome of low-grade fever, arthralgias, myalgias	Prodrome of high fever, cough, malaise, headache, arthralgias
Management	Supportive care	Supportive care	Supportive care
	Acyclovir may prevent recurrence	Erythromycin or azithromycin if *M. pneumoniae* is suspected	Stop offending drug
			Ophthalmology consultation
		Stop offending drug	Consider steroids, IVIG, burn unit
Prognosis	Good; possible recurrence	Good	High morbidity and mortality (5%)

IVIG = intravenous immune globulin.

V. Infections of the Skin

A. **Fungal (dermatophyte) infections** can involve hair, skin, and nails.
   1. **Tinea capitis** is a fungal infection of the scalp hair.
      a. **Etiology.** Tinea capitis is most commonly caused by *Trichophyton tonsurans* (95%), acquired from human-to-human contact, and *Microsporum canis* (5%), often acquired from animals, such as cats and dogs.
      b. **Clinical features**
         1. **Patchy hair loss** in which the hairs break off at the scalp (**black dot ringworm**) or in which the broken hairs may be thickened and white
         2. Infected areas may have **pustules and scale.**
         3. **Kerion** (large red boggy nodule/plaque) may be present and represents a hypersensitivity reaction to the dermatophyte.
         4. **Occipital and posterior cervical lymphadenopathy** are suggestive of tinea capitis.
      c. **Diagnosis.** The basis of diagnosis is microscopic evaluation of hairs with 10% KOH to identify fungal hyphae or a positive fungal culture. Hairs fluoresce under Woods light if *M. canis* is the infecting organism.
      d. **Management.** Treatment includes **systemic oral antifungal therapy** (e.g., griseofulvin or terbinafine) for 6–8 weeks. **Topical antifungal agents are ineffective for infections of the hair.** Topical 2.5% or 5% selenium sulfide shampoo may be used as an adjunct to reduce infectivity.
   2. **Fungal infection of the skin** may include **tinea corporis** (infection on the body), **tinea pedis** (infection on the foot), **tinea cruris** (infection in the groin), and **tinea faciei** (infection on the face).
      a. **Etiology.** Pathogens include *M. canis*, *T. tonsurans*, and other *Trichophyton* species.
      b. **Clinical features**
         1. **Tinea corporis** ("ringworm") presents as a **circular or annular scaly erythematous patch with partial central clearing** and an "active" border, which means that the advancing edge or border of the skin lesion is more erythematous and/or scaly than the central portion.
         2. **Tinea pedis** (athlete's foot) presents most commonly in **postpubertal adolescents** with scaling, erythema, and maceration between the toes or on the plantar aspect of the foot. Vesicles may also be seen.
         3. **Tinea cruris** usually presents as well-defined scaling and erythema in the groin and inguinal creases.
      c. **Diagnosis.** Clinical features are often the basis of diagnosis. 10% KOH examination of skin scrapings for fungal hyphae or fungal culture can confirm the diagnosis.
      d. **Management.** Treatment includes topical antifungal medications (e.g., terbinafine, ketoconazole, itraconazole).
   3. **Tinea unguium (onychomycosis)** is a fungal infection of the nails characterized by thickening and yellow discoloration of one or several nails (usually toenails). Topical management is not very effective; treatment requires prolonged therapy and is often unsuccessful as onychomycosis tends to recur. Systemic medications, such as griseofulvin, terbinafine, and itraconazole, are therapies of choice and are given for long courses (12+ weeks).
   4. **Tinea versicolor** is a common disorder seen more often in adolescents and young adults. It is caused by a yeast of the *Malassezia* species (rather than a fungus) that invades the stratum corneum.

a. **Clinical features** vary and include fine, scaly oval macules on the trunk, proximal arms, and face. Macules may be hypo- or hyperpigmented and become more prominent with sun exposure. Infection is usually asymptomatic.
b. **Diagnosis** is usually made by clinical examination but can also be made by identification of fungal hyphae or circular spores on KOH examination of skin scrapings *("spaghetti and meatballs"* appearance) or by yellow-green fluorescence on Woods light evaluation. The *Malessezia* yeast does not grow well on culture.
c. **Management.** Treatment includes overnight application of 2.5% selenium sulfide weekly for 3–4 weeks, ketoconazole shampoo or cream, or systemic antifungal medications (ketoconazole, itraconazole).

B. **Bacterial infections,** including **impetigo, cellulitis, erysipelas, scarlet fever, toxic shock syndrome, and staphylococcal scalded skin syndrome,** are discussed in Chapter 7, section IX.

C. **Viral infections**

1. **Viral exanthem** refers to a skin rash associated with a viral infection. Any virus may cause an exanthem, and the rash may take many forms. An **enanthem** (describing involvement of the oral mucosa) may also be present.
   a. **Morbilliform:** refers to a "measleslike" appearance with diffuse involvement of red macules on the skin
   b. **Papulovesicular:** refers to a rash composed of papules and vesicles
2. **Measles and rubella** (see Chapter 7, sections XIII.C and D)
3. **Erythema infectiosum (fifth disease)**
   a. **Epidemiology.** Fifth disease is most common in school-age children, although it can occur at any age.
   b. **Etiology**
      1. The cause is **parvovirus B19.**
      2. Fifth disease is transmitted by respiratory secretions.
   c. **Clinical features**
      1. Fifth disease begins with upper respiratory symptoms (cough, fever, rhinorrhea) that are followed within 1–2 weeks by a bright red macular rash on the cheeks ("**slapped-cheek**" appearance) that lasts several days. Patients are generally **no longer contagious when the characteristic facial rash appears.**
      2. **A lacy, reticulate rash** on the limbs and then the trunk follows the facial rash and generally lasts 3–5 days. In some patients, exercise, heat, or sunlight can induce the lacy rash to recur.
      3. **Arthralgias** may be present, although they are more common in adults.
      4. Parvovirus B19 infection may also cause *aplastic crisis* (especially in patients with hemoglobinopathies), *prolonged anemia* in immunosuppressed patients, and *fetal hydrops* or *miscarriage* in pregnant women.
   d. **Management.** Treatment is **supportive.** However, intravenous immune globulin may be used treat prolonged anemia in immunosuppressed patients.
4. **Roseola infantum (exanthem subitum)**
   a. **Epidemiology.** Roseola is most common in children between 6 months and 3 years of age.
   b. **Etiology.** Roseola is most commonly caused by **human herpes virus 6 and 7.** Other causes include adenovirus, parvovirus B19, and echovirus 16.
   c. **Clinical features.** Roseola begins with **3–5 days of high fever** and irritability. Once the fever resolves, a usually asymptomatic pink papular eruption occurs on the trunk that generally fades within 24–48 hours.
   d. **Management.** Treatment is **supportive.**

5. **Gianotti–Crosti syndrome (papular acrodermatitis)** most often occurs in children between the ages of 6 months and 12 years. Gianotti–Crosti is associated with **hepatitis B**, Epstein–Barr virus, and enterovirus and echovirus infections. Clinical features include the development of red or flesh-colored flat-topped papules on the extremities with accentuation over the elbows and knees. The cheeks and buttocks can also be involved, but the rash classically spares the trunk. Skin lesions may last for several weeks and may recur. Upper respiratory symptoms may precede the eruption. Treatment is supportive.
6. **Varicella (chickenpox)**
    a. **Epidemiology.** The incidence of varicella has decreased as a result of routine early childhood immunization in many states. Varicella may occur at any age in unimmunized children and adolescents.
    b. **Clinical features**
        1. Intensely pruritic erythematous macules develop acutely after a **7- to 21-day incubation period.** The macules develop central vesicles within 1–2 days. The classic lesion is described as a "**dew drop on a rose petal**" or a vesicle on a red background.
        2. **Crops of lesions** appear during the course of 2–5 days. Hundreds of vesicles may be present, which will crust over.
        3. **Fever is common.**
    c. **Management.** Treatment includes antipyretics, management of bacterial superinfection, antihistamines for itching, and monitoring and treatment of complications. Acyclovir is generally administered intravenously for patients with varicella pneumonia and encephalitis, orally for those at high risk for complications, and topically in the eyes for those with ophthalmic involvement.
    d. **Complications** (Table 19-2)
7. **Herpes simplex virus infection (HSV-1 and HSV-2)**
    a. **Pathophysiology**
        1. **Neonatal infection** is generally acquired during passage through the birth canal of a mother with primary HSV infection. Two-thirds of neonatal infections are caused by HSV-2 and one-third are caused by HSV-1.
        2. **Gingivostomatitis** is the most common HSV infection during infancy and childhood and is almost always caused by HSV-1.
    b. **Clinical features**
        1. **Characteristic lesions are grouped vesicles on an erythematous base.**
        2. **Gingivostomatitis** presents most often in young infants with grouped vesicles and ulcers on the lips, in the corners of the mouth, and on the tongue. Pain on swallowing, drooling, and fever may be present. Infection lasts 1–2 weeks.
        3. **Neonatal HSV** commonly presents in the first week of life with variable signs and symptoms. Neonates may have only a few vesicles at the site (often the scalp) that was in contact with the infecting maternal lesion, or they may present with signs and symptoms of sepsis, including apnea, lethargy, irritability, and seizures. **Serious sequelae** include **meningoencephalitis,** hepatitis, sepsis, shock, and death.
        4. **Herpetic whitlow** describes HSV-1 infection of the thumb or fingers that is usually secondary to thumb- or finger-sucking by a child with an oral HSV lesion.
        5. HSV resides in the **dorsal root ganglion** after initial infection, and therefore, **recurrent HSV infection** may occur. Recurrent HSV lesions are more mild and less symptomatic than primary infection and generally occur on the lip. Fever, illness, ultraviolet light exposure, emotional stress, and trauma may all

reactivate the latent virus.

c. **Diagnosis.** HSV may be diagnosed by identification of epidermal giant cells on microscopic evaluation of a Tzanck preparation, by detection of HSV antigen on **direct fluorescent antibody (DFA) testing**, or by culture of the base of the lesion. **Polymerase chain reaction (PCR)** technology is commonly used to identify HSV in the cerebrospinal fluid.

d. **Management**

1. **Neonatal HSV infection** is a **medical emergency** and requires immediate hospitalization and treatment with intravenous acyclovir.
2. **Cutaneous and oral HSV** may be treated with **oral acyclovir,** although treatment must be started promptly to alter the disease course. Oral acyclovir, when given daily, may also prevent recurrent infection.

8. **Hand–foot–mouth disease and herpangina**

a. **Etiology.** Hand–foot–mouth disease and herpangina are caused by infection with enterovirus, usually **coxsackievirus types A16 (most common)**, A2, A5, A6, and A10. It is usually seen in children less than 5 years of age.

b. **Clinical features** include vesicles, papules, or pustules on the palms, soles, or fingertips and shallow ulcers or erosions on the soft palate or tongue. The rash also sometimes affects the buttocks. If only oral lesions are present, the disorder is termed **herpangina.** Fever may occur with both forms. In some cases, shedding of finger- and toenails, called onychomadesis, is observed a few weeks after the infection.

c. **Management.** Treatment is supportive.

9. **Warts**

a. **Etiology.** The cause is **human papillomavirus.**

b. **Clinical features.** Warts may occur on any skin surface and appear as irregularly shaped discrete flesh-colored papules that may be smooth or rough. Warts often increase in size, are contagious, and may spread to adjacent skin. **Condylomata acuminata** is the term used to describe multiple external warts in the genital area (see Chapter 3, section VII.B.6).

c. **Management.** Most warts resolve spontaneously within 1–2 years. Treatment to remove or destroy warts may include liquid nitrogen, salicylic acid, cantharidin, podophyllin, laser therapy, and surgical excision. Newer immune therapies are also used to treat warts, which include injections with candida antigen and topical agents used to stimulate the immune system (e.g., squaric acid, imiquimod). Recurrence after any treatment is high.

10. **Molluscum contagiosum**

a. **Etiology.** The cause is a **poxvirus.**

b. **Clinical features**

1. Small asymptomatic **flesh-colored papules with central umbilication** are characteristic.
2. Lesions may be present anywhere on skin with hair follicles, although the proximal extremities and trunk are most commonly involved.
3. Lesions are **contagious.**
4. **Human immunodeficiency virus (HIV) infection** may be associated with extensive eruptions of molluscum.

c. **Management.** Treatment is often observation with expected resolution over months to years without therapy. Removal can be accomplished by curettage or application of cantharidin, podophyllin, trichloroacetic acid, liquid nitrogen, or salicylic acid.

D. **Ectoparasites**

1. **Louse infestation** may involve the scalp (**head lice**), body (**body lice**), or groin (**pubic lice**).
    a. **Etiology.** Causative organisms include ***Pediculus humanus,*** the cause of head and body lice, and ***Phthirus pubis,*** the cause of pubic lice. The louse is a small six-legged insect that attaches to the skin and ingests blood.
    b. **Epidemiology.** Louse infestations are associated with crowded living conditions and sharing of hats, clothes, combs, and hairbrushes.
    c. **Clinical features**
        1. **Head lice** are associated with **itching.** The **nits** (eggs) may be seen as oval white bodies attached to the hair shaft. The louse may be found on the scalp.
        2. **Body lice** are associated with papules and pustules on the trunk with excoriations.
        3. **Pubic lice** are associated with lice or nits in the groin and black-crusted papules or blue macules (macula cerulea).
    d. **Management**
        1. **Head lice** are treated with 1% permethrin shampoo and a comb to remove the nits. Five percent permethrin, malathion, ivermectin, and therapies meant to suffocate the lice are sometimes used for resistant lice.
        2. **Body and pubic lice** are treated with topical agents that contain malathion, permethrin, or a pyrethrin.
2. **Scabies**
    a. **Etiology.** Scabies is caused by the mite ***Sarcoptes scabiei***.
    b. **Clinical features.** Pruritic papules or vesicles are most commonly located on the abdomen, dorsum of the hands, groin, axilla, flexor surfaces of the wrists, and interdigital spaces. Infants may have facial and neck involvement. **Itching is severe,** and S-shaped **burrows** may be seen.
    c. **Diagnosis.** Microscopic examination of a scraping from an unscratched burrow demonstrating the mite, eggs, or mite feces is diagnostic.
    d. **Management.** Treatment includes an overnight application of 5% permethrin lotion or 1% lindane (adolescents and adults only). Scabies is highly contagious, and therefore, all household contacts should be treated. Treatment should be repeated 7–10 days after the first application of the antiscabetic to catch the newly hatched mites. Itching may persist for up to 30 days after treatment. All bed sheets, pillowcases, and clothing should be washed in hot water.

Table 19-2
Complications of Varicella Infection

Bacterial superinfection (often *Staphylococcus aureus*)
Necrotizing fasciitis (often Group A *Streptococcus*)
Scarring
Reye syndrome (associated with simultaneous ingestion of salicylates/aspirin)
Pneumonia
Encephalitis
Acute cerebellar ataxia
Hepatitis
Herpes zoster (reactivation of virus)
Infection during pregnancy:
Teratogenic effects ("congenital varicella syndrome" due to maternal infection during the first 20 weeks of gestation: zigzag scarring of the skin, shortened or malformed extremities, central nervous system damage, and eye abnormalities such as cataracts or chorioretinitis)
"Neonatal varicella" is severe varicella infection in a neonate due to peripartum maternal infection within 1 week of delivery or postnatal exposure. May be fatal.

VI. Pigmentary Disorders

A. **Hypopigmentation.** Causes include the following:
   1. **Postinflammatory hypopigmentation** may follow any skin inflammation (e.g., atopic dermatitis) and generally resolves over months to years.
   2. **Pityriasis alba** is thought to be related to atopic dermatitis. It is characterized by hypopigmented, dry, scaly patches, most commonly on the cheeks. Treatment includes moisturizers, sun protection, and low-potency topical corticosteroids or immunomodulators.
   3. **Vitiligo** is a **complete loss of skin pigment** in patchy areas that is caused by autoimmune melanocyte destruction. Treatment with high-potency topical steroids, topical immunomodulators, and/or ultraviolet light may sometimes produce repigmentation.
   4. **Oculocutaneous albinism** is caused by a genetic defect in melanin synthesis. Clinical features include white skin and hair, blue eyes, and other eye findings, such as photophobia and nystagmus. There is no treatment.

B. **Neurocutaneous disorders.** Table 19-3 summarizes the clinical features of **tuberous sclerosis and neurofibromatosis**.

C. **Nevocellular nevi** are pigmented lesions that may be congenital or acquired.
   1. **Congenital nevi.** These black, brown, tan, or flesh-colored papules or plaques are first detected between birth and 6 months of age. They occur in 1–2% of neonates. **All congenital nevi may have an increased risk of malignancy,** but **giant nevi** (>20 cm in diameter) have a 6–7% lifetime risk of development of malignant melanoma. Management of giant nevi often includes excision, if possible, or careful observation.
   2. **Acquired nevi** (moles). Peak ages of development are 2–3 years and 11–18 years of age. Moles are characterized as well-demarcated brown or black papules that increase in size and number during puberty or pregnancy and following sun exposure. Most acquired nevi in childhood are **junctional nevi.** The risk of malignant transformation is much lower for acquired than that for congenital nevi. Management is careful observation.

Table 19-3
Clinical Features of Two Neurocutaneous Syndromes

	Tuberous Sclerosis	**Neurofibromatosis Type 1 (NF-1)***
Inheritance	Autosomal dominant	Autosomal dominant
Skin findings	**Ash-leaf spots** (hypopigmented macules seen best under Woods light)	**Café-au-lait spots (Figure 19-1)**
	Axillary or inguinal freckling	
	Angiofibromas on nose or face (**adenoma sebaceum**)	Plexiform neurofibroma or skin **neurofibromas** (soft flesh-colored nodules)
Shagreen patch (thickened orange peel appearance)		
	Ungual fibromas	
CNS findings	Seizures (95%), including **infantile spasms**Intracranial calcifications Cortical or subependymal *tubers*	Optic glioma (usually present by 3 years of age)Intracranial calcifications CNS neurofibromas
Systemic findings	Renal cysts	**Lisch nodules** (iris hamartoma)
Cardiac rhabdomyomas (**leading cause of neonatal cardiac tumors**)	Osseous lesions (present by 1 year of age): sphenoid dysplasia or thinning of long bone cortex	
Retinal astrocytoma or hamartoma	Scoliosis	
Mental retardation	Hypertension	
	Learning problems	

*Neurofibromatosis type 2 accounts for 10% of all cases of neurofibromatosis and is characterized by bilateral acoustic neuromas. Skin findings of café-au-lait spots and neurofibromas are less common findings as compared with neurofibromatosis type 1.

CNS = central nervous system.

Note: *Diagnosis of neurofibromatosis type 1 requires two of the following seven clinical findings:* six or more café-au-lait spots (≥5 mm in children or 15 mm in adults); two or more neurofibromas or one plexiform neurofibroma; freckling in the axilla or groin; optic glioma; two or more Lisch nodules; characteristic osseous lesion; and first-degree relative with neurofibromatosis type 1.



FIGURE 19.1 In pediatric patients with neurofibromatosis type 1, café-au-lait spots usually are larger than 55 mm in diameter, the edges are well defined, and the intensity of the coloration is uniform.

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VII. Disorders of the Hair

A. **Alopecia areata**
   1. **Etiology.** The cause is thought to be *autoimmune lymphocyte-mediated injury* to the hair follicle.
   2. **Epidemiology.** Alopecia areata affects 1 in 1000 persons.
   3. **Clinical features**
      a. **Complete hair loss** occurs as sharply demarcated areas of alopecia without inflammation or scaling. The hair loss is described as occurring suddenly, and the underlying skin is smooth and soft. The hair loss can occur on the scalp or other hair-bearing areas such as the beard, eyebrows, eyelashes, etc.
      b. Pitting of the nails occurs in 40% of patients.
      c. Subtypes of alopecia areata include **alopecia totalis** (loss of all scalp hair) and **alopecia universalis** (loss of all body and scalp hair).
   4. **Management.** Most patients have regrowth of hair within months to years without any treatment. Hair regrowth may be stimluated with the use of topical or injected corticosteroids, topical minoxidil, and topical irritants (anthralin, squaric acid). Wigs and counseling may be necessary owing to the psychological consequences of the significant hair loss.

B. **Tinea capitis** is a common cause of hair loss [see section V.A.1].

C. **Traumatic alopecia** is also a common cause of childhood hair loss and may be one of the following two types:
   1. **Trichotillomania** is hair loss that occurs as a result of **conscious or unconscious pulling or twisting of hair.** Clinical features include irregularly bordered areas of hair loss in which hairs are broken off at different lengths. The scalp may show perifollicular petechiae and excoriations. Eyelashes and eyebrows may also be involved. The cause is unknown, although it may be associated with anxiety. Management includes stress management or counseling and investigation into precipitating events.
   2. **Traction alopecia** is hair loss caused by constant traction or friction and may be the result of tight hair braids, curlers, vigorous scalp massage, or constant rubbing. Clinical features include patchy and jagged, irregularly shaped areas of alopecia especially along the hair line, with thinned, small hairs, and broken hairs. Management is to stop the inciting trauma.

D. **Telogen effluvium** is the second most common type of alopecia after male pattern baldness. It is caused by any **acutely stressful event** (e.g., pregnancy, surgery, acute illness, high fever, trauma) that converts hairs from a growing phase (**anagen**) to a final resting phase (**telogen**). Clinical features include complaints of **generalized excessive hair loss** (hair loss > 100 hairs per day compared to normal hair loss of 50–100 hairs per day) 1–3 months after the precipitating event. Hair loss continues for 3–4 months, and then spontaneous regrowth occurs.

E. **Other conditions that cause hair loss** include hypothyroidism, diabetes mellitus, hypopituitarism, nutritional disorders (e.g., hypervitaminosis A, marasmus, zinc deficiency also known as "acrodermatitis enteropathica"), medications (e.g., warfarin, heparin, chemotherapy, cyclophosphamide, isotretinoin), ectodermal dysplasias, and hair shaft structural defects.

VIII. Acne Vulgaris

Acne is the **most common skin disease,** and its sequelae may include scarring and disfigurement with resultant adverse effects on psychosocial development, such as depression and other emotional problems.

A. **Pathophysiology.** *Acne* is caused by a combination of the following processes:
   1. Excessive shedding and cohesion of cells that line the sebaceous follicles located on the chest, back, and face
   2. Increased production of **sebum** by sebaceous glands under the influence of androgens. Obstruction of sebum outflow from the follicle leads to the formation of **comedones**.
   3. **Inflammation** as a result of the proliferation of the bacteria**,** ***Propionibacterium acnes***, and the host immune response to the bacteria

B. **Clinical features**
   1. Acne usually begins 1–2 years before puberty.
   2. **Noninflammatory (comedonal) acne** is characterized by **open comedones** (blackheads) and **closed comedones** (whiteheads).
   3. **Inflammatory acne** is characterized by erythematous papules, pustules, nodules, and cysts.
   4. Most patients have a combination of comedomal and inflammatory acne.

C. **Management.** Treatment is individualized based on the disease severity and on the location and type of lesions.
   1. Benzoyl peroxide, retinoids (Retin-A) (particularly useful for comedonal acne), sulfur, and salicylic acid are effective topical agents for acne.
   2. Antibiotics (oral or topical) are used in combination with the aforementioned medications for more inflammatory acne.
   3. Oral contraceptives are helpful in treating acne in teenage girls and young adult women.
   4. **Systemic isotretinoin (Accutane)** is highly effective for all types of acne, including nodular and cystic acne. Females must be tested for pregnancy before and during treatment, and must use effective birth control during treatment to prevent pregnancy because of the risk of **teratogenic effects** associated with the use of systemic isotretinoin.

IX. Vascular Skin Lesions

A. **Nevus simplex/flammeus,** often called "stork bites," are congenital capillary malformations present in about 25–50% of newborns that are located on the midline upper face, scalp, and nuchal area. The lesions usually fade over the first 1–2 years of life.

B. **Infantile hemangiomas** are common vascular skin lesions seen in approximately 5% of infants.

   1. **Clinical features**
      a. Hemangiomas often appear shortly after birth and exhibit a growth phase lasting up to 5 months, followed by slow involution (shrinkage and loss of color) over several years.
      b. Hemangiomas can present anywhere on the skin (as well as in internal organs such as the liver) as red papules and plaques, deep blue nodules, or both.
   2. **Management.** Most hemangiomas do not require treatment, but treatment can be considered for those that are likely to cause disfigurement, as in the case of facial lesions, or obstruction of vital structures, as can be seen in the periocular location, or when they arise in the airway. Treatments may involve the use of topical and oral β-blockers to prevent growth and speed involution, or laser therapy.

C. **Port wine stains** (capillary malformations) are present at birth and do not proliferate or involute. They can present anywhere on the skin and are associated with certain syndromes when found in specific locations (e.g., Sturge–Weber Syndrome when located on the face in the distribution of the first or second branches of the trigeminal nerve). Port wine stains can be lightened with laser treatments.

D. **Pyogenic granulomas** are proliferations of capillaries on the skin, which often arise in response to some sort of trauma. They are most commonly seen during the first 5 years of life and often present as red friable glistening papules or nodules that bleed easily. Surgical removal is the treatment of choice, but laser can be used for small lesions.

Review Test

1. A 1-week-old female infant has several vesicles on her scalp. She also has a 1-day history of fever (temperature up to 38.2°C [100.8°F]) and irritability. She is breastfed and is eating slightly less vigorously than usual. The mother's pregnancy was uncomplicated. Which of the following statements regarding the presumptive diagnosis is correct?
   A. Herpes simplex virus type 1 is the most likely causative pathogen.
   B. The infection was likely acquired after birth.
   C. A Tzanck smear of the base of one of the vesicles may demonstrate epidermal giant cells.
   D. Oral acyclovir should be started immediately.
   E. Oral antibiotics to cover staphylococcal and streptococcal infection should be started promptly.
2. A 9-year-old girl is brought to the office by her parents. She has a 1-month history of two large well-demarcated areas of hair loss in the parietal scalp. On examination, no inflammation or scaling of the skin is apparent, and the underlying skin is smooth and soft. Which of the following statements regarding the likely diagnosis is correct?
   A. The fingernails are likely to be normal.
   B. Autoimmune destruction of the hair follicle is likely the cause of this disorder.
   C. Oral griseofulvin should be prescribed after cultures.
   D. The child and her parents should be counseled to loosen her braids and ponytails when styling her hair.
   E. The hair loss is likely to be permanent.
3. A 6-year-old boy presents with a 1-month history of patchy alopecia in the occipital region of the scalp. Examination reveals a well-circumscribed area of hair loss in which all the hairs appear to be broken off at the scalp surface. Occipital lymph nodes are prominent. Which of the following statements regarding the likely diagnosis is correct?
   A. This infection is contagious, and brushes, combs, and hats should not be shared.
   B. Topical management with clotrimazole is the initial appropriate treatment.
   C. Exposure to dogs or cats is the most likely cause of infection.
   D. Hairs are likely to fluoresce under Woods light examination.
   E. Oral antifungal therapy should be administered for 2 weeks.
4. A 5-year-old boy presents with a 6-week history of scaling, nongreasy erythematous plaques in the occipital region of the scalp and in the inguinal region. The lesions have a "silvery scale" appearance. Which of the following statements regarding the likely disorder is correct?
   A. Low-potency corticosteroids are likely to be effective in treating this condition.
   B. It would be unusual for other family members to also have this disorder.
   C. New lesions may develop at any site of skin trauma.
   D. Nail changes would not be expected with this condition.
   E. Arthritis is likely to occur in this patient.
5. A 10-year-old girl presents with a history of malaise and a headache that was followed 4 days later with a body rash. Examination reveals a 3-cm scaly erythematous plaque on the upper arm and oval, red macules and papules on the back that follow skin lines. Which of the following management steps is the least appropriate?
   A. Therapy with topical corticosteroids for pruritus
   B. Natural ultraviolet exposure
   C. Topical clotrimazole
   D. Oral antibiotics
   E. Reassurance only
6. A 4-month-old male infant is brought to the office by his parents for a routine health

maintenance examination. On examination, you note significant hypopigmentation in the inguinal area. Medical history is remarkable for suspected diaper dermatitis treated with zinc oxide and high-potency corticosteroids for 3 weeks. Which of the following statements regarding this patient and his clinical findings is most correct?

A. Topical antifungal therapy should now be prescribed to treat suspected fungal superinfection.
B. Zinc oxide should be immediately discontinued.
C. Atrophy of skin in the inguinal area may also be present.
D. The child should be referred to genetics to consider the diagnosis of tuberous sclerosis.
E. Ultraviolet light therapy should be prescribed.

7. A 4-year-old boy with a history of atopic dermatitis presents for evaluation of his skin. Examination shows that the skin on his upper and lower extremities is very dry and irritated. You would like to suggest a moisturizer in addition to topical corticosteroids. Which of the following types of moisturizers is most appropriate?

A. Lotion
B. Cream
C. Ointment
D. Solution
E. Gel

8. A 13-year-old boy is brought to the office by his parents because of concerns regarding his acne. Examination reveals scattered open and closed comedones on the forehead and nose. Which of the following statements regarding this condition is correct?

A. Topical benzoyl peroxide is an appropriate first-line treatment.
B. Oral isotretinoin is an appropriate first-line treatment.
C. Oral clindamycin is an appropriate first-line treatment.
D. Sebum plays little role in the pathophysiology at this stage of acne.
E. Reassurance only should be given because the patient's skin findings are currently of little consequence.

For statements 9–13, the response options are the same. You will be required to select one answer for each statement in the following set.

A. Papule
B. Macule
C. Pustule
D. Nodule
E. Vesicle
F. Cyst
G. Wheal
H. Target lesion
I. Plaque

Match the disorder with its most characteristic skin lesion.

1. A 3-year-old boy with herpes simplex virus infection involving the upper and lower lips.
2. A 7-year-old boy with suspected vitiligo involving both hands.
3. A 15-month-old girl with molluscum contagiosum on the cheeks and forehead.
4. A 6-year-old boy with erythema multiforme major.
5. A 10-year-old girl with suspected Gianotti–Crosti syndrome.

For statements 14 and 15, the response options are the same. You will be required to select one

answer for each statement in the following set.

A. Neurofibromatosis type 1
B. Neurofibromatosis type 2
C. Tuberous sclerosis

For each patient, select the most likely associated neurocutaneous syndrome.

1. A 3-year-old boy with seizures and Lisch nodules on ophthalmologic examination.
2. A 12-month-old infant with infantile spasms.

Answers and Explanations

1. **The answer is C** [V.C.7.c–d]. This patient's clinical presentation is most consistent with neonatal herpes simplex virus (HSV) infection. Diagnosis is by identification of (1) the virus by culture or (2) the viral antigen by rapid testing techniques. Infection may also be diagnosed by identification of epidermal giant cells on a Tzanck preparation. Two-thirds of HSV infections acquired during the neonatal period are caused by HSV-2, and this infection is most often acquired during passage through the birth canal of a mother infected with the virus. Neonatal HSV infection is a medical emergency that requires prompt admission and management with intravenous acyclovir. Oral antibiotics are not useful.
2. **The answer is B** [VII.A]. This patient's presentation with well-demarcated hair loss with-out scalp inflammation is likely caused by alopecia areata. The cause of alopecia areata is thought to be an autoimmune lymphocyte-mediated injury to the hair follicle. Associated findings include nail pitting in 40% of patients. The clinical presentation is not consistent with tinea capitis, which would present with localized areas of hair loss associated with scalp inflammation, scaling, and broken hairs. Thus, griseofulvin is not indicated in this case. This presentation is also not consistent with traction alopecia due to hair care or styling practices, which is characterized by patchy and jagged, irregularly shaped areas of alopecia, especially along the hair line, containing small, thin, and broken hairs. In the case of alopecia areata, regrowth of hair within months to years occurs in the majority of patients.
3. **The answer is A** [V.A.1]. Clinical features of alopecia with hairs broken off at the scalp and occipital lymphadenopathy suggest tinea capitis, a fungal infection of the hair. The most common causal pathogen is *Trichophyton tonsurans,* acquired from human-to-human contact, including by sharing hats, brushes, and combs. Topical antifungal therapy is not effective for tinea capitis. Dogs and cats are a source of infection with *Microsporum canis*, which currently causes only 5% of tinea capitis infections. Infection with *M. canis* is characterized by thickened, white broken hairs, and only hairs infected with *M. canis* fluoresce under Woods light, whereas hairs infected with *Trichophyton tonsurans* do not fluoresce. Treatment of tinea capitis involves 6–8 weeks of oral antifungal therapy.
4. **The answer is C** [III.E.3]. Skin lesions with a silvery scale appearance suggest psoriasis. Lesions of psoriasis may also demonstrate the Koebner phenomenon, in which new lesions develop at sites of skin injury. Corticosteroids of moderate to high potency are the most effective treatment agents. Psoriasis is inherited in an autosomal dominant fashion, and therefore, other family members may also have the disorder. Nail involvement is often seen in individuals with psoriasis. Psoriatic arthritis is uncommon during childhood.
5. **The answer is C** [III.D.3–4]. This patient's clinical presentation and examination findings are consistent with pityriasis rosea. Pityriasis rosea may be an immune response to a viral infection, although its true cause is unknown. Pityriasis rosea resolves without medications, although antihistamines and topical corticosteroids may relieve any associated itching. Exposure to ultraviolet light and short courses of oral antibiotics (for anti-inflammatory properties) may shorten the disease course. Clotrimazole is not an appropriate therapy for pityriasis rosea.
6. **The answer is C** [I.D.6.a]. The hypopigmentation in the inguinal region is most likely a side effect of the high-potency corticosteroid therapy. Only low-potency corticosteroids should be applied to the groin because the epidermis of the groin is very thin and absorption of corticosteroids is higher in this area. Local side effects of high-potency topical steroids include pigmentation changes, skin atrophy, acne, folliculitis, and telangiectasias. Neither antifungal medications nor ultraviolet light is indicated. Discontinuation of zinc oxide will not affect this patient's skin findings. Although tuberous sclerosis is associated with

hypopigmented skin lesions, the history in this case is more suggestive of localized topical steroid use as the cause of the hypopigmentation. In the case of suspected tuberous sclerosis, the individual should have more than one hypopigmented skin lesion, a history of seizures or infantile spasms, and/or a family history of the disorder.

7. **The answer is C** [I.D.2]. Adequate hydration of the skin is crucial in many dermatologic conditions, especially atopic dermatitis. Ointments are especially useful for very dry skin because they have maximal water-retaining properties and would be the best choice for this patient. Lotions are helpful for minimal dryness, and creams are useful for average dryness. Both solutions and gels are most useful for hair-bearing surfaces.
8. **The answer is A** [VIII.C]. This patient's skin findings are consistent with acne. The open and closed comedones are characteristic of noninflammatory acne, and a topical agent is most appropriate. Benzoyl peroxide is very effective for both noninflammatory and inflammatory acne and is an appropriate initial treatment for this patient. Neither oral antibiotics nor isotretinoin is a first-line treatment for noninflammatory acne. Oral antibiotics are most useful in inflammatory acne. Systemic isotretinoin is helpful in all types of acne; however, it is indicated for severe cystic or nodular acne. Obstruction to sebum outflow from the follicle leads to comedone development and therefore is important in the pathophysiology. Acne should never be dismissed as of no consequence, even in the early stages, because it may be associated with future scarring and may have effects on a child's psychosocial development.
9. **The answers are E, B, A, H, and A, respectively** [V.C.7.b, VI.A.3, V.C.10.b.(1), IV.C.2, V.C.5, and Table 19-1]. Herpes simplex virus is characterized by grouped vesicles on an erythematous base. Vitiligo is a depigmentation disorder characterized by hypopigmented macules. Molluscum contagiosum is characterized by flesh-colored papules with central umbilication. Erythema multiforme major is characterized by target lesions. Erythematous or flesh-colored papules are characteristic of Gianotti–Crosti syndrome.
10. **The answers are A and C, respectively** [Table 19-3]. The 3-year-old boy has neurofibromatosis type 1, which is characterized by café-au-lait spots, axillary freckling, and neurofibromas in the skin and other organs. Seizures may occur because of central nervous system involvement that may include intracranial calcifications, neurofibromas, and optic glioma. Characteristic eye findings include Lisch nodules or iris hamartomas. The 12-month-old infant has tuberous sclerosis, which is associated with characteristic skin findings including ash-leaf spots, angiofibromas, and shagreen patch. Almost all children with tuberous sclerosis have seizures because of central nervous system involvement, and the condition is frequently associated with infantile spasms.

CHAPTER 20

Emergency Medicine

Calvin G. Lowe

I. Infant and Child Cardiopulmonary Resuscitation (CPR)

A. **General concepts**
   1. The **most common cause of cardiac arrest in a child** is a **lack of oxygen supply** to the heart secondary to a **pulmonary problem** (e.g., choking, suffocation, airway or lung disease, drowning), respiratory arrest, or shock. Cardiac arrest can often be prevented if assisted breathing is initiated promptly.
   2. **Heart disease is an uncommon cause of cardiac arrest** in infants and children.
   3. **Chances for survival increase dramatically** if CPR and advanced life support are begun quickly.
   4. **If a patient is found unresponsive and not breathing, then CPR should be initiated.**

B. **Sequence of CPR is C–A–B: Circulation–Airway–Breathing.** In 2010 (and subsequently - reaffirmed), the American Heart Association recommended that CPR for infants and children be initiated with chest compressions rather than rescue breaths (C–A–B rather than A–B–C). When approaching an unresponsive victim, the rescuer should shout for nearby help and activate the emergency response system. The rescuer should look for breathing or gasping and simultaneously check for a pulse.
   1. **Circulation**
      a. **Chest compressions are administered for asystole or bradycardia.**
      b. **Rescuers should compress the chest at least one-third of the anterior–posterior diameter of the chest.**
         1. **1½ inches in most infants**
         2. **2 inches (5 cm) in most children**
      c. **Chest compressions are delivered at a rate of 100/minute.**
   2. **Airway**
      a. **After the first set of compressions are given, the vicitim's airway is opened.**
      b. **The victim's tongue is the most common cause of airway obstruction.**
      c. **The airway may be opened by the head tilt method, which lifts the tongue from the back of the throat, or by the jaw-thrust method if the child has suspected neck or cervical spine injury. (Cervical spine injury should be suspected in face, head, or neck trauma.)**
   3. **Breathing**
      a. **After the airway is opened,** assessment for breathing is performed by the **look, listen, and feel method,** in which the rescuer **looks** for a rise and fall in the chest, **listens** for exhaled air, and **feels** for exhaled airflow.
      b. **Rescue breathing** must be performed if spontaneous breathing is absent.

C. **CPR cycles**
   1. **Ratio of chest compressions for one-rescuer CPR is 30 compressions:2 breaths.**
   2. **Ratio of compressions of two-rescuer CPR is 15 compressions:2 breaths.**
   3. **After 2 minutes of compressions/breaths or five cycles, a reassessment of the patient for a pulse or spontaneous respirations should be performed.**

II. Shock

A. **General concepts**
   1. **Definition.** Shock is a clinical state characterized by **inadequate delivery of oxygen and metabolic substrates to meet the metabolic demands of tissues**.
   2. *Shock may be present with normal or decreased blood pressure.*

B. **Classification.** Shock may be classified by the degree of compensation and by the cause.
   1. **Shock classification** by the degree of compensation includes **compensated, decompensated, or irreversible**.
      a. **Compensated shock** is characterized by **normal blood pressure** and cardiac output with **adequate tissue perfusion** but **maldistributed blood flow** to essential organs.
      b. **Decompensated shock** is characterized by **hypotension,** low cardiac output, and **inadequate tissue perfusion**.
      c. **Irreversible shock** is characterized by **cell death** and is **refractory** to medical treatment.
   2. **Shock** may also be classified on the basis of the **cause**.
      a. **Hypovolemic shock** is the **most common cause** of shock in children and is caused by any condition that results in decreased circulating blood volume, such as **hemorrhage** or **dehydration** (e.g., from acute gastroenteritis). The amount of volume loss determines the success of compensatory mechanisms, such as **endogenous catecholamines,** in maintaining blood pressure and cardiac output. Volume losses greater than 25% result in decompensated shock.
      b. **Septic shock** occurs secondary to an inflammatory response to invading microorganisms and their toxins, and it results in abnormal blood distribution. There are two clinical stages:
         1. **Hyperdynamic stage** is characterized by normal or high cardiac output with **bounding pulses,** warm extremities, and a wide pulse pressure.
         2. **Decompensated stage** follows the hyperdynamic stage if aggressive treatment has not been initiated. It is characterized clinically by impaired mental status, cool extremities, and diminished pulses.
      c. **Distributive shock** is associated with distal pooling of blood or fluid extravasation, and it is typically caused by anaphylactic or neurogenic shock or as a result of medications or toxins.
         1. **Anaphylactic shock** is characterized by acute angioedema of the upper airway, bronchospasm, pulmonary edema, urticaria, and hypotension because of extravasation of intravascular fluid from permeable capillaries (see Chapter 15, section I).
         2. **Neurogenic shock,** typically secondary to spinal cord transection or injury, is characterized by a total loss of distal sympathetic cardiovascular tone, with hypotension resulting from pooling of blood within the vascular bed.
      d. **Cardiogenic shock** occurs when cardiac output is limited because of primary cardiac dysfunction. Causes include dysrhythmias (e.g., supraventricular tachycardia), congenital heart disease (e.g., any lesion that impairs left ventricular outflow), and cardiac dysfunction after cardiac surgery. Clinical features are the signs and symptoms of congestive heart failure (CHF; see Chapter 8, section I.D).

C. **Diagnosis**
   1. *Recognition of shock may be difficult because of the presence of compensatory mechanisms that prevent hypotension until 25% of intravascular volume is lost. Therefore, the index of suspicion for shock must be high.*

2. **Historic features** that may suggest the presence of shock include the following:
    a. **Severe vomiting and diarrhea**
    b. **Trauma with hemorrhage**
    c. **Febrile illness,** especially in an immunocompromised patient
    d. **Exposure to a known allergic antigen**
    e. **Spinal cord injury**
3. **Physical examination**
    a. **Blood pressure may be normal** in the initial stages of hypovolemic and septic shock.
    b. **Tachycardia almost always accompanies shock** and occurs before blood pressure changes in children.
    c. **Tachypnea** may be present as a compensatory mechanism for severe metabolic acidosis.
    d. **Mental status changes** may indicate poor cerebral perfusion.
    e. **Capillary refill** may be prolonged with cool and mottled extremities.
    f. **Peripheral pulses** may be **bounding** in early septic shock.
4. **Laboratory studies** should include the following:
    a. **Complete blood count (CBC)** to assess for blood loss and infection
    b. **Electrolytes** to assess for metabolic acidosis and electrolyte abnormalities
    c. **Blood urea nitrogen and creatinine** to evaluate renal perfusion and function
    d. **Lactate** to assess adequacy of tissue perfusion
    e. **Calcium and glucose** to assess for frequently encountered metabolic derangements
    f. **Coagulation factors** to evaluate for disseminated intravascular coagulation (DIC), which may accompany shock
    g. **Toxicology screens** to evaluate for a poisoning, which could cause shock
    h. **Blood and urine cultures** to evaluate for infections that could cause shock

D. **Management**
1. **Initial resuscitation** includes:
    a. **Supplemental oxygen**
    b. **Early endotracheal intubation** to secure the airway and decrease the patient's energy expenditure
    c. **Vascular access** with appropriate **fluid resuscitation**. Fluids should initially include a 20 mL/kg bolus of normal saline or lactated Ringer solution.
2. **To restore intravascular volume, intravenous crystalloid or colloid** solutions should generally be used before administration of inotropic and vasopressor agents.
3. **Inotropic and vasopressor medications** (e.g., dobutamine, dopamine, epinephrine) are indicated if the blood pressure increase in response to fluids is inadequate.
4. **Metabolic derangements,** such as metabolic acidosis, hypocalcemia, or hypoglycemia, should be treated.
5. **Other considerations** include administration of **broad-spectrum antibiotics** for septic shock, **blood products** for hemorrhage, and **fresh-frozen plasma** for DIC.

III. Trauma

A. **General concepts**
   1. **Trauma is the leading cause of death** in the United States in children older than 1 year.
   2. **Motor vehicle accidents are the leading cause of trauma.**
   3. **Anatomic and physiologic differences** between a child and an adult account for the child's unique response to trauma.
      a. **Head injuries** are **common** because a child's head comprises a **larger percentage of total body mass**.
      b. The **neck** of a child is **shorter** and supports a relatively **greater weight**.
      c. The **rib cage** of a child is more pliable, leading to greater energy transmitted to internal organs, such as the **spleen** and **liver**.
      d. The **growth plates** in the bones of a growing child result in a relatively **weak epiphyseal–metaphyseal junction**. Ligaments are stronger than the growth plate; therefore, with injury, the **growth plate is at the highest risk** for fracture.

B. **Primary survey.** This rapid initial assessment of the patient should be performed within 5–10 minutes of arrival in the emergency department. The primary survey can be recalled using the mnemonic **ABCDE: Airway** maintenance, **Breathing** and ventilation with 100% oxygen, **Circulation** and control of hemorrhage, **Disability** assessment using the **Glasgow coma score (GCS**, which is used to assess the extent of neurologic impairment based on physical examination (Table 20-1), and **Exposure/Environmental** control, in which the patient is undressed completely to facilitate examination and then warmed to prevent hypothermia.

C. **Adjuncts to the primary survey**
   1. **Electrocardiographic (ECG) monitoring** is mandatory for all patients.
      a. **Dysrhythmias** may indicate cardiac injury.
      b. **Pulseless electrical activity** may indicate cardiac tamponade, tension pneumothorax, or profound hypovolemia.
   2. A **urinary catheter** should be placed to monitor urine output, and a **nasogastric tube** to reduce abdominal distension.
   3. **Diagnostic** studies typically include **radiographs of the cervical spine, chest, and pelvis, and computed tomographic (CT) scans of the head and abdomen.**

D. **Secondary survey.** This head-to-toe evaluation includes a thorough physical examination.

E. **Specific injuries** in the pediatric trauma patient
   1. **Head trauma**
      a. **Seizures** are **common** after head trauma but are **self-limited**.
      b. **Infants** are at risk for bleeding in the **subgaleal** and **epidural spaces** because of **open fontanelles and cranial sutures**. However, these open structures may also allow infants to be more tolerant of expanding intracranial masses.
      c. **Intracranial bleeding** may occur in the epidural space, subdural space, or within the brain parenchyma itself after even mild head trauma without skull fracture or loss of consciousness.
         1. **Epidural hematoma** is bleeding between the inner table of the skull and the dura. It is associated with *tearing of the middle meningeal artery* typically following a high-risk injury (direct blow to the side or back of the head, or fall from a significant height).
            a. **Clinical features** are the signs and symptoms of increased intracranial pressure (ICP; see Table 20-2 and section III.E.1.d). A classic history could include an initial loss of consciousness, a **lucid interval for several hours, followed by abrupt decompensation and coma**.

b. **Diagnosis** is by **head CT,** which shows a **lenticular density** representing blood within the epidural space.
c. **Management** is immediate surgical drainage.
d. **Prognosis** is generally good if surgery can be performed rapidly.

2. **Subdural hematoma** is blood beneath the dura. It is associated with *tearing of the bridging meningeal veins* by direct trauma or shaking. It is **more common than epidural hematoma** and is seen most commonly in infancy.
   a. **Clinical features** include seizures and signs and symptoms of increased ICP (see Table 20-2 and section III.E.1.d). Subdural hematomas are bilateral in 75% of cases, and symptoms develop more slowly than with an epidural bleed.
   b. **Diagnosis** is by **head CT,** which shows a **crescentic density** representing blood in the subdural space.
   c. **Management** includes neurosurgical consultation and usually surgical drainage.
   d. **Prognosis** is variable and may be poor if the underlying brain is also injured.
3. **Intracerebral hematoma** is bleeding within the brain parenchyma. Frontal and temporal lobes are most often affected, usually on the opposite side of the impact injury **(contrecoup injury)**. Management is surgical drainage if the hematoma is accessible.

d. **Increased ICP**
1. **Clinical features**
   a. **Headache** is the **first symptom**.
   b. **Pupillary changes** and **altered mental status** are the **first signs**.
   c. **Table 20-2** lists the clinical features of increased ICP.
2. **Complications. Increased ICP** may lead to cerebral herniation, most commonly **transtentorial or uncal herniation,** in which the temporal lobe or uncus is displaced into the infratentorial compartment. Clinical features of herniation include the following:
   a. **Bradycardia,** which is an **early sign of herniation in children younger than 4 years**
   b. **Fixed and dilated ipsilateral pupil**
   c. **Contralateral hemiparesis**
   d. **Pupils will eventually become bilaterally fixed and dilated.**
   e. **Bilateral hemiparesis** will also eventually occur.
   f. **Cushing triad, a late sign,** is characterized by **bradycardia, hypertension,** and **irregular breathing**.
3. **Management.** The goal of treatment is to prevent secondary brain injury and includes the following:
   a. **Mild hyperventilation** with **100% oxygen** to lower $PaCO_2$ to 30–35 mm Hg, which in turn mildly vasoconstricts cerebral vessels. Aggressive hyperventilation can lead to worsening cerebral ischemia.
   b. **Elevation** of the head to 30°–45°, which encourages venous drainage
   c. **Diuretics** (e.g., mannitol, 3% hypertonic normal saline)
   d. Neurosurgical consultation

2. **Spinal cord injury.** Injury to the spinal cord may occur in children. Even in the presence of serious injury, radiographs of the cord may be normal. Note that **spinal cord injury without radiographic abnormality ("SCIWORA")** occurs more commonly in children than in adults.

3. **Chest trauma**
    a. A child's **soft and pliable chest wall** allows transmission of forces to the lung parenchyma.
    b. **Tension pneumothorax** may occur and is **life-threatening**.
        1. **Clinical features** include **distended neck veins, decreased breath sounds,** hyperresonance to percussion, **displaced trachea,** pulseless electrical activity, and shock.
        2. **Management** is emergent chest decompression by needle thoracotomy. **Waiting for radiographic confirmation of the diagnosis can lead to a patient's death**.
4. **Abdominal trauma** is common because of underdeveloped abdominal musculature.
    a. **Duodenal hematoma** often occurs secondary to injury to the right upper quadrant, commonly from a **bicycle handle bar**. Clinical features include abdominal pain and vomiting. Bowel obstruction is found on radiographic evaluation.
    b. **Lap belt injuries** from a motor vehicle accident include a **chance fracture** (flexion disruption of the lumbar spine), liver and spleen lacerations, and bowel perforation.
    c. **Spleen, liver, and kidneys** are often injured by blunt trauma.

TABLE 20-1
Glasgow Coma Scale (GCS)*

Verbal Patient	GCS Score	Nonverbal Patient (Child)
	Eye opening	
Spontaneously	4	Spontaneously
Response to voice	3	Response to voice
Response to pain	2	Response to pain
No response	1	No response
Best motor response		
Obeys commands	6	Normal movements
Localizes pain	5	Localizes pain
Flexion withdrawal	4	Flexion withdrawal
Decorticate posturing	3	Flexion abnormal
Decerebrate posturing	2	Extension abnormal
No response	1	No response
Best verbal response		
Oriented/appropriate	5	Cries normally, smiles, and coos
Disoriented conversation	4	Cries
Inappropriate words	3	Inappropriate crying and screaming
Incomprehensible words	2	Grunts
No response	1	No response

*This scale is used to assess the level of neurologic impairment on the basis of a patient's physical examination (eye opening, motor response, and verbal response). A GCS of 13–15 indicates mild head injury; a GCS of 9–12 indicates moderate head injury; and a GCS < 8 indicates severe head injury.

Table 20-2
Symptoms and Signs of Elevated Intracranial Pressure

Symptom	Sign
Headache	Papilledema
Vomiting	Cranial nerve palsies
Stiff neck	Stiff neck
Double vision	Head tilt
Transient loss of vision	Retinal hemorrhage
Episodic severe headache	Percussion of skull—"cracked pot sound"
Gait disturbance	Obtundation
Dulled intellect	Unconsciousness
Irritability	Progressive hemiparesis

IV. Burns

A. **Epidemiology.** *More than 40% of deaths from burns occur in children younger than 4 years.*
   1. **Scalding injuries** from hot liquids are the **most common type of burn**.
   2. **Not all burns are accidental, and child abuse should be considered** (see section VI.B.2.c).

B. **Classification** of burns is on the basis of **degree** (depth of skin injured) and **body surface area** (BSA).
   1. **First-degree burns** involve only the **epidermis** and are characterized by **red, blanching, painful skin** that heals without scarring (e.g., sunburn).
   2. **Second-degree burns** (partial-thickness burns) involve the **entire epidermis and part of the dermis.**
      a. **Superficial partial-thickness burns** involve the entire epidermis and outer portion of the dermis. Burns are moist, painful, and red. They **blister** but usually do not scar.
      b. **Deep partial-thickness burns** involve destruction of the entire epidermis and lower portion of the dermis. Burns are **pale white**. They may **blister** and they heal **with scarring**.
   3. **Third-degree burns or full-thickness burns** involve the **complete destruction of the epidermis, dermis, and part of the subcutaneous tissue.** Burns are **dry, white, and leathery** to the touch, and skin grafts are needed. Because nerve endings are burned, the victim is usually **insensitive to pain**.
   4. **BSA** burned is expressed in percentage. The Lund–Browder classification may be used to help measure the burned area. Although the *"rule of 9's"* is used to measure percent BSA burned in adolescents and adults (each arm = 9%, each leg = 18%, anterior trunk = 18%, posterior trunk = 18%, head and neck = 9%), this rule overestimates burns in a child because of a child's relatively larger head and smaller legs. Another estimate of percent BSA burned used in children uses the size of the patient's palm to measure the burned area; the palm is approximately equivalent to 1% BSA. First-degree burns are not included in the calculation of the BSA burned.

C. **Management**
   1. **Initial resuscitation** should include the **ABCs**.
      a. **Endotracheal intubation** should be performed in any victim suspected of **inhaling** hot gases, which may burn the upper airway and lead to progressive edema and airway obstruction.
      b. **Assess oxygenation** by pulse oximetry. Administer 100% oxygen and assess for carbon monoxide inhalation (see section VIII.D.6).
      c. **Intravenous access** should be obtained through nonburned skin.
   2. **Fluid resuscitation** is **critical,** because large volumes of fluid may be lost from burned skin and leaky capillaries.
      a. Lactated Ringer solution is the isotonic crystalloid fluid of choice in burn resuscitation.
      b. The Parkland formula calculates the volume of fluid replacement within the first 24 hours.
         1. The replacement volume is approximately 4 mL/kg body weight per percent BSA burn.
         2. Half of the replacement volume is given over the first 8 hours postburn, and the remaining half over the next 16 hours.
   3. **Skin care** depends on the degree of burn.

a. **First-degree burns** require only moisturizers and analgesics.
b. **Second-degree burns** require appropriate analgesics (e.g., opiates) and debridement of dead skin to prevent infection. Bullae (large blisters), if intact, are generally not removed because the skin of the bullae forms a barrier to infection and prevents fluid loss. Bullae that have ruptured should be removed.
c. **Third-degree burns** require skin grafting and hydrotherapy. **Escharotomy** (i.e., surgical removal of a constricting scar) may be needed if the burn restricts blood flow or chest expansion.
d. **Antibiotics,** usually topical 1% silver sulfadiazine, are applied to second- and third-degree burns to decrease the risk of infection.

4. **Hospitalization** is required for partial-thickness burns >10% BSA, full-thickness burns >2% BSA, burns to specific areas of the body (e.g., face, perineum, hands, feet, burns overlying a joint, or circumferential burns), suspected inhalation injury, and suspected nonaccidental trauma (i.e., inflicted burn).

V. Drowning

A. **Definition.** Drowning is the process of experiencing respiratory impairment from submersion/immersion of liquid.
   1. **Nonfatal drowning** refers to a person who is rescued at any time, and the process of drowning is interrupted.
   2. **Fatal drowning** refers to a person who dies any time as a result of drowning.
   3. Terms such as "**near drowning," "dry or wet drowning," "secondary drowning," or "active and passive drowning"** are no longer used.

B. **Epidemiology.** *Submersion-related injuries* are the *leading cause of death among children ages 1–4 years* in the United States. There is a bimodal age distribution in childhood.
   1. **Older infants and toddlers,** who may wander into unfenced pools or tip over into water containers (e.g., toilets and buckets)
   2. **Adolescents,** most commonly males, whose submersion injury is typically associated with alcohol or drug ingestion

C. **Pathophysiology**
   1. **Victims** may suffer asphyxia from aspirating liquid or from laryngospasm.
   2. **Both fresh and salt water drowning** result in denaturing of surfactant, alveolar instability and collapse, and pulmonary edema.
   3. The end result is decreased pulmonary compliance, increased airway resistance, increased pulmonary artery pressures, and impaired gas exchange.

D. **Clinical features**
   1. **Respirations** may be absent or irregular, and the victim may cough up **pink, frothy material**.
      a. **Physical examination** may reveal rales, rhonchi, and wheezes.
      b. **Pneumonia** from **aspiration of fluid containing mouth flora** may develop **after 24 hours**.
      c. **Slow deterioration** of pulmonary function (e.g., hypoxemia and hypercarbia) may occur during the first 12–24 hours.
   2. **Neurologic** insult (hypoxic central nervous system [CNS] injury) is directly related to the length and severity of the hypoxia. The victim may appear alert initially or may be agitated, combative, or comatose.
   3. **Cardiovascular** abnormalities include dysrhythmias and myocardial ischemia.
   4. **Hematologic** abnormalities include hemolysis and DIC.
   5. **Renal failure** may occur.

E. **Management.** Treatment is the **same regardless of whether the drowning occurred in salt or fresh water**.
   1. **Initial resuscitation** includes the **ABCs,** cervical spine immobilization (because of the possibility of coexistent head trauma), and removal of wet clothing to reduce heat loss.
   2. **Intubation and mechanical ventilation** with high positive end-expiratory pressures (PEEPs) are indicated for patients with respiratory failure.
   3. **Rewarming** of body core with warm saline gastric lavage, bladder washings, or peritoneal lavage should be performed if needed. In severely hypothermic patients, resuscitation should continue until the patient is rewarmed to 32°C (89.6°F).
   4. **Attention** should be paid to fluid and electrolyte imbalance.

F. **Prognosis.** In general, children have a better outcome from drowning because their primitive dive reflex shunts blood to vital organs, such as the heart, brain, and liver. However, prognosis is poor for the following victims:
   1. **Children younger than 3 years**

2. **Submersion time > 5 minutes**
3. **Resuscitation delay > 10 minutes**
4. **CPR required**
5. **Abnormal neurologic examination or seizures**
6. **Arterial blood pH < 7**

VI. Child Abuse

A. **General concepts**
   1. In most states, health care personnel have a **legal obligation to report suspected child abuse or neglect** to appropriate protective service or law enforcement agencies.
   2. The **index for suspicion of abuse should be high,** especially in situations in which injuries found on examination are unaccounted for or are inconsistent with the caregiver's history or the child's developmental abilities.
   3. Child abuse includes **physical abuse, psychological abuse, neglect, and sexual assault**.

B. **Physical abuse**
   1. **Epidemiology**
      a. **Any child is at risk for abuse.** The **risk of abuse is greatest,** however, in children with the following characteristics:
         1. **Age younger than 4 years,** especially younger than 1 year
         2. **Mental retardation, developmental delay**, severe handicaps, hyperactivity, or challenging temperament (including colic or frequent tantrums)
         3. **History** of premature birth, low birth weight, neonatal separation from parents, or multiple births
         4. **Chronic illness**
      b. Child abusers come from all socioeconomic, cultural, and ethnic groups. **Risk factors** for an **abusive caregiver** include the following:
         1. **Low self-esteem, social isolation, depression, or history of substance abuse**
         2. **History of abuse as a child**
         3. **History of mental illness**
         4. **History of violent temperament**
         5. **Family dynamics** that include single parenthood, unemployment, poverty, marital conflicts, domestic violence, poor parent–child relationships, and unrealistic expectations of the child
   2. **Clinical features**
      a. **Bruises**
         1. **Bruises on fleshy or protected areas,** such as the face, neck, back, chest, abdomen, buttocks, and genitalia, are often consistent with **inflicted injury**. In contrast, bruises on exposed areas, such as the shins, knees, elbows, and forehead, are typically from noninflicted trauma.
         2. **Patterns** of bruising may help determine the type of object used to inflict the trauma (e.g., distinctive marks are left by belt loops, buckles, hangers, and hands).
      b. **Human bites** may be found anywhere on the body, including the genitalia and buttocks of infants.
      c. **Burns** often have distinguishable patterns.
         1. **Accidental burns** have an **irregular, splashlike** configuration. In contrast, **nonaccidental burns** typically have a **clear line of demarcation** (e.g., "stocking" or "glovelike" pattern, suggesting submersion injury).
         2. **Objects** used to burn may be **branded** to the skin (e.g., irons and cigarettes).
      d. **Fractures** that are inconsistent with the history or with the child's developmental ability may be secondary to abuse (see Chapter 17, section V.G). The following fractures are considered highly suggestive of abuse:
         1. **Metaphyseal fractures ("bucket handle" or corner fractures),** which are caused by torsional force on the limb (i.e., pulling and twisting) or by violent

shaking
2. **Fractures** of the **posterior or first ribs, sternum, scapula, and vertebral spinous process**
3. **Multiple fractures in different stages of healing**

e. **Head injuries,** caused by trauma, asphyxiation, or shaking, are the **leading cause of death and morbidity from child abuse**. **Shaken baby syndrome** may occur in a child younger than 2 years of age who is violently shaken. (This syndrome is termed "shaken impact syndrome" if the child is thrown after the shaking.) **Retinal hemorrhages, subdural hematomas, metaphyseal fractures, and significant brain injury are characteristic.**

f. **Visceral injuries** are the **second leading cause of death from child abuse** and include rupture and injury of the intestinal tract, liver, and spleen.

3. **Diagnosis**

a. **History is critical** in differentiating inflicted from noninflicted trauma. **Child development should correlate with the nature of the injury.** Delays in seeking medical attention, implausible histories, and histories that change or are inconsistent among caregivers are suspicious for abuse.

b. **Physical examination** should focus both on acute injuries and on identifying old lesions that may be secondary to abuse. If shaken baby syndrome is suspected, a **dilated ophthalmoscopic evaluation** for retinal hemorrhages should be performed (see Chapter 18, section V.A).

c. **Accessory tests** should include a **skeletal survey** to evaluate for old or healing fractures and **head and abdominal CT** scans to evaluate for acute injuries.

4. **Management. Child protective services or law enforcement agencies must be notified if there is a suspicion of abuse.** Hospitalization may be required if medically indicated or until a safe location for the child has been identified.

C. **Sexual abuse**

1. **General concepts**

a. Unlike physical abuse, there are typically **no overt physical signs of trauma**.

b. **Perpetrators** are often **known to the child** before the abuse.

2. **Epidemiology.** Eighty percent of sexual abuse occurs in **females**.

3. **Diagnosis**

a. **History is critical** to confirm abuse.

1. **Obtaining a history of abuse from a young child is difficult.** Ideally, the history should be obtained with open-ended questions from an interviewer trained in sexual abuse evaluation.
2. **Sexually abused children** typically present with multiple **nonspecific complaints,** including abdominal and urogenital symptoms.
3. **Sexual behavior** in young children raises red flags for abuse.

b. **Physical examination** should be performed after rapport with the patient has been established.

1. **Signs of trauma** should be noted.
2. **Genital and perianal examination** should be performed last and should include inspection of the hymen, vagina, and perianal areas (penis, scrotum, and perianal areas in males), with notation of any discharge, injury, or bleeding.
3. **Physical examination is normal in most victims.**

c. **Laboratory studies** to collect forensic evidence should be performed if the abuse occurred within 72 hours of presentation, and should include cultures or serologic testing for sexually transmitted infections (STIs), including human

immunodeficiency virus (HIV). If appropriate, testing for pregnancy and assessment of vaginal fluid for spermatozoa should also be performed.

d. **Management**
    1. **Safety of the child** should be the **highest priority** in determining placement.
    2. **Child protective services** or social services must be notified and should arrange follow-up and support.
    3. **Pregnancy may be prevented** with high-dose oral contraceptives (morning-after pills).
    4. **Antibiotics** are often prescribed to empirically treat STIs.

VII. Sudden Infant Death Syndrome (SIDS)

A. **Definition.** SIDS is the **death of an infant younger than 1 year whose death remains unexplained after a thorough case investigation** that includes autopsy, death scene evaluation, and review of the clinical history.

B. **Epidemiology**
   1. **SIDS** is the **most common cause of death in children younger than 1 year**.
   2. **Incidence** is approximately 1 in 2500 live births. Peak incidence is at 2–4 months of age.
   3. The **typical victim** is found dead in the morning in bed after being put to sleep at night.
   4. **Risk factors** associated with SIDS may be found in Chapter 9, section IV.E.2.b.

C. **Management**
   1. **Resuscitation** should be attempted on all patients because of the difficulty in ascertaining the period of time the infant has been apneic and pulseless.
   2. **If resuscitation is unsuccessful,** the child's body is referred to the medical examiner for autopsy. Postmortem examination may demonstrate **intrathoracic petechiae** (the most common autopsy finding in 80% of cases, but one whose cause is unknown), pulmonary congestion or edema, small airway inflammation, and evidence of hypoxia.

VIII. Poisonings

A. **General concepts**
   1. **Epidemiology**
      a. **Sixty percent of all poisonings** occur in children **younger than 6 years**.
      b. **Ninety percent of poisonings are accidental.** The majority of poisonings occur at **home** when the child's **caregiver is distracted**.
      c. Most poisons are ingested, although poisons may also be inhaled, spilled on the skin or into the eyes, or injected intravenously.
      d. **Mortality is < 1%.**
   2. **Etiology.** The most common toxic exposures involve **commonly used household products**.
      a. **Cosmetics** and **personal care products (most common toxic exposure)**
      b. **Cleaning agents**
      c. **Cough and cold preparations**
      d. **Vitamins, including iron**
      e. **Analgesics (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs, aspirin)**
      f. **Plants (6–7% of all ingestions)**
      g. **Alcohols** *(e.g.,* **ethanol)** and **hydrocarbons** (e.g., gasoline, paint thinner, furniture polish)
      h. **Carbon monoxide (see section VIII.D.6)**
      i. **Prescription medications**

B. **Evaluation**
   1. **Consider poisoning** in patients presenting with **nonspecific signs and symptoms,** such as seizures, severe vomiting and diarrhea, dysrhythmias, altered mental status or abnormal behaviors, shock, trauma, or unexplained metabolic acidosis.
   2. **History** obtained from caregivers typically identifies the poison.
      a. **Information about the toxin** should include the type or name of toxin, toxin concentration (if known), and the route of exposure.
         1. **Potential poison dose** is calculated for the **worst-case scenario**. Toxicity is typically on the basis of the amount ingested per kilogram of body weight.
         2. **Consider multiple agents** in adolescents.
      b. **Information about the environment** should include location of victim when discovered, and medications, plants, vitamins, herbs, and chemicals in the home. Time of occurrence, if known, is very important.
   3. **Physical examination** should be comprehensive and may provide additional clues to the identity of the toxin. **Figure 20-1** shows the link between some typical physical findings and associated toxins.
   4. **Laboratory studies**
      a. **Screening laboratory tests** include serum glucose, serum and urine toxicology screens, and electrolytes.
         1. **Anion gap** $[Na^+ - (Cl^- + HCO_3^-)]$ should be calculated.
         2. **Causes of an increased anion gap (>16)** may be recalled using the mnemonic **AMUDPILES** (**a**lcohol, **m**ethanol, **u**remia, **d**iabetic ketoacidosis, **p**araldehyde, **i**ron and **i**soniazid, **l**actic acidosis, **e**thylene glycol, **s**alicylates).
      b. **Radiographic imaging** of the abdomen may reveal *radiopaque substances*. These may be recalled using the mnemonic **CHIPE** (**c**hloral hydrate and **c**alcium, **h**eavy metals, **i**odine and **i**ron, **p**henothiazines, **e**nteric-coated tablets).

C. **General management principles**

1. The **ABCs** are the initial management priority.
2. If the patient has **altered mental status,** administer **dextrose** for hypoglycemia and **naloxone** for possible opiate overdose.
3. A **poison control center** may be consulted to assist with management.
4. **Gastric decontamination**
    a. **Activated charcoal** has a **very large adsorptive surface area** that **binds toxins** and minimizes their absorption.
        1. *Activated charcoal should be considered for all poisonings*. However, it is **ineffective** for some poisons such as **iron**, lithium, alcohols, ethylene glycol, iodine, potassium, and arsenic. In addition, activated charcoal interferes with visualization during endoscopy and therefore should not be used for caustic ingestions.
        2. **Evidence** suggests that activated charcoal **improves clinical outcomes,** especially if given within 1 hour after an ingestion.
    b. **Whole-bowel irrigation** (WBI) is rapid, complete emptying of the intestinal tract accomplished using **polyethylene glycol** (an osmotic agent) and an **electrolyte solution** (to prevent electrolyte imbalance). Preliminary studies show that WBI may be effective for ingestions of iron and other heavy metals and sustained-release medications.
    c. **Antidotes** exist for a relatively small number of compounds **(Table 20-3)**.

D. **Specific poisonings**
1. **Acetaminophen.** This drug is one of the most common medications ingested by children and adolescents. Doses >150 mg/kg are associated with toxicity.
    a. **Pathophysiology**
        1. **Hepatic damage,** the major sequelae of toxicity, is directly related to the *depletion of glutathione,* a cofactor used during the metabolism of acetaminophen by the cytochrome P-450 system.
        2. **Toxic intermediates** produced when glutathione is depleted bind directly to hepatocytes, causing hepatocellular necrosis.
    b. **Clinical features.** There are **four stages** of acetaminophen poisoning *(***Table 20-4***)*.
    c. **Management**
        1. **Activated charcoal**
        2. **Obtain serum acetaminophen level 2–4 hours** after ingestion. The level should be plotted on the **Matthew–Rumack nomogram** to determine the potential for hepatitis.
        3. If the nomogram predicts hepatitis, the antidote, ***N*-acetylcysteine (NAC),** a glutathione precursor, is indicated.
            a. **NAC** is given orally as a 140 mg/kg loading dose and is followed with 70 mg/kg every 4 hours for 17 doses.
            b. **NAC** may be given **intravenously as an infusion for more than 21 hours**.
            c. **NAC is hepatoprotective** if given **within 8 hours** of ingestion. It may still be helpful up to 72 hours after ingestion.
2. **Salicylates.** Salicylate poisoning has decreased as acetaminophen's usage has increased; however, salicylates remain as an ingredient in many over-the-counter compounds, such as Pepto-Bismol, Ben-Gay, and oil of wintergreen. Doses >150 mg/kg are associated with toxicity.
    a. **Pathophysiology**
        1. **Salicylates directly stimulate respiratory centers.** This causes hyperventilation that may overcompensate for metabolic acidosis produced by

the salicylate (it is a weak acid), resulting in a **respiratory alkalosis**.
2. **Salicylates uncouple oxidative phosphorylation,** producing lactic **acidosis** and enhancing ketosis.

b. **Clinical features.** Common signs and symptoms include fever, diaphoresis, and flushed appearance; tinnitus; vomiting; headache; lethargy, restlessness, coma, and seizures; hyperpnea; and dehydration.

c. **Laboratory findings**
1. **Respiratory alkalosis with an anion-gap metabolic acidosis is the most common acid–base disturbance.**
2. Hyperglycemia, followed later by hypoglycemia
3. Hypokalemia

d. **Management**
1. **Activated charcoal** is effective and may be **readministered every 4 hours** in severe poisonings.
2. **Obtain serum salicylate level** at least **6 hours** after ingestion. The level should then be plotted on the **Done nomogram** to assess for potential toxicity.
3. **Alkalinization of urine with sodium bicarbonate to a urine pH > 7** and large-volume intravenous fluids enhance renal excretion of salicylates.
4. **Dialysis** may be required for life-threatening ingestions.

3. **Iron**

a. **Epidemiology**
1. Iron is one of the most common and potentially fatal childhood poisonings. As little as 20 mg/kg of iron is toxic.
2. Adult-strength ferrous sulfate tablets and **iron in prenatal vitamins** are the most common sources of accidental iron ingestion.

b. **Pathophysiology**
1. **Direct damage to the gastrointestinal tract** leading to hemorrhage
2. **Hepatic injury and necrosis**
3. **Third spacing and pooling of blood** in the vasculature leading to hypotension
4. **Interference** with oxidative phosphorylation

c. **Clinical features.** There are four stages of iron toxicity *(***Table 20-5***)*.

d. **Management**
1. *Activated charcoal does not bind to iron.* However, if a polyingestion is suspected, activated charcoal should be given**.**
2. Hypovolemia, blood loss, and shock should be anticipated and treated.
3. **WBI** should be considered for life-threatening ingestion.
4. **Serum iron level should be obtained 2–6 hours after ingestion.**
5. **Intravenous deferoxamine,** an iron-binding ligand, should be given if any of the following condition exists:
   a. **If serum iron levels > 500 μg/dL,** or if **> 300 μg/dL** and acidosis, hyperglycemia, or leukocytosis are present
   b. **If severe gastrointestinal symptoms** are present
   c. **If more than 100 mg/kg of iron** is ingested
6. Before the serum iron level is known, a test dose of **deferoxamine** may be administered. If the patient's urine then turns red or pink *(***vin rose***)* (the color of chelated iron), the challenge is considered positive, indicating a clinically significant iron ingestion. Intravenous deferoxamine should then be continued.

4. **Lead**

a. **Sources of lead** include ingestion of lead-based paint chips, water carried by

outdated lead pipes, improperly glazed or foreign-made ceramic food or water containers, and pica (compulsive eating of nonnutrient substances such as dirt, paint, and clay). (See Chapter 1, section IV.J.)

b. **Clinical features.** Lead poisoning is typically a **chronic ingestion;** however, children may also present with **acute lead intoxication**.
    1. **Abdominal complaints** include colicky pain, constipation, anorexia, and vomiting.
    2. **CNS complaints** include listlessness, irritability, seizures, and decreased consciousness with encephalopathy.
    3. **Peripheral blood smear** may show **microcytic anemia, basophilic stippling,** and red blood cell precursors.
    4. Radiopacities may be seen on **abdominal radiographs,** and **dense metaphyseal bands** may be seen on radiographs of the knees and wrists **(lead lines)**.
c. **Diagnosis.** An **elevated lead level** or *elevated erythrocyte protoporphyrin* is the basis of diagnosis.
d. **Management.** Treatment for significant toxicity includes dimercaprol, British anti-lewisite (BAL), or calcium disodium ethylenediaminetetraacetic acid (EDTA).

5. **Caustic agents.** These are **acids or alkalis with corrosive potential**.
    a. **Pathophysiology**
        1. **Acids** (e.g., toilet bowl cleaner) cause **coagulation necrosis** that leads to **superficial damage** to the mouth, esophagus, and stomach. More severe injury results from compounds that have a pH <2.
        2. **Alkalis** (e.g., oven and drain cleaners, bleach, laundry detergent) cause **liquefaction necrosis** that produces **deep and penetrating damage,** most commonly to the mouth and esophagus. More severe injury results from compounds that have a pH >12.
    b. **Clinical features**
        1. **Immediate burning** sensation with intense **dysphagia, salivation,** retrosternal chest pain, and vomiting
        2. **Obstructive airway edema** (especially with acid ingestion)
        3. **Gastric perforation** and peritonitis may follow acid ingestion.
        4. **Esophageal perforation with mediastinitis** may follow alkali ingestion.
    c. **Management.** Treatment initially includes the ABCs.
        1. **No attempt should be made to neutralize the caustic agent,** because the combination of acid and alkali will generate an exothermic reaction and worsen any burn.
        2. **Activated charcoal is contraindicated** because it interferes with endoscopy.
        3. **Endoscopy** is performed to assess the degree of damage.
        4. **Household bleach** has less corrosive potential and generally does not require treatment.

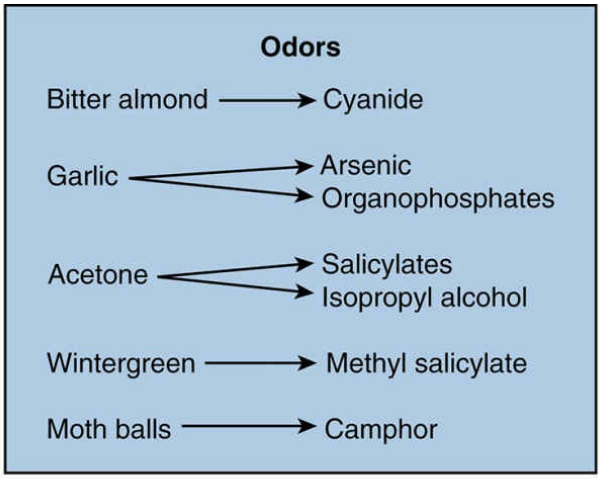
6. **Carbon monoxide poisoning**
    a. **Epidemiology.** Carbon monoxide (CO) is a by-product of incomplete combustion of carbon-containing material. Excessive exposure may occur from fires, tobacco, faulty home heaters, car exhaust, and industrial pollution. **CO** is **odorless, tasteless,** and **colorless**.
    b. **Pathophysiology. CO interferes with oxygen delivery and utilization.**
        1. **Carbon monoxide displaces oxygen** from the hemoglobin molecule, forming **carboxyhemoglobin (CO-Hb),** which can no longer carry oxygen. The bond between CO and hemoglobin is more than 200 times stronger than the bond

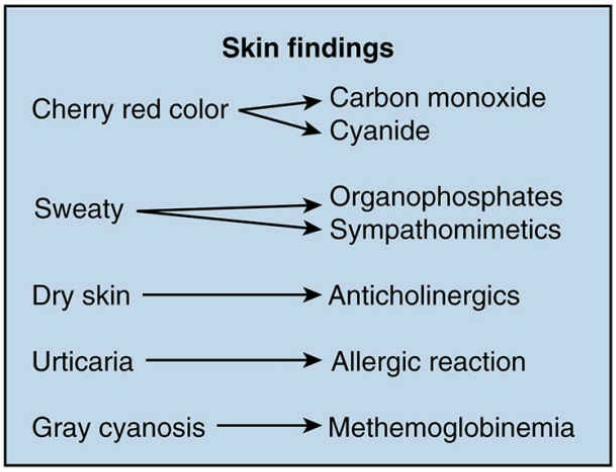
between oxygen and hemoglobin.
2. The **oxygen–hemoglobin dissociation curve** is shifted to the **left**. This leads to tighter binding of the remaining oxygen bound to hemoglobin and impaired release of oxygen to tissues.
3. *Carbon monoxide* also interferes with cellular oxidative metabolism.

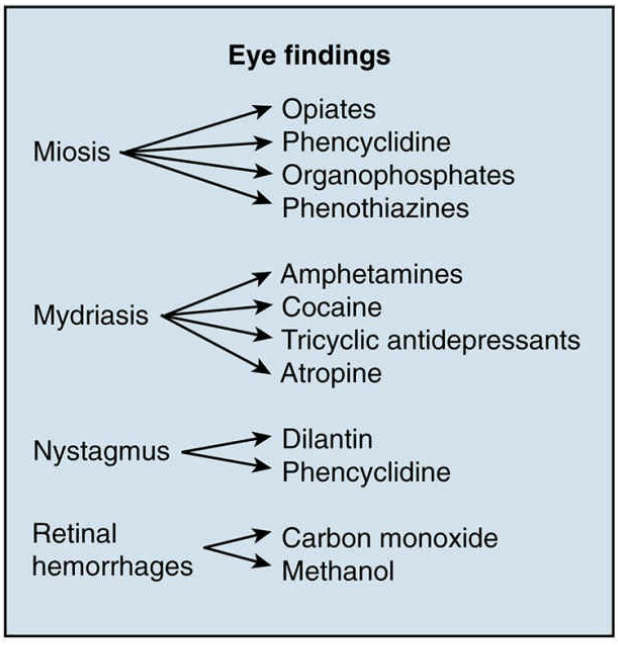
c. *Clinical features depend on the CO-Hb level*.
1. **Low levels** are associated with **nonspecific symptoms** such as **headache, flulike illness,** dyspnea with exertion, and dizziness.
2. **High levels** are associated with **visual and auditory changes,** vomiting, **confusion** and later syncope, slurred speech, cyanosis, myocardial ischemia, coma, and death.
3. **Classic physical examination findings,** although uncommon, include **cherry red skin** (venous blood carries more oxygen than normal as a result of impaired release of oxygen to tissues) and **retinal hemorrhages.** Tachycardia and tachypnea may be present.
4. **Young children** (<8 years) have more symptoms at lower CO-Hb levels. Young children are also more likely to have gastrointestinal symptoms (e.g., vomiting and diarrhea) instead of neurologic symptoms.
5. **Delayed permanent neuropsychiatric syndrome,** consisting of memory loss, personality changes, deafness, and seizures, may occur in some victims up to 4 weeks after CO exposure.

d. **Diagnosis** is made by measuring the **CO-Hb level**. It is important to remember that CO-Hb levels are not always indicative of the degree of CO exposure and may even be low in victims with significant intoxication. Other abnormal findings include anion-gap metabolic acidosis, low oxygen saturation (however, PaO_2 may be normal), and evidence of myocardial ischemia on ECG or elevated cardiac enzymes.

e. **Management**
1. **One hundred percent oxygen** is administered to displace CO from hemoglobin.
2. If available, **hyperbaric oxygen** more rapidly displaces CO from hemoglobin as compared with oxygen alone and also improves oxygen delivery to tissues.
3. **Hospitalization** is indicated for CO-Hb levels > 25%, CO-Hb levels > 10% during pregnancy, history or presence of neurologic symptoms, or presence of metabolic acidosis or ECG changes.


Odors
Bitter almond
Cyanide
Garlic
Arsenic
Organophosphates
Acetone
Salicylates
Isopropyl alcohol
Wintergreen
Methyl salicylate
Moth balls
Camphor


Skin findings
Cherry red color
Carbon monoxide
Cyanide
Sweaty
Organophosphates
Sympathomimetics
Dry skin
Anticholinergics
Urticaria
Allergic reaction
Gray cyanosis
Methemoglobinemia


Eye findings
Miosis
Opiates
Phencyclidine
Organophosphates
Phenothiazines
Mydriasis
Amphetamines
Cocaine
Tricyclic antidepressants
Atropine
Nystagmus
Dilantin
Phencyclidine
Retinal hemorrhages
Carbon monoxide
Methanol

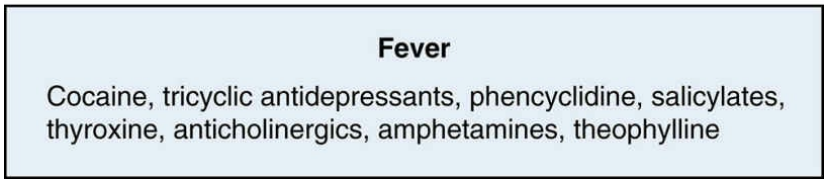

Fever
Cocaine, tricyclic antidepressants, phencyclidine, salicylates, thyroxine, anticholinergics, amphetamines, theophylline

FIGURE 20.1 Selected physical examination findings and their associated toxins.

Table 20-3
Selected Toxins and Their Antidotes

Toxin	Antidote
Acetaminophen	NAC
Anticholinergic agents	Physostigmine
Benzodiazepines	Flumazenil
Black widow spider envenomation	Antivenin *Latrodectus mactans*
Carbon monoxide	Oxygen
Coral snake envenomation (Eastern U.S. or Texas coral snake)	Antivenin *Micrurus fulvius*
Cyanide	Cyanide antidote kit (contains amyl nitrite, sodium nitrite, sodium thiosulfate)
Hydroxocobalamin (vitamin B_{12})	
Digitalis glycosides	Digoxin-specific Fab antibodies
Heavy metals (e.g., mercury, manganese, copper, gold, nickel, zinc, lead, arsenic)	d-Penicillamine (for lead, mercury, arsenic, copper)
	Dimercaprol (British anti-lewisite [BAL] in oil) for all the heavy metals and lewisite (chemical weapon)
	DMSA (for lead and possibly mercury, arsenic, other metals)
	EDTA, calcium (for lead, nickel, zinc, manganese)
Inducers of dystonia	Diphenhydramine
Benztropine	
Inducers of methemoglobinemia	Methylene blue
Iron	Deferoxamine
Isoniazid	Pyridoxine (vitamin B_6)
Methanol; ethylene glycol	Ethanol, fomepizole
Narcotics	Naloxone
Organophosphates; carbamate pesticides	Atropine
Pralidoxime (for organophosphates)	
Pit viper snake bite (rattlesnake, water moccasin, copperhead envenomation)	Crotalidae polyvalent, antivenin, *Crotalidae* polyvalent Fab antibodies
β-Blockers; calcium-channel blockers	Glucagon
Sulfonylurea oral hypoglycemic agents	Octreotide
	Glucagon

EDTA = ethylenediaminetetraacetic acid; *DMSA* = dimercaptosuccinic acid; *NAC* = *N*-acetylcysteine.

Table 20-4
Stages of Acetaminophen Toxicity

Stage	Time After Ingestion	Signs and Symptoms
1	30 minutes–24 hours	**Asymptomatic,** or vomiting and diarrhea
2	24–72 hours	**Gastrointestinal symptoms resolve;** at 36 hours, hepatic transaminases begin to increase
3	72–96 hours	**Hepatic necrosis,** jaundice, hypoglycemia, lactic acidosis, hepatic encephalopathy, coagulopathy, and renal failure
4	4 days–2 weeks	Resolution of symptoms, progressive liver damage requiring liver transplantation, or death

Table 20-5
Stages of Iron Toxicity

Stage	Time After Ingestion	Signs and Symptoms
1	1–6 hours	Abdominal pain, vomiting, diarrhea, GI bleeding
		Shock from bleeding and vasodilation
		Fever and leukocytosis
2	6–12 hours	Resolution of stage 1 symptoms
3	12–36 hours	Metabolic acidosis

		Circulatory collapse
		Hepatic and renal failure
		DIC
		Neurologic deterioration
4	2–6 weeks	Late sequelae includes pyloric or intestinal scarring with stenosis

DIC = disseminated intravascular coagulation; *GI* = gastrointestinal.

IX. Mammalian Bites

A. **Epidemiology**
   1. **Dogs** (80% of bites), cats, rodents, other wild or domesticated animals, and humans (2–3% of bites) may all cause a bite injury.
   2. Most bites occur in **boys** during the spring and summer months.

B. **Dog bites**
   1. **Clinical features**
      a. **Bites range in severity** from scratches, punctures, and lacerations to severe soft tissue injury. Note that the jaw pressure of a dog may exceed 200–450 pounds per square inch.
      b. **Young children** are typically bitten on the **head and neck,** whereas older children are bitten predominantly on the extremities.
      c. **Secondary infections** may result from anaerobic and aerobic organisms, such as *Staphylococcus aureus*, *Pasteurella multocida,* and *Streptococcus* species.
   2. **Management.** Treatment includes meticulous and prompt local wound care.
      a. **Copious wound irrigation**
      b. **Wounds on the face or large wounds should be sutured if less than 12 hours old.** Facial wounds <24 hours old can be sutured because the face has increased vascularity, which assists with healing and minimizes the risk of infection.
      c. **Wounds at high risk for infection** include those on the hand, wrist, and foot, and small puncture wounds.
      d. **Antibiotic prophylaxis,** such as amoxicillin–clavulanic acid, should be administered.
      e. **Tetanus prophylaxis** should be given if needed.
         1. **Tetanus toxoid vaccine should be given if the most recent tetanus vaccine was given greater than 5 years ago.**
         2. **Tetanus immune globulin may also be recommended if the date of the last tetanus vaccine is unknown.**

C. **Cat bites**
   1. **Clinical features**
      a. **Puncture wounds** to the upper extremity are most common.
      b. **Victims have a high risk of infection** due to ***P. multocida***.
      c. **Cat scratch disease** (regional lymphadenitis) may also develop (see Chapter 7, section XVII.B).
   2. **Management.** Treatment is similar to the management of dog bites. Because the injury is typically a puncture wound, adequate irrigation is often difficult.

D. **Human bites**
   1. **Clinical features**
      a. **Wound** is typically located on the trunk or face in young children. If the wound occurred during a fistfight, it is typically located at the **metacarpophalangeal (MP) joint**. Wounds to the MP joint are extremely serious, because infection may penetrate the avascular fascial layers, resulting in deep infection and tendonitis.
      b. **Infection rate is high.**
         1. **Mixed bacterial infection** is often present. Pathogens include *Streptococcus viridans, S. aureus,* and anaerobic bacteria such as *Bacteroides, Peptostreptococcus,* and *Eikenella corrodens.*
         2. **Other systemic infections**, such as hepatitis B, HIV, and syphilis, may also be transmitted.

c. **Management.** Treatment includes copious wound irrigation, closure of large lacerations, and antibiotics (e.g., amoxicillin–clavulanic acid).

X. Biologic Poisonings (Venoms)

A. **Black widow spider (*Latrodectus* species)**
   1. **General concepts**
      a. The black widow spider is characterized by a **red or orange hourglass marking** on the ventral surface.
      b. Only the **female spider** is dangerous, and the female spider **only bites if provoked**.
      c. The **web** is located in dark recesses, such as closets, woodpiles, and attics.
      d. Black widows are found in temperate regions throughout the world, which include the United States, southern Europe and Asia, Australia, Africa, and much of South America.
   2. **Clinical features** result from the venom, a potent **neurotoxin**.
      a. The **bite causes few local symptoms,** except for burning or a sharp pinprick sensation.
      b. **Pathognomonic signs and symptoms** include **severe hypertension and muscle cramps**.
      c. **Nonspecific symptoms,** such as headache, dizziness, nausea, vomiting, anxiety, and sweating, may also occur.
   3. **Management**
      a. **Local wound care,** including wound irrigation and tetanus prophylaxis (if needed), is important.
      b. Benzodiazepines and narcotics may relieve muscle cramps.
      c. ***Latrodectus* antivenin** is given for signs and symptoms suggesting severe envenomation.

B. **Brown recluse spider (*Loxosceles* species)**
   1. **General concepts**
      a. The brown recluse spider (also called the **fiddleback spider**) is characterized by a **brown violin-shaped** marking on the dorsum of the thorax.
      b. The spider **only bites if provoked**.
      c. The **web** is located in dark recesses.
      d. The known **geographic range** of the brown recluse spider extends from Nebraska to Ohio and across the south from Texas to Florida.
   2. **Clinical features** result from the venom, a **cytotoxic** compound containing **tissue-destructive enzymes**.
      a. The **bite** results in little initial pain. However, 1–8 hours later, a painful itchy papule that increases in size and discolors during the course of 3–4 days develops at the site of the bite.
      b. Some patients develop a **necrotic and ulcerated deep lesion** at the bite site.
      c. **Systemic reactions** may occur 24–48 hours after the bite with fever, chills, weakness, vomiting, joint pain, DIC, hemolysis, and renal failure from myoglobinuria.
   3. **Management.** Treatment includes local wound care and tetanus prophylaxis, if needed. Treatment of a necrotic ulcer is controversial but may include steroids, skin grafting, dapsone, and hyperbaric oxygen. There is no antivenin.

C. **Pit viper snakes (family *Crotalidae*)** account for more than **95%** of all snakebites. **Rattlesnake, cottonmouth, and copperhead snakes** are members of the *Crotalidae* family.
   1. **Pathophysiology**
      a. **Bite location** and **amount of venom injected** determine the severity of envenomation. Head and trunk bites are most severe.

b. **Venom** is a complex mixture of **proteolytic enzymes**.

2. **Clinical features**
   a. **Local findings** include puncture marks and progressive severe swelling and ecchymosis.
   b. **Systemic effects** include **paresthesias** of the scalp, periorbital fasciculations, **weakness,** diaphoresis, dizziness, nausea, and a **metallic taste** in the mouth.
   c. **Coagulopathy, thrombocytopenia, hypotension, and shock** may also develop.
3. **Management.** Treatment involves local wound care, tetanus prophylaxis if needed, immobilization of the bitten extremity, and **immediate transport** to the nearest emergency department.
   a. **Incision and suction are not recommended.**
   b. **Tourniquets,** ice, and direct pressure on the wound may **cause more injury**.
   c. ***Crotalidae*** **polyvalent antivenin** should be considered for **all bites**.
      1. **Children** require **more antivenin** because they receive proportionally more venom per kilogram body weight.
      2. **Antivenin** is **most effective** if given within **4–6 hours** of the bite.
      3. **Complications** of antivenin are common and include **serum sickness and anaphylaxis**.
   d. **Crotalidae polyvalent immune Fab** is also available for envenomation and is safe, more potent, and very effective.

D. **Coral snakes (family *Elapidae)*** account for **1–2%** of all snakebites. Coral snakes may be identified by their stripe pattern using the mnemonic **"red next to yellow, kill a fellow; red next to black, venom lack**."

1. **Clinical features** result from the **neurotoxic** venom and include mild local swelling and tenderness and **severe systemic symptoms,** such as paresthesias, vomiting, weakness, diplopia, fasciculations, confusion, and respiratory depression.
2. **Management** should be aggressive and includes **antivenin** (available only for the Eastern U.S. and Texas coral snake), local wound care, and supportive care.

Review Test

1. You are summoned urgently to the waiting room of the emergency department by a clerk after she witnessed a 3-year-old boy collapse. You are concerned that he may be in cardiac arrest. Which of the following is the correct order of steps for the initial management of a child found in full cardiopulmonary arrest?
   A. Open the airway, check for a pulse, administer rescue breaths, and start chest compressions.
   B. Check for a pulse, open the airway, start chest compressions, and administer rescue breaths.
   C. Check for a pulse, start chest compressions, open the airway, and administer rescue breaths.
   D. Open the airway, administer rescue breaths, start chest compressions, and check for a pulse.
   E. Check for breathing and a pulse, and start chest compressions.
2. A 2-year-old boy sustains severe head trauma in a three-story fall. Which of the following statements regarding head injury in a patient of this age is correct?
   A. Epidural hematoma has a crescentic density on head computed tomography.
   B. The prognosis is better if he has a subdural hematoma rather than an epidural hematoma.
   C. Cushing triad is an early sign of increased intracranial pressure.
   D. The occipital lobe is the most common site of intracerebral hematoma.
   E. Bradycardia is an early sign of herniation.
3. A 1-year-old girl has been involved in a motor vehicle accident, and you suspect she has sustained head injury. On examination, she is unconscious but she opens her eyes to pain and also has abnormal flexion of her extremities to pain. She does not cry but rather grunts with stimulation. What is her Glasgow coma score?
   A. 4
   B. 5
   C. 6
   D. 7
   E. 8
4. A 19-month-old male infant has a burn on his right hand that occurred 3 hours ago. On examination, the burn appears to be in a "stocking glove" distribution. The involved area is moist, painful, and red and contains two moderate-sized intact blisters. Which of the following statements regarding this burn is correct?
   A. This patient has suffered a superficial partial-thickness burn.
   B. This burn will most likely scar.
   C. Child abuse is unlikely based on the burn's characteristics.
   D. Blisters should be ruptured and debrided.
   E. Hospitalization is not needed.
5. A 2-year-old girl is found submerged in a lake. She is suspected to have been under the water for more than 15 minutes. Paramedics find her apneic and pulseless. On arrival at the hospital, her core body temperature is 82.4°F (28°C). Which of the following statements regarding the management, expected clinical findings, and prognosis in this patient is correct?
   A. Management is dependent on whether the lake contains fresh or salt water.
   B. Because the child was found apneic and pulseless, resuscitative efforts should not be attempted.
   C. Cervical spine immobilization is unnecessary.

D. Pulmonary function would be expected to improve during the next 18 hours.
E. The prognosis is poor.

6. A 17-year-old girl is brought by her parents to the emergency department after a possible suicide attempt. She discloses that she swallowed 100 aspirin tablets 4 hours ago. Which of the following acid–base relationships would most likely be found on an arterial blood gas study of this patient?
   A. Metabolic alkalosis and respiratory acidosis
   B. Metabolic alkalosis and respiratory alkalosis
   C. Metabolic acidosis and respiratory acidosis
   D. Metabolic acidosis and respiratory alkalosis
   E. Respiratory alkalosis only
7. A 2-year-old girl is brought to the emergency department by her parents. She swallowed an unknown amount of industrial-strength drain cleaner from her father's plumbing van 30 minutes ago. Which of the following statements regarding the clinical findings and management of this incident is correct?
   A. The drain cleaner will cause coagulation necrosis
   B. Activated charcoal should be administered.
   C. Nasogastric tube for lavage should be avoided.
   D. Lower intestinal perforation is a possible complication.
   E. The drain cleaner should be neutralized with acetic acid.
8. A 14-year-old boy is involved in a fistfight with another teenager at school. He is brought to the emergency department 2 hours later with a laceration on the dorsum of his right hand over the knuckle secondary to a human bite. Which of the following statements regarding this human bite is correct?
   A. If infection develops, it is usually secondary to both anaerobes and aerobes.
   B. If irrigated appropriately, human bites are unlikely to become infected.
   C. This wound most likely involves an interphalangeal joint.
   D. Antibiotics should not be prescribed until an infection develops because of the risk of selection of resistant organisms.
   E. If infection develops, it is most likely caused by *Pasteurella multocida.*
9. A 5-year-old girl is brought to a rural emergency department after being bitten on the leg by a rattlesnake. The bite occurred 30 minutes ago. No antivenin is available at the hospital, and transfer to another hospital is pending. Which of the following should be performed immediately?
   A. Local wound care, leg immobilization, and supportive care only.
   B. Incise the wound and apply suction to remove the venom.
   C. Apply direct pressure to the wound.
   D. Apply a tight tourniquet proximal to the wound to prevent venom from spreading.
   E. Rub ice over the fang marks.

The response items for statements 10 and 11 are the same. You will be required to select one answer for each statement in the set.

A. Black widow spider
B. Brown recluse spider

For each of the following patients, select the most likely spider bite.

1. A 5-year-old girl with severe muscle cramps and hypertension.
2. A 10-year-old boy with fever, chills, vomiting, and disseminated intravascular coagulation 24 hours after a suspected bite. Five days later, a necrotic, ulcerated skin lesion is evident.

The response items for statements 12–14 are the same. You will be required to select one answer for each statement in the set.

A. Distributive shock
B. Septic shock
C. Cardiogenic shock
D. Hypovolemic shock
E. Neurogenic shock

For each patient, select the most likely type of shock.

1. A 10-month-old female infant presents with hypotension. An electrocardiogram reveals supraventricular tachycardia.
2. A 10-year-old boy presents with a 2-day history of high fever, chills, vomiting, diarrhea, and weakness. Examination reveals hypotension with bounding pulses and warm extremities.
3. A 5-year-old boy presents with acute onset of wheezing, urticaria, stridor, and hypotension.
4. A 2-year-old girl is brought to the emergency department after ingesting her mother's prenatal vitamins 60 minutes ago. Which of the following statements regarding the clinical findings, diagnosis, and management of this type of poisoning is correct?
    A. Activated charcoal is effective.
    B. Basophilic stippling is seen on peripheral blood smear.
    C. A test dose of deferoxamine should be the first step in management.
    D. An abdominal radiograph may reveal the ingested poison.
    E. Shock is uncommon.

Answers and Explanations

1. **The answer is E** [I.B]. The CABs (Circulation, Airway, Breathing) should begin every resuscitation of a child. If the victim is unresponsive, the rescuer should shout for help and activate the emergency response system. While looking for breathing, the rescuer should simultaneously feel for a pulse. The airway should be opened by either a chin lift–head tilt maneuver or by a jaw-thrust maneuver if the patient has suspected neck or cervical spine injury. If the patient is bradycardic or asystolic, chest compressions are administered.
2. **The answer is E** [III.E.1.d]. In children younger than 4 years, bradycardia is often the initial sign of cerebral herniation. Epidural hematomas have a lenticular appearance on head computed tomography, whereas subdural hematomas generally have a crescentic appearance. Patients with subdural hematomas generally have a worse prognosis compared with those with epidural hematomas, because of the bleeding directly on the surface of the brain parenchyma. Cushing triad (in which bradycardia is seen with hypertension and an irregular breathing pattern) is a late finding of increased intracranial pressure. The frontal and temporal lobes are the most common sites of intracerebral bleeding.
3. **The answer is D** [Table 20-1]. The Glasgow coma score (GCS) is used to assess the level of neurologic impairment on the basis of the patient's physical examination. It includes assessment of three components: eye opening, motor response, and verbal response. This scoring system has been modified for the nonverbal pediatric patient. This patient has a GCS score of 7; she opens her eyes to pain (2), has abnormal extremity flexion to pain (3), and grunts with stimulation (2). A GCS of less than 8 signifies severe head injury.
4. **The answer is A** [VI.B.2.c, IV.B.2.a, and IV.C]. This patient's burn is classified as a superficial partial-thickness burn on the basis of the presence of pain, blisters, and erythema. Superficial partial-thickness burns involve the epidermis and outer dermis and do not scar. Child abuse must be considered for well-demarcated burns (e.g., "stocking glove" distribution) that suggest submersion injury. If intact, blisters should not be ruptured because the risk of infection and loss of fluid from the skin would increase. All patients with burns to the hands, feet, perineum, face, and skin overlying joints should be hospitalized for treatment.
5. **The answer is E** [V.D–F]. A poor prognosis is associated with age younger than 3 years, submersion times greater than 5 minutes, and the need for cardiopulmonary resuscitation, all of which are present in this patient. In general, however, the outcome of drowning in children is better than that in adults, because children have a primitive dive reflex that preferentially shunts blood to vital organs such as the brain, heart, and liver. Management is the same regardless of the type of water in which the patient was submerged. Despite the apnea and asystole, this patient should be resuscitated, and efforts at resuscitation should continue until the core body temperature reaches at least 89.6°F (32°C). Head and neck trauma should always be suspected, and therefore cervical spine immobilization is important. Pulmonary function tends to deteriorate during the 12–24 hours after submersion injury.
6. **The answer is D** [VIII.D.2.d]. Salicylates are weak acids and cause an anion-gap metabolic acidosis. However, salicylates also directly stimulate the respiratory centers in the brainstem. The stimulation of the respiratory center causes hyperventilation, which overcompensates the metabolic acidosis, producing a respiratory alkalosis. Therefore, the most common acid–base finding in a patient who has ingested a toxic amount of salicylates is a metabolic acidosis and a respiratory alkalosis.
7. **The answer is C** [VIII.D.5.b–c]. Drain cleaners are alkalis, which typically cause severe deep burns to the mouth and esophagus by liquefaction necrosis. In contrast, acids cause coagulation necrosis that produces superficial damage. Because the esophagus may be injured, a nasogastric tube for suction or lavage is contraindicated. Activated charcoal should be

avoided as well because it interferes with endoscopy. Neither acids nor alkalis cause lower intestinal perforation. Neutralization with an acid produces an exothermic reaction that results in further injury.

8. **The answer is A** [IX.D]. Human bites have a very high infection rate despite appropriate wound cleaning. Infection is typically a mixed infection consisting of both aerobes and anaerobes. The hand, specifically the metacarpophalangeal joint, is most commonly bitten in a fistfight. Antibiotics should always be prescribed. Infection with *Pasteurella multocida* occurs in cat and dog bites, but not in human bites. Other infections such as syphilis, human immunodeficiency virus, and hepatitis B also may be transmitted by human bites.
9. **The answer is A** [X.C.3]. Management of a rattlesnake bite involves the immediate administration of snake antivenin. If antivenin is unavailable, the victim should be transported to a facility that has antivenin. Local wound care (including tetanus prophylaxis if needed) and immobilization of the affected extremity are all that are needed until antivenin becomes available. Incision and suction are not recommended, and direct pressure, tourniquets, and ice may aggravate the injury.
10. **The answers are A and B, respectively** [X.A and X.B]. The black widow spider (*Latrodectus* species) generally produces few local symptoms; however, muscle cramps and systemic hypertension are pathognomonic. The brown recluse spider (*Loxosceles* species) produces significant local signs and symptoms in some patients, including a deep necrotic ulcerated skin lesion. In some patients, systemic symptoms, such as disseminated intravascular coagulation, vomiting, fever, chills, hemolysis, and joint pain, may occur 24–48 hours after the bite.
11. **The answers are C, B, and A, respectively** [II.B.2.d, II.B.2.b and II.B.2.c]. The 10-month-old female infant with supraventricular tachycardia has cardiogenic shock, which is generally caused by cardiac dysrhythmias. The 10-year-old boy has signs and symptoms of infection. Shock associated with infection may include septic shock and hypovolemic shock. However, bounding pulses and warm extremities are found only in the initial hyperdynamic stage of septic shock. The 5-year-old boy has signs and symptoms of anaphylaxis. Shock associated with anaphylaxis is distributive shock, which may also be secondary to spinal cord injury and drug poisoning.
12. **The answer is D** [VIII.B.4.b, VIII.D.3.d and Table 20-5]. Prenatal vitamins contain iron, a cause of childhood poisoning. Iron tablets are radiopaque and may be seen on imaging studies of the abdomen. There are four clinical stages of iron ingestion, including the first stage in which gastrointestinal bleeding can occur along with shock and vasodilation. Management of suspected iron ingestion includes whole-bowel irrigation if poisoning is severe, and treatment with deferoxamine, an iron chelator. Activated charcoal is not effective for iron ingestion. Basophilic stippling is seen in lead intoxication. A test dose of deferoxamine may be very helpful in the management of this patient, but it would not be the first step in management.

Comprehensive Examination

1. At a routine health maintenance visit, the parents of a well-appearing 2-week-old female infant have no concerns other than jaundice, which they have noted since the infant was 1 week of age. The patient is alert and feeding well. Laboratory evaluation reveals a total bilirubin level of 14.2 mg/dL and a direct bilirubin level of 6.2 mg/dL. Which of the following studies is most likely to be diagnostic of this patient's condition?
   A. Hepatic ultrasound
   B. Complete blood count and blood culture
   C. Coombs testing
   D. Levels of thyroxine and thyroid-stimulating hormone (TSH)
   E. Osmotic fragility test
2. The parents of a 15-month-old boy bring him to the office for a routine health maintenance visit. Which of the following is a contraindication to administering the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at this time?
   A. Signs and symptoms of an upper respiratory illness with a temperature up to 38.3°C (101°F)
   B. A history of intravenous immune globulin infusion for immune thrombocytopenic purpura at 9 months of age
   C. A 4-year-old sibling in the household receiving chemotherapy
   D. A history of moderate swelling at the injection site after the 6-month DTaP vaccination
   E. Uncontrolled epilepsy
3. A 6-year-old girl with a 3-week history of malaise, decreased appetite, and intermittent tactile fevers is brought to see you by her parents for evaluation of a "purplish rash" around her eyes. On further questioning, you learn that the child also has less energy, which the parents attribute to the "flu." Joint swelling, abdominal pain, oral ulcers, cough, nausea, vomiting, and diarrhea are absent. Physical examination reveals an afebrile, tired-appearing child with a periorbital violaceous rash that crosses the nasal bridge. There is no evidence of arthritis, although the patient has an erythematous hypertrophic rash over the knuckles. Which of the following laboratory or diagnostic studies is most consistent with the most likely diagnosis?
   A. Abnormal electromyography findings
   B. Increased serum immunoglobulin levels against Epstein–Barr virus
   C. Positive antinuclear antibody
   D. Positive urine culture for cytomegalovirus
   E. Low creatine kinase levels
4. A 13-year-old previously healthy boy is injured when his scooter collides with a parked car. On arrival at the emergency department, he is unconscious, and you suspect head injury. On examination, he does not open his eyes to voice or to pain. He has decerebrate posturing of the extremities to pain, and he moans with stimulation (you are unable to understand any of his words). Which of the following is this patient's Glasgow coma score (GCS)?
   A. 4
   B. 5
   C. 6
   D. 7
   E. 8
5. A 5-year-old boy has a 2-week history of persistent daily fevers and a 1-week history of pain in his right arm. Physical examination reveals a very pale child with a markedly enlarged liver

and spleen and generalized lymphadenopathy. His right arm is nontender to palpation with normal range of motion. On the basis of his clinical presentation and examination, you suspect acute lymphocytic leukemia (ALL). Which of the following statements about the presenting features of ALL is most accurate?

A. The age at presentation is unusual.
B. Bone pain is a common presenting symptom.
C. The disease is more common in females.
D. Pallor is an uncommon sign at presentation.
E. White blood cell count is almost always high (>50,000 cells/mm^3).

6. A 7-year-old boy presents to the emergency department with swelling in his knee. His parents state that the swelling developed very rapidly over 30 minutes after their son bumped his knee into a door. On physical examination, you note that his knee is very swollen with what appears to be blood. Based on his presentation, you consider an evaluation for hemophilia A. Which of the following statements regarding this diagnostic possibility is correct?

A. Activated partial thromboplastin time (aPTT) is prolonged.
B. Males and females are equally affected.
C. Management includes replacement of factor IX.
D. Bleeding time is prolonged.
E. The cause is a deficiency of a vitamin K–dependent coagulation factor.

7. A 3-year-old boy has a 2-week history of viral upper respiratory symptoms and a 2-day history of swelling around his eyes. Physical examination reveals normal vital signs and moderate periorbital edema, mild scrotal edema, and mild edema of the feet. Urinalysis reveals 3+ proteinuria. Which of the following statements regarding the likely diagnosis is most accurate?

A. Serum cholesterol level is low.
B. He is predisposed to hemorrhage.
C. Should the patient become febrile, management involves administration of empiric antibiotics to cover encapsulated organisms.
D. Referral for a diagnostic renal biopsy is warranted.
E. The patient is not likely to respond to corticosteroid therapy and will likely require treatment with cyclophosphamide or cyclosporin.

8. A 16-year-old girl presents with a 1-week history of gray-white vaginal discharge with a strong "fishy" odor. On physical examination, you confirm the fishy odor and note minimal vulvar inflammation. Which of the following is correct regarding her likely condition?

A. Treatment of her sexual partners is necessary.
B. Wet-mount saline preparation will demonstrate motile protozoa.
C. The infection is caused by a change in the normal vaginal flora.
D. Topical antiyeast medication should be prescribed.
E. Oral doxycycline and intramuscular ceftriaxone should be administered after obtaining appropriate cultures.

9. A 7-year-old girl is brought to the emergency department with a 5-day history of fever, malaise, and anorexia. Her past medical history is significant for aortic stenosis. Physical examination reveals a loud systolic ejection murmur at the cardiac base that radiates to the carotids and a systolic ejection click. Splenomegaly and a petechial eruption on the patient's palms and soles are also present. Laboratory studies reveal a white blood cell count of 19,000 cells/mm^3 and an erythrocyte sedimentation rate of 78 mm/hour. Which of the following statements regarding the most likely diagnosis is correct?

A. Abnormal rheumatoid factor is unusual.
B. Transthoracic echocardiogram is the most sensitive test for detecting vegetations.
C. Gram-negative rods are the most common causative agents.

D. Ophthalmologic evaluation is useful in diagnosis.
E. Antibiotics should be administered promptly without waiting for blood cultures to be drawn.

10. A 6-month-old male infant is referred to you for evaluation of failure to thrive. The parents report that their child has always been a "poor feeder" and they deny any vomiting, diarrhea, or frequent infections. Physical examination reveals generalized weakness with particularly poor head control owing to weakness of the neck flexor muscles. One of the diagnostic possibilities is juvenile myasthenia gravis. Which of the following statements regarding juvenile myasthenia gravis is most accurate?
    A. Most patients with this condition have fasciculations.
    B. This condition is most likely related to ingestion of honey.
    C. Bilateral ptosis is the most common presenting sign of this condition.
    D. Deep tendon reflexes are diminished.
    E. The Tensilon test demonstrates increased weakness.
11. A 6-year-old girl has a history of daily fevers to 102°F (38.9°C) for the past 2 weeks. Preliminary workup and physical examination have not revealed a diagnosis. Which of the following statements regarding this patient's fever of unknown origin (FUO) is correct?
    A. The FUO is likely caused by a rare illness.
    B. The FUO is most likely caused by a rheumatologic disorder.
    C. Hospitalization is not indicated unless the patient becomes more ill.
    D. The FUO is likely to resolve without a diagnosis having been made.
    E. The FUO is likely caused by an unusual presentation of a common infection.
12. You are called to evaluate a 1-day-old infant born at 32 weeks' gestation who develops respiratory distress at 12 hours of life. Which of the following diagnoses is the most likely cause of this infant's respiratory distress?
    A. Meconium aspiration syndrome
    B. Bronchopulmonary dysplasia
    C. Respiratory distress syndrome
    D. Neonatal sepsis
    E. Intraventricular hemorrhage
13. A 7-month-old male infant is born at 29 weeks' gestation. While hospitalized in the neonatal intensive care unit, he develops necrotizing enterocolitis and undergoes a resection of the majority of his small intestine. He is now dependent on total parenteral nutrition for his calories and growth. Which of the following is a complication associated with the treatment of his disorder?
    A. Gastrointestinal bleeding
    B. Gallstones
    C. Chronic constipation
    D. Pancreatic insufficiency
    E. Inflammatory bowel disease
14. A 9-year-old girl is brought to the emergency department after falling off her bicycle. She complains of pain in her right leg. Radiography reveals a tibial fracture that extends from the epiphysis, through the physis, and into the metaphysis. Which of the following is the Salter–Harris grade of this fracture?
    A. Grade I
    B. Grade II
    C. Grade III
    D. Grade IV
    E. Grade V
15. A 6-month-old male infant has an asymmetrically shaped head. A computed tomography scan

of the skull reveals premature closure of a cranial suture. Which of the following is the most likely cause of this condition?

A. Perinatal asphyxia
B. Genetic syndrome
C. Positional, from sleeping on the back
D. Unknown
E. Congenital muscular torticollis

The response options for statements 16 and 17 are the same. You will be required to select one answer for each statement in the following set.

A. Strawberry hemangioma
B. Nevus flammeus
C. Erythema toxicum neonatorum
D. Pustular melanosis
E. Milia
F. Cutis marmorata
G. Acrocyanosis
H. Neonatal acne

For each patient, select the skin lesion described or associated with the clinical presentation.

1. A 6-month-old male infant has seizures. Computed tomography of the head reveals intracranial calcifications.
2. A 5-day-old female infant has papules and pustules on her trunk. Microscopic evaluation of the fluid within a lesion reveals eosinophils.
3. A 16-year-old boy with homocystinuria is on a methionine-restricted diet. He is also taking folic acid and pyridoxine. Which of the following medications should you add to his medical regimen?

   A. Propranolol
   B. Vitamin C
   C. d-Penicillamine
   D. Betaine
   E. Zinc

The response options for statements 19–21 are the same. You will be required to select one answer for each statement in the following set.

A. Turner syndrome
B. Prader–Willi syndrome
C. Kallmann syndrome
D. Laurence–Moon–Biedl syndrome
E. McCune–Albright syndrome

For each patient, select the most likely diagnosis.

1. A 3-year-old girl has bilateral femur fractures and Tanner stage 2 breast development.
2. A 15-year-old girl has delayed puberty and a decreased sense of smell.
3. A 6-month-old infant has hypotonia, small hands and feet, and small gonads. Weight and height are at the fifth percentile.
4. An 18-month-old boy is brought to your clinic by authorities for an examination. Neighbors called the police after they noticed that the child had multiple bruises and appeared

malnourished and unkempt. The police are concerned about possible child abuse. Which of the following findings, by itself, is most suggestive of child abuse?

A. Bruises on the knees, shins, and elbows in different stages of healing
B. Metaphyseal ("corner") fracture of the distal left humerus
C. Burns to the right arm that have an irregular, splashlike configuration
D. Nondisplaced spiral fracture of the left tibia
E. Displaced supracondylar fracture of the right elbow

5. An 11-month-old male infant is brought to your office by his mother. She is concerned because her son coughs and wheezes day and night for 2 weeks after every cold, and he seems to have a cold every month. He uses no medication for these symptoms. He is otherwise well with normal growth and development. The patient's father smokes cigarettes but always away from his son. Which of the following statements about this patient's condition is correct?

A. Asthma is very unlikely because of his young age.
B. A trial of prophylactic inhaled cromolyn sodium may be beneficial.
C. Smoking cigarettes in a separate room should not affect the patient's symptoms.
D. An albuterol inhaler should be prescribed for prevention of his symptoms.
E. Inspiratory and expiratory radiographs should be performed to rule out a foreign body.

6. A 9-month-old male infant is brought to the emergency department in cardiac arrest. His parents found him unconscious, and cardiopulmonary resuscitation was initiated immediately. Which of the following is the most common cause of cardiac arrest in a child?

A. Poisoning
B. Cardiac dysrhythmia secondary to heart disease
C. Seizures
D. Hypoxia
E. Trauma

7. During a routine health maintenance examination, an obese 13-year-old girl is noted to have acanthosis nigricans. Your counseling of the patient includes a discussion of the association between acanthosis nigricans and type 2 diabetes mellitus. Which of the following is also associated with type 2 diabetes mellitus?

A. Human leukocyte antigen (HLA) haplotypes DR3 and DR4
B. Environmental triggers, such as coxsackievirus
C. Islet cell antibodies
D. Peripheral tissue resistance to insulin
E. Insulin antibodies

8. A 7-month-old male infant is brought to your office with a 1-month-long history of fussiness, intermittent vomiting, and nonbloody, foul-smelling stools. He has not gained weight since his 6-month health maintenance examination. His diet consists of formula and wheat cereal that was introduced at 6 months of age. Which of the following is the most likely diagnosis?

A. Lactase deficiency
B. Celiac disease
C. Crohn disease
D. Gastroesophageal reflux disease
E. Cow's milk protein intolerance

9. You are called urgently to the newborn nursery to evaluate a "blue" infant. On administration of 100% oxygen, there is no significant increase in the patient's PaO^2. Which of the following is the most likely diagnosis?

A. Neonatal pneumonia
B. Tetralogy of Fallot
C. Respiratory distress syndrome
D. Truncus arteriosus

E. Meconium aspiration syndrome

10. A 3-year-old girl is diagnosed with cervical adenitis and is discharged home with a 7-day course of amoxicillin–clavulanic acid. Five days into therapy, she presents for reevaluation with no decrease in the size of the enlarged cervical node. The child's fevers have also been persistent. Physical examination is remarkable for a febrile toddler with conjunctivitis, pharyngitis, right anterior cervical adenopathy (the node is 2 cm in diameter), and an erythematous macular rash on the chest and back. Which of the following courses of management would be most appropriate at this time?
    A. Send the patient home on oral penicillin with a presumptive diagnosis of scarlet fever.
    B. Perform a tuberculin skin test and discharge the patient on oral dicloxacillin, with follow-up in 48 hours.
    C. Admit the patient for a rule-out sepsis workup that includes evaluation of the blood, urine, and cerebrospinal fluid for bacterial infection.
    D. Admit the patient for high-dose intravenous immune globulin therapy.
    E. Admit the patient for high-dose corticosteroid therapy.

The response items for statements 29 and 30 are the same. You will be required to select one answer for each statement in the following set.

A. Dilated cardiomyopathy
B. Hypertrophic cardiomyopathy
C. Restrictive cardiomyopathy

For each patient, select the associated cardiomyopathy.

1. A female newborn is born at full term by cesarean section weighing 9 pounds 8 oz. Her mother developed diabetes during pregnancy. The newborn is admitted to the neonatal intensive care unit because of tachypnea. On examination, a harsh systolic ejection murmur is heard.
2. A 12-year-old boy presents to the emergency department after an episode of chest pain that occurred during baseball practice. Electrocardiography reveals evidence of myocardial infarction. Because of this unusual presentation, you suspect he may have anomalous origin of the left coronary artery from the pulmonary artery.
3. A 3-year-old girl is brought to the office with a 2-week history of melena. Physical examination and vital signs are normal. A complete blood count reveals a hemoglobin of 6 g/dL. Which of the following is the next most appropriate step to evaluate the cause of her anemia and bleeding?
    A. Computed tomography of the abdomen
    B. Meckel scan
    C. Colonoscopy
    D. Chest and abdominal radiography
    E. Upper endoscopy
4. A 3-year-old boy is brought to the office for evaluation of a rash. The parents report that 1 week earlier he had the "stomach flu," characterized by fever, abdominal pain, and foul-smelling loose stools with occasional blood streaks. The gastrointestinal symptoms resolved spontaneously. For the past 2 days, he has been less active than usual and somewhat irritable with a decreased appetite. On physical examination, the patient is irritable but consolable, with mild periorbital edema, pale mucous membranes, and a petechial eruption on the abdomen. Laboratory studies reveal a leukocyte count of 12,000 cells/mm^3, a hemoglobin count of 7.5 g/dL, and a platelet count of 34,000/μL. The serum creatinine is 1.4 mg/dL. Which of the following statements regarding this patient's most likely diagnosis is most accurate?

A. The thrombocytopenia is most likely caused by antibody-mediated destruction.
B. Antibiotic therapy is not indicated.
C. The anemia is most likely secondary to blood losses associated with his prior episodes of bloody diarrhea.
D. The prognosis is poor.
E. The most common pathogen associated with this condition in North America is *Shigella dysenteriae* type 1.

5. The parents of an 18-month-old girl return to see you for a follow-up of their child's anemia. You prescribed iron (5 mg/kg per day) when you discovered that the girl had a microcytic, hypochromic anemia with a hemoglobin (Hgb) of 10.1 g/dL on routine anemia screening. Today, her Hgb is 10 g/dL despite iron therapy for the past 3 months. She is asymptomatic. Which of the following is an appropriate course of management at this time?
   A. Represcribe iron and suggest that it be given daily with orange juice.
   B. Represcribe iron and suggest that it be given daily with whole cow's milk.
   C. Consider referral for a red blood cell transfusion if the Hgb does not respond to iron within the next month.
   D. Order an Hgb electrophoresis and iron level to rule out other causes of anemia before restarting iron.
   E. Prescribe folic acid.
6. The parents of a 3-month-old female infant are concerned about their child's vomiting. For the past 6 weeks, their daughter has spit up after each feed. She takes both breast milk and a cow's milk–based formula and spits up after either is given. She does not seem bothered by the spitting up, and her parents deny that she has diarrhea, fever, cough, apnea, cyanosis, or discomfort. She weighed 7 pounds 4 oz at birth and now weighs 11 pounds 1 oz. Physical examination is normal. Which of the following is the most appropriate next step in management?
   A. Provide education and reassurance that her spitting up is common and normal and will resolve without treatment.
   B. Order a pH probe study to document gastroesophageal reflux.
   C. Change her diet to a hydrolyzed amino acid formula.
   D. Prescribe an H^2-blocker as a therapeutic trial.
   E. Order a barium upper gastrointestinal study to evaluate the esophagus, stomach, and duodenum.
7. The mother of a 2-year-old girl calls you urgently, concerned that her child fell in the backyard and traumatically avulsed her maxillary incisor. Which of the following is the most appropriate management at this time?
   A. The mother should wrap the tooth in a clean, dry towel and bring the tooth to the dentist within 24 hours.
   B. The mother should store the avulsed tooth in milk and seek emergency dental care immediately.
   C. The mother should scrub the tooth, rinse it with water, and replace it in the socket.
   D. The mother should replace the tooth in the socket and seek emergency dental care immediately.
   E. No intervention is required.
8. A 3-year-old boy is brought to the office with a 1-week history of upper respiratory symptoms and the acute onset of a limp. Physical examination is notable for a petechial eruption on the thighs. Laboratory analysis reveals a normal platelet count. Which of the following statements regarding the most likely diagnosis is most accurate?
   A. This patient has a multiorgan system vasculitis associated with increased serum IgE levels.

B. Recurrences of this condition are rare.
C. Steroids are contraindicated for the treatment of this condition.
D. The rash in this condition typically begins on the palms and soles.
E. The renal manifestations of this condition may not become clinically apparent for up to 3 months after the initial presentation.

9. A 4-year-old previously healthy boy is brought to the emergency department after being bitten by a dog 18 hours ago. He has two small puncture wounds on his left wrist. Which of the following regarding the dog bite in this patient is correct?
   A. Wound irrigation is the most appropriate initial treatment.
   B. The wound should be sutured.
   C. Infection, if it develops, is most commonly caused by *Bartonella henselae.*
   D. Antibiotics should be withheld until infection is clinically present.
   E. Tetanus immunization is not needed for dog bites.

The response items for statements 38–41 are the same. You will be required to select one answer for each statement in the following set.

A. Topical tobramycin drops
B. Topical acyclovir drops
C. Baby shampoo scrubs of the eyelids
D. Topical mast cell stabilizer drops
E. Oral erythromycin
F. Oral acyclovir
G. Intravenous penicillin

For each patient, select the most appropriate initial management.

1. A 7-day-old male infant with bilateral conjunctival discharge.
2. An 8-year-old girl with burning, crusting, and scales at the eyelash base.
3. A 9-month-old female infant with purulent conjunctival discharge.
4. A 3-year-old boy with conjunctival redness, itching, and watery discharge.
5. A 6-year-old boy is brought to the office with complaints of sore throat, mild fatigue, and headache for 2 days. On physical examination, he is febrile to 38.3°C (101°F) and is well hydrated, comfortable, and without distress. White exudates on his tonsils and anterior cervical lymphadenopathy are present. Which of the following is the most important initial management step?
   A. Initiate antibiotic therapy for "strep throat."
   B. Order a monospot test.
   C. Obtain a throat culture.
   D. Recommend supportive care with acetaminophen and throat lozenges.
   E. Obtain a lateral neck radiograph.
6. You are called to the emergency department to evaluate a 3-year-old girl referred for evaluation of a 2-day history of fever, emesis, and progressive lethargy. Computed tomography of the head demonstrates marked dilation of the ventricular system consistent with communicating hydrocephalus. Which of the following is the most likely cause of this condition?
   A. Brain atrophy
   B. Chiari type II malformation
   C. Bacterial meningitis
   D. Aqueductal stenosis
   E. Dandy–Walker malformation

The response options for statements 44 and 45 are the same. You will be required to select one answer for each statement in the following set.

A. Vitamin A deficiency
B. Vitamin B^1 deficiency (thiamine)
C. Vitamin B^6 deficiency (pyridoxine)
D. Vitamin B^{12} deficiency (cobalamin)
E. Vitamin C deficiency
F. Vitamin D deficiency
G. Vitamin K deficiency

For each patient, select the most likely vitamin deficiency.

1. A 2-year-old boy is a "picky" eater and has anemia, swollen gums, and a deep abrasion to the right leg that has taken almost 3 weeks to heal.
2. A 4-year-old girl has dry eyes and difficulty seeing in the dark.
3. A 17-year-old boy presents with dysuria and increased urinary frequency. He has had several sexual partners and indicates that he uses condoms "most of the time." Which of the following statements regarding the likely diagnosis is correct?
   A. Trimethoprim–sulfamethoxazole should be given for a presumed urinary tract infection.
   B. Evidence of greater than five white blood cells per high-power field on a Gram stain of his urethral secretions is sufficient for a presumptive diagnosis.
   C. This diagnosis is more common in females.
   D. The causative agents almost always cause symptoms that lead to the diagnosis.
   E. Obtaining a culture from a urethral swab is the only method that provides a definitive diagnosis.
4. A 7-year-old boy is brought to the office with a 3-day history of painful swelling anterior to his left ear. On physical examination, a small amount of pus can be expressed from Stensen duct. Which of the following statements regarding the most likely diagnosis is correct?
   A. Placement of a skin test for tuberculosis should be considered.
   B. Supportive care for probable mumps infection is indicated.
   C. Epstein–Barr virus or cytomegalovirus infection is the most likely cause of the infection.
   D. Surgery should be immediately consulted to drain the infection.
   E. Antibiotics to cover *Streptococcus pneumoniae* are indicated.
5. The parents of a 6-week-old male infant bring him to the office for an evaluation because of concerns about their infant's color. They note that he turns "purple" whenever he cries and is very fussy. He is otherwise well. He feeds vigorously, and his weight is 1 pound 3 oz above his birth weight. He is pink and happy when not crying. On physical examination, a systolic murmur is heard at the upper left sternal border. Which of the following is the most likely diagnosis?
   A. Transposition of the great arteries
   B. Tetralogy of Fallot
   C. Tricuspid atresia without a ventricular septal defect
   D. Total anomalous pulmonary venous connection
   E. Truncus arteriosus

The response items for statements 49–53 are the same. You will be required to select one answer for each statement in the following set.

A. Seborrheic dermatitis
B. Contact dermatitis

C. Tinea corporis
D. Pityriasis rosea
E. Miliaria rubra
F. Psoriasis
G. Fifth disease

For each patient, select the most likely diagnosis.

1. An 8-year-old boy has oval scaly erythematous patches on the upper extremity with partial central clearing.
2. A 15-year-old boy has red greasy scales and crusts in the nasolabial skin folds.
3. A 13-year-old girl has scaling papules and plaques. When she injures her skin, new lesions develop at the site of the trauma.
4. A 6-month-old female infant has small erythematous pruritic papules on the chest and neck in the summertime.
5. A 3-year-old boy has erythematous papules in a "Christmas tree" distribution on the trunk.
6. An 18-month-old boy with a history of myelomeningocele repair at birth and subsequent ventriculoperitoneal shunt placement is brought to the office for a routine health maintenance visit. Medical history is also significant for an extensive stay in the neonatal intensive care unit, which was complicated by sepsis. Since the neonatal period, he has been relatively well, although his mother notes occasional rashes described as "red welts." Considering this patient's medical history, this patient is most likely to be allergic to which of the following?
   A. Penicillin
   B. Cow's milk protein
   C. Dust mites
   D. Latex
   E. Wool
7. At birth, a newborn has thrombocytopenia, enlarged liver and spleen, hearing loss, heart murmur, and bilateral cataracts. His mother recalls a brief viral illness during her first trimester of pregnancy. Congenital infection with which of the following organisms is the most likely cause of this infant's symptoms?
   A. Toxoplasmosis
   B. Rubella
   C. Varicella
   D. Herpes simplex virus
   E. Cytomegalovirus
8. An infant is brought to the office for a routine health maintenance visit. The infant can sit with support, vocalize with mixed vowel and consonant sounds, and has just learned to transfer objects from hand to hand. Which is the most likely age of this infant?
   A. 4 months of age
   B. 6 months of age
   C. 8 months of age
   D. 9 months of age
   E. 10 months of age
9. A 4-year-old girl is brought to the office with a persistent cough. Her mother is concerned because she has had a wet-sounding cough for the past 4–5 months without improvement. Past medical history is significant for three episodes of pneumonia in the past 18 months; each episode was treated with antibiotics. Her mother is also concerned that she has been underweight for the past 12 months. On physical examination, the patient is afebrile, and her respiratory rate is 24 breaths/minute. Her weight and height are both less than the fifth percentile. Lung examination reveals diffuse crackles and wheezes. Which of the following

tests would reveal her most likely underlying diagnosis?

A. Chest radiograph
B. Sputum culture
C. Sweat chloride assessment
D. Bilateral decubitus radiographs
E. Cold agglutinins

The response options for statements 58–60 are the same. You will be required to select one answer for each statement in the following set.

A. Viral meningitis
B. Bacterial meningitis
C. Tuberculous meningitis
D. Partially treated bacterial meningitis
E. Brain abscess
F. Fungal meningitis

For each patient, select the most likely diagnosis.

1. A 14-month-old boy has fever and irritability. Cerebrospinal fluid (CSF) analysis reveals a white blood cell (WBC) count of 7500 cells/mm^3 with a polymorphonuclear leukocyte predominance, a low glucose, and a high protein.
2. A 5-year-old girl has had fevers for 2 weeks and is now confused and sleepy. Cerebrospinal fluid (CSF) analysis reveals a white blood cell (WBC) count of 200 WBCs/mm^3 with a lymphocyte predominance, a very low glucose, a very elevated protein, and a negative Gram stain.
3. A 9-year-old boy presents with headache, photophobia, and 1 day history of fever. Cerebrospinal fluid (CSF) analysis reveals a white blood cell (WBC) count of 350 WBCs/mm^3 with a polymorphonuclear leukocyte predominance, a normal glucose, a normal protein, and a negative Gram stain.
4. A 6-week-old male infant is brought to the office in September with a 2-day history of cough and increased work of breathing. Past medical history is significant for vaginal delivery without complications at 38 weeks. At 10 days of age, he was treated with erythromycin ointment for conjunctivitis. On physical examination, the patient is afebrile. He is coughing rapidly and has a respiratory rate of 54 breaths/minute. Diffuse wheezes are present throughout the lung fields along with mild subcostal retractions. Which of the following is the most likely cause of the patient's signs and symptoms?
   A. *Mycoplasma pneumoniae*
   B. *Chlamydia trachomatis*
   C. Respiratory syncytial virus
   D. *Streptococcus pneumoniae*
   E. Asthma
5. A 13-year-old boy has a 3-hour history of severe pain in his right scrotum. On physical examination, his right testicle is diffusely tender and swollen. The right cremasteric reflex is absent. Which of the following statements regarding this patient's likely diagnosis is correct?
   A. Radionuclide imaging will demonstrate increased uptake to the right testicle.
   B. Definitive diagnosis can be made on the basis of relief of pain when the right testicle is elevated.
   C. Management includes oral doxycycline and oral cefixime for presumptive epididymitis.
   D. Surgery consultation within the next 12 hours is indicated for possible surgical intervention.

E. Surgical intervention will involve both testicles.

6. A 7-year-old boy is brought to the office with a 6-month history of daytime enuresis. Which of the following findings would be most important in prompting you to order imaging studies?
   A. Positive family history of enuresis in the patient's father, who wet the bed until he was 12 years of age
   B. Onset of symptoms when the parents separated
   C. Abnormal anal wink reflex
   D. Constipation without encopresis
   E. Frequent voiding of small amounts of urine

The response items for statements 64–66 are the same. You will be required to select one answer for each statement in the following set.

A. Acute dactylitis
B. Sequestration crisis
C. Acute chest syndrome
D. Hyperhemolytic crisis
E. Aplastic crisis

For each patient with sickle cell disease, select the type of sickle cell crisis.

1. A 3-year-old boy has pallor, jaundice, and fatigue. He has an increased reticulocyte count, increased bilirubin level, and decreased hemoglobin (Hgb).
2. A 4-year-old girl has pallor and fatigue. Her reticulocyte count and hemoglobin (Hgb) levels are decreased.
3. A 2-year-old boy has pallor, fatigue, tachycardia, and hypotension. His reticulocyte count is high, and his hemoglobin (Hgb) level is low.
4. A 4-month-old female infant is brought to the office for a routine health maintenance visit. Which of the following motor skills accurately describes the expected developmental abilities of this infant?
   A. When the infant is pulled from a supine to a sitting position, her head lags behind her shoulders.
   B. In the prone position, the infant can raise her head slightly but cannot push up with her arms.
   C. In the prone position, the infant can push up using her arms and hold her head up.
   D. When pulled from a supine to a sitting position, the infant anticipates the movement and leads with her head.
   E. In the prone position, the infant can roll to a supine position and can then get into a sitting position.
5. A 15-month-old boy is brought to the office for a routine health maintenance visit. His parents are concerned that he has not yet started to walk. Other motor milestones and verbal milestones are on target. On examination, you note normal strength and movement of all extremities; however, his thigh folds are asymmetric, and there appears to be a limb length discrepancy of 1 inch. Which of the following is the most likely diagnosis?
   A. Transient synovitis
   B. Developmental hip dysplasia
   C. Legg–Calvé–Perthes disease
   D. Femoral anteversion
   E. Slipped capital femoral epiphysis

The response items for statements 69–71 are the same. You will be required to select one answer

for each statement in the following set.

A. Wilms tumor
B. Neuroblastoma
C. Lymphoma
D. Pheochromocytoma
E. Rhabdomyosarcoma

For each patient, select the most likely malignancy.

1. A 3-year-old girl presents with the acute onset of an unsteady gait. On physical examination, she has random jerking eye movements in all directions, myoclonus, and ataxia with ambulation.
2. A 18-month-old girl presents for a routine health maintenance evaluation. On physical examination, she has a left-sided abdominal mass, absence of her bilateral irides, and hypertrophy of her right thigh and right leg.
3. A 5-month-old female infant diagnosed with an abdominal malignancy has a localized tumor with metastases to her bone marrow and right femur. Without treatment, her tumor regresses.
4. A 23-day-old male infant has a 2-day history of streaks of blood and mucus with each stool. His parents report no fever, vomiting, or ill contacts. Which of the following is the most likely cause of his symptoms?
   A. Juvenile polyp
   B. Meckel diverticulum
   C. Infectious enterocolitis
   D. Allergic colitis (protein intolerance)
   E. Inflammatory bowel disease

The response options for statements 73 and 74 are the same. You will be required to select one answer for each statement in the following set.

A. Head ultrasound
B. Dental evaluation
C. Ophthalmologic evaluation
D. Thyroid screen
E. Flexion and extension cervical spine radiographs

For each patient, select the most appropriate screening test to be used to evaluate for a complication of the condition.

1. A short 16-year-old girl with delayed puberty, a webbed neck, and shield chest.
2. A 4-year-old boy with fragile bones, easy bruisability, and blue sclerae.
3. You are called to the emergency department to evaluate a severely ill 5-year-old child who collapsed while at kindergarten. On physical examination, you find a comatose child whose respirations are irregular with no particular pattern. This patient's respiratory pattern is most suggestive of which of the following?
   A. Cerebellar injury
   B. Cerebral stroke
   C. Narcotic ingestion
   D. Impending brain death
4. A 3-year-old boy recently adopted from an international adoption agency is referred to you for evaluation of short stature. The details of the patient's past medical history are unknown. Physical examination reveals an alert child whose weight is at the third percentile and whose

height is well below the third percentile for age (50th percentile for a 16-month-old child). The patient's upper-to-lower body segment ratio is high (i.e., above the expected ratio for age). Which of the following causes might explain this patient's short stature?

A. Malnutrition
B. Child neglect
C. Growth hormone deficiency
D. Fetal alcohol syndrome
E. Rickets

5. A previously healthy 4-year-old boy is admitted to the hospital for a 5-day history of fever and severe right leg pain. There is no history of trauma. On examination, the boy is nontoxic; however, his right tibia above the ankle is warm, erythematous, and indurated. You suspect he may have osteomyelitis. Which of the following statements regarding this diagnosis is correct?
   A. A plain radiograph demonstrates periosteal elevation and should be the initial diagnostic study.
   B. The infection was most likely acquired by hematogenous seeding.
   C. The most likely pathogen is *Salmonella typhi.*
   D. Blood culture will be positive in almost all patients with osteomyelitis.
   E. An oral first-generation cephalosporin should be started for outpatient treatment of osteomyelitis because the child is nontoxic.
6. You are performing an initial physical examination on a term newborn in the delivery room. The presence of which of the following leads you to suspect an underlying congenital anomaly?
   A. Umbilical hernia
   B. Hypospadias
   C. Single umbilical artery
   D. Nevus simplex on the right upper eyelid
   E. Diastasis recti
7. A 17-year-old boy presents to your office for a routine health maintenance evaluation. He has been well with the exception of some fatigue for the past few months and vague, nonspecific discomfort in his abdomen. On physical examination, the spleen is significantly enlarged, extending down to the left lower quadrant of his abdomen. On the basis of his symptoms and the splenomegaly, chronic myelogenous leukemia is in your differential diagnosis. Which of following statements regarding the most likely type of chronic myelogenous leukemia in this patient is correct?
   A. Further examination will likely reveal an eczematous-like facial rash and petechiae.
   B. The Philadelphia chromosome is present on cytogenetic analysis of leukemic cells.
   C. Radiation therapy is effective.
   D. The illness is very likely to be fatal within months.
   E. The white blood cell count will likely be $^{<}30{,}000$ cells/mm^3.
8. A 6-year-old girl who lives in Vermont develops fever, headache, muscle and joint aches, and several enlarged lymph nodes. On physical examination, an erythematous ringlike skin rash with a clear center is evident on her trunk. Which of the following would be the most appropriate treatment at this time?
   A. Oral doxycycline
   B. Oral amoxicillin
   C. Intravenous penicillin
   D. Intravenous ceftriaxone
   E. No antibiotic treatment
9. An 18-month-old female infant is brought to the office with a 3-day history of nasal congestion

and rhinorrhea. Today she developed a fever with temperature up to 38.3°C (101°F) and a barky cough. She is eating well and has remained active. On initial evaluation in the emergency department, she has a normal respiratory rate with no respiratory distress, is playful, and has no stridor. However, when you begin your examination, she begins to cry and immediately you hear inspiratory stridor. As she calms down, the stridor resolves completely. The remainder of the examination is normal. Which of the following should be your management approach?

A. Supportive care only
B. A 10-day course of oral corticosteroids
C. Nebulized albuterol
D. Nebulized racemic epinephrine
E. Nebulized ribavirin

10. A 3-year-old boy has a focal seizure involving his left arm and left leg. Computed tomography (CT) of the head reveals a calcified cyst within the brain parenchyma. Which of the following statements regarding the most likely diagnosis is correct?

A. Surgical excision of the cyst is indicated.
B. Anticonvulsant therapy alone is indicated.
C. Ingestion of contaminated poultry is the likely cause.
D. Ova and parasite stool examination is a reliable and sensitive diagnostic technique.
E. The cyst noted on CT scan is evidence of active infection.

11. A 13-year-old girl who resided outside of the United States for 6 months visited a physician while abroad for knee and ankle pain. She was diagnosed with systemic lupus erythematosus (SLE). She now has returned to the United States, and she is brought to your office for a second opinion. She currently has no symptoms other than mild joint pains. A negative or normal result of which of the following tests makes the diagnosis of SLE most dubious?

A. Erythrocyte sedimentation rate
B. Anti–double-stranded DNA antibody
C. Anti-Smith antibody
D. Antinuclear antibody
E. Rheumatoid factor

The response items for statements 84–88 are the same. You will be required to select one answer for each statement in the following set.

A. Naloxone
B. Oxygen
C. Deferoxamine
D. Ethanol
E. Atropine
F. Pyridoxine
G. Diphenhydramine
H. *N*-acetylcysteine
I. Flumazenil
J. Glucagon
K. d-Penicillamine
L. Pralidoxime

For each poisoning, select the appropriate antidote.

1. A 15-month-old boy has severe vomiting and bloody stools 3 hours after swallowing 30 prenatal vitamin tablets.

2. A 15-year-old girl has vomiting and abdominal pain 2 hours after swallowing 18 extra-strength acetaminophen tablets.
3. A 6-year-old boy presents in the winter with acute onset of headache, vomiting, confusion, blurry vision, and slurred speech. On examination, his skin is cherry red in color.
4. An 8-year-old boy who is developmentally delayed presents with seizures. His mother found an empty bottle of isoniazid recently prescribed for tuberculosis infection in his bedroom.
5. A 4-year-old girl develops dystonia while being treated with an antiemetic (a phenothiazine) for acute gastroenteritis.
6. A 15-year-old sexually active girl presents with a 6-month history of frequent painful irregular menstrual periods. She describes her periods as occurring every 2–3 weeks and each lasting 10–12 days. The amount of bleeding is very heavy. Which of the following statements regarding her condition is correct?
   A. The term menometrorrhagia describes the vaginal bleeding.
   B. Management involves hormonal contraception; pelvic examination is not necessary.
   C. The bleeding is likely secondary to excessive progesterone production.
   D. Laboratory testing is not indicated because her diagnosis is a clinical diagnosis.
   E. Dilation and curettage is indicated.
7. A 5-year-old boy is brought to the emergency department. His parents state that he is unable to walk. On physical examination, the patient is afebrile with normal vital signs. He is very irritable and scared. Neurologic examination shows significant symmetric weakness and diminished deep tendon reflexes in the lower extremities. Strength and deep tendon reflexes of the upper extremities are preserved. Sensation is normal in both the upper and lower extremities. Which of the following features is most consistent with the most likely diagnosis?
   A. Symmetric descending paralysis
   B. Elevated cerebrospinal fluid protein with low cell counts
   C. Normal nerve conduction studies
   D. Abnormal spinal magnetic resonance imaging
   E. Concurrent diarrheal infection with *Clostridium botulinum*
8. A 3-year-old boy is brought to your office for evaluation of a limp. For the past 2 days he has been limping and crying intermittently, saying that he is in pain and pointing to his left thigh. The patient has been afebrile, and his parents deny any trauma. Medical history further reveals an upper respiratory infection 2 weeks ago that resolved rapidly. On physical examination, the boy appears healthy but anxious, and he refuses to walk. His temperature is 36.4°C (97.6°F). When lying on the examination table, he holds his left hip in external rotation and abduction. Movement of his left hip results in mild pain. Laboratory evaluation reveals a white blood cell count of 11,000 cells/mm^3 and an erythrocyte sedimentation rate of 18 mm/hour. Which of the following is the most likely diagnosis?
   A. Septic arthritis of the hip
   B. Osteomyelitis of the hip
   C. Slipped capital femoral epiphysis
   D. Transient synovitis
   E. Toddler's fracture
9. During a routine health maintenance visit, the mother of a 3-year-old boy expresses concern that her son has had "too many infections." On further questioning, you discover he had pneumonia at 6 months of age and at 20 months of age, and "many, many ear infections" since infancy. Most recently, he was treated with a 2-week course of antibiotics for suspected sinusitis. Despite these infections, the child has been growing and developing normally. Which of the following laboratory studies would confirm the most likely diagnosis?
   A. Complete blood count
   B. Anergy skin test

C. Quantitative serum IgA level
D. Assessment of T-cell response to mitogens
E. Total hemolytic complement

10. The parents of a 4-year-old boy are concerned about their son's bowed legs. The bowing has been apparent ever since he began to walk. However, they are a bit concerned now because the bowing in his right leg has become more pronounced, whereas his left leg appears to be improving. On physical examination, the right leg is bowed laterally to a greater degree than his left leg, and when he walks, his body shifts laterally away from midline. Which of the following is the most appropriate management of this patient?
    A. Standing anterior–posterior radiograph of the lower extremities
    B. Referral for physical therapy to strengthen the muscles of the lower extremities
    C. Parental reassurance that the condition is genu varum and will resolve without treatment
    D. Parental reassurance that the condition is genu valgum and will resolve without treatment
    E. Referral to a podiatrist for orthotic shoes
11. A 9-year-old girl has a 2-week history of restlessness, episodes of excessive crying, and increased difficulty writing her name. Magnetic resonance imaging of her head is normal. Which of the following is the most likely diagnosis?
    A. Migraine
    B. Complex partial epilepsy
    C. Sydenham chorea
    D. Hydrocephalus with increased intracranial pressure
    E. Tourette syndrome
12. A 12-year-old boy returns from a camping trip in the Arkansas mountains. He has fever and severe headache. As you are examining him, a petechial rash suddenly appears on his hands and feet. Which of the following statements regarding the most likely cause of his illness is correct?
    A. The illness is caused by infection with a spirochete.
    B. Definitive serologic evidence of infection should be obtained before the initiation of therapy.
    C. Thrombocytopenia and anemia may be present.
    D. Prophylactic antibiotics are indicated to prevent this infection.
    E. Incidence of infection is highest in infants and very young children.
13. A 10-year-old boy presents with fever, hypotension, diarrhea, and diffuse erythroderma of the skin. Nikolsky sign is absent. Laboratory studies reveal thrombocytopenia and an elevated creatine kinase. Cultures of his blood, urine, and cerebrospinal fluid are negative. Which of the following is the most likely cause of the infection?
    A. Group A β-hemolytic streptococcus
    B. *Borrelia burgdorferi*
    C. *Staphylococcus aureus*
    D. Kawasaki disease
    E. *Escherichia coli* O157:H7

The response options for statements 97–100 are the same. You will be required to select one answer for each statement in the following set.

A. High serum ceruloplasmin
B. Low serum copper
C. High serum copper
D. Low serum zinc
E. Low serum calcium

F. High serum calcium
G. Low serum glucose
H. High serum ammonia

For each patient, select the likely laboratory finding.

1. A 12-year-old boy with ataxia, seizures, abnormal behavior, elevated transaminases, and yellowish discoloration of the peripheral cornea.
2. A 6-year-old boy with myoclonic seizures, mental retardation, and hair that is easily breakable and unmanageable.
3. A 12-month-old boy with vesicles and scales in the diaper area, failure to thrive, and chronic diarrhea.
4. A 2-year-old boy with interrupted aortic arch, recurrent fungal infections, a small chin, and short palpebral fissures.
5. On routine examination in the newborn nursery, a healthy 2-day-old female infant born at 39 weeks' gestation is incidentally noted to have a palpable abdominal mass. The infant is otherwise asymptomatic. She is feeding, voiding, and stooling appropriately. Which of the following is the most common etiology?
   A. Wilms tumor
   B. Hepatomegaly
   C. Ovarian torsion
   D. Hydronephrosis
   E. Neuroblastoma
6. A 1-day-old full-term male infant is having difficulty feeding with frequent episodes of emesis immediately after feeding. He is transferred to the neonatal intensive care unit, and passage of an oral gastric tube is attempted. The tube is met with resistance, and a chest radiograph confirms the tube is in the upper part of the thorax. On reviewing the infant's prenatal course, which of the following would be the most likely finding?
   A. Hepatomegaly
   B. Oligohydramnios
   C. Meconium-stained amniotic fluid
   D. Congenital diaphragmatic hernia
   E. Polyhydramnios

The response items for statements 103–105 are the same. You will be required to select one answer for each statement in the following set.

A. First-degree atrioventricular (AV) block
B. Second-degree AV block, type I
C. Second-degree AV block, type II
D. Third-degree AV block
E. Long QT Syndrome
F. Wolff–Parkinson–White
G. Supraventricular tachycardia

For each scenario, select the most likely arrhythmia.

1. This heart block is associated with children born to mothers with systemic lupus erythematosus (SLE).
2. Risk for lethal ventricular arrhythmias, particularly torsades de pointes
3. Progressive prolongation of the PR interval leading to failed atrioventricular (AV) conduction
4. A 17-year-old female patient with a strict and restrictive vegan diet for the last 3 years presents

to clinic with increasing symptoms of fatigue, clumsiness and pallor for the last several months. On examination, she is noted to have a smooth red tongue, hyporeflexia and mild gait ataxia. Which of the following abnormalities in the laboratory finding would be most likely?

A. Macrocytic anemia
B. Hyponatremia
C. Low white blood cell count
D. Normocytic anemia
E. Prolonged international normalized ratio (INR)

The response items for statements 107–109 are the same. You will be required to select one answer for each statement in the following set.

A. Down syndrome
B. Trisomy 18
C. Trisomy 13
D. Ataxia telangiectasia
E. Turner syndrome (XO)
F. Klinefelter syndome (XYY)
G. CHARGE syndrome

Select the most likely genetic condition associated with the following hematologic/oncologic disorders.

1. A 17-year-old female with gonadoblastoma.
2. A 4-year-old child with transient myeloproliferative disorder who goes on to develop acute myelogenous leukemia.
3. An 11-year-old with recurrent sinopulmonary infections, chronic lung disease, and newly diagnosed lymphoma.
4. The parents of a 3-year-old boy bring him to clinic because of concern that he is walking "pigeon toed". The child began to walk at age 12 months and has had no other developmental concerns. He has no pain, limp, or frequent falling. On examination, the patient has a normal gait with mild, symmetric intoeing. His thigh–foot angle has 0° of external rotation. Which of the following is the most likely diagnosis?
   A. Femoral anteversion
   B. Internal tibial torsion
   C. Genu varum
   D. Talipes equinovarus
   E. Metatarsus adductus
5. Your office receives a call from the newborn screening office that a 1-day-old female infant had an elevated thyroid-stimulating hormone (TSH) level on the newborn screen. What should be your next step?
   A. Contact the family next week.
   B. Begin levothyroxine.
   C. Contact the family and obtain a TSH and thyroxine (T4) immediately.
   D. Refer to pediatric endocrinology.
   E. Order a thyroid ultrasound.
6. You are performing a well-child examination on a 12-year-old male. The parents express concern that members of the family did not enter puberty until very late. They ask you if their son has started puberty. As you begin your physical examination, which of the following is the most common initial sign of puberty in a male?
   A. Voice change

B. Apocrine odor
C. Facial hair
D. Growth spurt
E. Testicular enlargement

7. A 7-month-old male infant presents to your office with a history of fever with temperature up to 103°F over the last 24 hours. He vomited twice, is not taking fluids well, and is irritable. He had prenatal hydronephrosis, and his family history is positive for a kidney transplant owing to vesicoureteral reflux in his paternal uncle. On examination, he is an alert but irritable infant. His temperature is 39°C, and he is tachycardic. He is uncircumcised, and his belly is soft but mildly tender to palpation. Otherwise his examination is normal. White blood cell (WBC) count is 18,000 with a left shift. A bagged urine sample shows 30–40 WBCs and positive nitrites. His serum creatinine is 0.7. What are the next appropriate steps?
   A. Obtain a catheterized urine culture, start empiric antibiotics until the culture results are back, and follow up in the office in 2 weeks.
   B. Obtain a catheterized urine culture, admit to the hospital for intravenous antibiotics, obtain a renal ultrasound, and schedule a voiding cystourethrogram for 2 weeks later.
   C. Obtain a catheterized urine culture, start empiric antibiotics, and schedule a renal ultrasound and voiding cystourethrogram for the next day.
   D. Obtain a catheterized urine culture but wait for the results before starting antibiotics.
   E. Obtain a bagged urine culture, treat with antibiotics, but do no imaging studies, as vesicoureteral reflux is a benign condition.
8. A 7-year-old female is noted to have a low-pitched continuous murmur. The murmur is noted mostly along the superior portion of the right sternal border. The murmur seems loudest when the patient is standing, and it disappears when she is supine. The patient is otherwise healthy and has no cardiovascular symptoms other than some occasional dizziness. Which of the following would you explain to the parents as the source of this murmur?
   A. Turbulence within the carotid artery
   B. A humming noise resulting from vibration as blood returns to the heart
   C. The residua of a fetal connection between the aorta and the pulmonary artery
   D. Transmission of heart sounds from the aortic valve
   E. A “musical” functional murmur due to turbulence as blood leaves the heart
9. A 15-year-old male with asthma complains of chest pain with running. He visits your office after experiencing one episode of syncope while running. He remembers very little about this episode, just that he “woke up on the ground.” The pain he experiences while running started about 2 weeks ago and is described as sharp and over the left precordium. It has not changed in character, and it gets better when he stops running. His physical examination is normal. Which of the following is the next best step in management of this patient?
   A. Increase the frequency and intensity of his asthma treatment
   B. Electrocardiogram and immediate consultation with a pediatric cardiologist
   C. Referral to a pediatric pulmonary specialist
   D. Chest x-ray
   E. Reassurance and allow the patient to return to normal activities
10. A 14-year-old female has the onset of sharp chest pain and shortness of breath several days after an upper respiratory infection. The pain is described as “sharp,” and is worse lying down. She feels much better sitting up. On examination, she is in mild respiratory distress and has a fever with a temperature of 38.6°C. Given her presentation and likely diagnosis, which of the following would be the most likely physical finding associated with her diagnosis?
   A. Bounding pulses
   B. Pulsus paradoxicus
   C. Apical click

D. Systolic ejection murmur
E. Crisp heart sounds

11. A 12-year-old gymnast comes to you for "sports clearance." She is new to your practice. Her past medical history is notable for an appendectomy performed at 5 years of age. Her family history is notable for a maternal grandmother who died suddenly at the age of 74 years with a history of high cholesterol. On examination, her blood pressure is 95/56 mm Hg. She has a grade 1-2/6 vibratory, musical systolic ejection murmur at the mid-left sternal border and apex that is louder when supine and is much softer when she sits up. Her pulses are easily felt in all four extremities. Which of the following would be the next best step for her evaluation and/or management?
    A. Schedule an exercise stress test.
    B. Check a fasting cholesterol panel.
    C. Clear her for all sports without any restrictions.
    D. Refer her to a pediatric cardiologist.
    E. Restrict her from participating in gymnastics until you reevaluate her in 3 months.
12. A 3-year-old girl presents with low-grade fever and decreased oral intake and activity over the past 24 hours. She is fully immunized and attends daycare. On physical examination, she is noted to have painful blisters on her hands and the bottom of her feet, as well as ulcers on her tongue. Which of the following choices is correct regarding this child's likely illness?
    A. This is typically an illness that will not resolve on its own.
    B. She should be prescribed amoxicillin.
    C. This is likely caused by an enterovirus.
    D. This is not contagious.
    E. She should be prescribed acyclovir.
13. A 4-year-old girl presents with a 6-day history of high fevers refractory to antipyretics, tachycardia, and irritable mood. Over the past few days, she has developed a nonpurulent conjunctivitis; dry, red cracked lips; a maculopapular rash on her trunk; and a unilateral 1.5 cm enlarged cervical lymph node. Of the following, what is the next best step in management?
    A. Continue treatment with antipyretics and return for medical evaluation if she does not defervesce over the next 72 hours.
    B. Prescribe broad spectrum antibiotics to cover *Staphylococcus aureus* as well as *Streptococcus pyogenes* infection.
    C. Start treatment with intravenous immune globulin (IVIG) and high-dose aspirin.
    D. Obtain a lumbar puncture to rule out meningitis.
    E. Initiate high-dose steroid therapy.
14. A 6-year-old female who immigrated from Peru at the age of 4 years is brought in for medical evaluation after a new-onset seizure. Over the past couple of weeks, the parents note that she has appeared tired and has complained of headaches. Computed tomography (CT) of the brain shows a single parenchymal cyst and no obstructive hydrocephalus. Which of the following statements is correct regarding this child's presentation and likely condition?
    A. Neurocysticercosis is one of the leading causes of epilepsy in the developing world.
    B. Seizures from this condition do not require anticonvulsant therapy.
    C. *Taenia* eggs on stool ova and parasite (O and P) studies are commonly found.
    D. This child requires surgical intervention as part of her treatment.
    E. She contracted this infection through ingestion of undercooked fish.
15. An 18-year-old male college student presents to the clinic with acute onset of bilateral parotitis, fever, and headache. Which of the following statements is most consistent with his likely diagnosis?
    A. The vaccine administered to prevent this infection is administered at 2, 4 and 6 months.

B. Diagnosis is best made by aspirating the parotid gland.
C. Viral causes of parotitis can include cytomegalovirus (CMV), Epstein–Barr virus (EBV), human immunodeficiency virus (HIV), and influenza.
D. Maternal mumps infection in the first trimester results in congenital mumps malformation.
E. This patient should have received a dose of measles, mumps, and rubella (MMR) vaccine before college entry.

16. During a well-child checkup, a father asks if his 4-year-old needs to be screened for tuberculosis. He recalls that his older daughter was screened when she started preschool years ago. You explain that recommendations have changed. Which of the following would necessitate screening for tuberculosis with a purified protein derivative (PPD) in this 4 year old?
A. Being born in California
B. Taking a 5 day-long vacation in Mexico
C. Living with an asymptomatic grandparent who is PPD-positive
D. Having a family member with tuberculosis with whom the patient has had no contact
E. Being born in Canada

17. A 14-year-old girl from California's Central Valley was recently diagnosed with juvenile idiopathic arthritis and is being treated with infliximab. She presents with fatigue, weight loss, and low-grade fevers over the past 2 weeks and now is in the emergency room with worsening fever, cough, and chest pain. She rapidly develops respiratory failure. Her complement fixation titer for coccidioidomycosis is >1:16. Which of the following statements is correct regarding coccidioidomycosis?
A. The most common presentation is meningitis.
B. Children younger than 1 year are usually protected by maternal antibody and have low risk of disease.
C. Impairment of T-lymphocyte function increases risk for severe primary infection, disseminated disease, or relapse of disease.
D. In addition to the Southwestern United States, endemic areas for coccidioidomycosis include the Mississippi River Valley.
E. Empiric therapy should be initiated with dicloxacillin.

18. A 7-year-old boy has just returned from a month long visit with his grandparents in the Midwest. He presents to the emergency room with complaints of headache and a fever with a temperature of 103.5°F. You note scattered petechiae on his wrists and ankles, and he appears unwell. Which of the following will be the most appropriate treatment?
A. Intravenous (IV) doxycycline
B. IV ceftriaxone
C. Amoxicillin–clavulanate
D. Supportive care
E. IV ceftriaxone and IV doxycycline

19. A 2-year-old boy is being evaluated for failure to thrive. He was adopted, and his birth history is unknown. You are planning on testing him for human immunodeficiency virus (HIV) infection and are reviewing common infections and the clinical presentation of children with HIV infection. In addition to failure to thrive, which of the following is a typical complication for a child with perinatally acquired HIV?
A. Cytomegalovirus (CMV) retinitis
B. Recurrent common bacterial infections
C. Central nervous system (CNS) lymphoma
D. Shingles (reactivation of varicella zoster virus)
E. Kaposi sarcoma

20. A 6-year-old girl presents with a 3-day history of bloody diarrhea and dehydration. She has decreased urine output and appears very pale. You plan to admit her to the hospital for management. Which of the following should be part of her management?
    A. Administration of trimethoprim/sulfamethoxazole (TMP/SMX) for probable infection with *Shigella*
    B. Stool sample for *Giardia intestinalis*–specific enzyme immunoassay (EIA)
    C. Examination of a peripheral smear for evidence of microangiopathic hemolytic anemia
    D. Administration of metronidazole empirically for the treatment of *Clostridium difficile*
    E. Rehydration with half normal saline (½ NS) with 20 mEq of KCl
21. During a well-child examination for a 12-year-old female, her mother refuses the human papilloma virus (HPV) vaccine, stating that her daughter "does not need the vaccine now because she is not going to be sexually active for a very long time." Which of the following statements about HPV and the vaccine is true?
    A. HPV is a rare cause of sexually transmitted disease in the United States.
    B. Vaccination during the preteen years is recommended to facilitate the development of an immune response before the initiation of sexual activity.
    C. HPV serotypes have been associated with cancers of the female reproductive tract but have not been associated with cancers in male patients.
    D. The HPV vaccine is universally recommended for females and is optional for males.
    E. Although recommended during the preteen years, HPV vaccine may be administered to sexually active individuals regardless of age.
22. A 2-week-old female infant is being fed both breast milk and infant formula. Which one of the following statements about vitamin D supplementation is correct?
    A. Vitamin D supplementation is not necessary as long as the mother continues supplementing with formula.
    B. The daily recommended intake of vitamin D in the first year of life is 200 IU.
    C. Early introduction of cow's milk can replace the need for vitamin D supplementation.
    D. Vitamin D supplementation in the breastfed infant is not necessary as long as the mother takes adequate amounts of vitamin D and calcium in her diet.
    E. Vitamin D supplementation is recommended for both breastfed and formula-fed young infants.
23. A 12-month-old female infant who was born at term with a birth weight of 3.5 kg presents now for a well-child visit. Her current weight is 8 kg, and her head circumference has increased by 12 cm since birth. Hemoglobin screening is 12.5 g/dL, and lead screening is <3 μg/dL. She is taking her first steps and says "mama," "dada," and "baba," which parents understand to be her bottle. Which of the following best describes how you will focus your discussion with her parents during this visit?
    A. Discuss routine anticipatory guidance because surveillance of her growth, development, and screening laboratory findings did not reveal concerning findings.
    B. Discuss starting ferrous sulfate for abnormal hemoglobin screen with a concern for iron-deficiency anemia.
    C. Discuss her abnormal weight gain and obtain a more detailed history to assess for failure to thrive.
    D. Discuss her abnormal head growth since birth and consider a diagnostic workup.
    E. Discuss her expressive language delay and recommend doing more reading with her.

Questions 130–134: You are on your way down to the emergency room to evaluate an 8-year-old with fever, headache, and emesis. You are worried that this child could have meningitis and are prepared to perform a lumbar puncture. Match each diagnosis in questions 130–134 with the mostly likely cerebrospinal fluid (CSF) profile from the choices below:

1. Enteroviral meningitis
2. Normal CSF profile
3. Tuberculous meningitis
4. Partially treated bacterial meningitis
5. Pneumococcal meningitis
6. A 12-month-old boy presents for a well-child checkup. You note that the child's vaccinations are not up-to-date. When discussing the recommended vaccines for the 12-month visit, the family expresses hesitation because they read on the internet that measles, mumps, and rubella (MMR) vaccine may cause autism. As you counsel the parents about vaccine administration, which of the following is true?
   A. Live attenuated vaccines such as MMR and varicella zoster virus (VZV) can cause symptoms such as fever and rash 1–2 weeks after immunization.
   B. Numerous reputable studies have shown an association between vaccines and autism.
   C. Thimerosal-containing vaccines are associated with an increased risk of autism, but routine childhood vaccines no longer contain thimerosal.
   D. A mild febrile illness is a contraindication to immunization.
   E. The MMR vaccine can be safely administered to children with compromised immunity.
7. A 4-year-old male child presents with a 1-week history of increasing facial edema and 4 days of "swollen feet" following an upper respiratory infection. The parents report that he is increasingly fussy with decreased appetite. Past medical history is unremarkable, and family history is noncontributory. Physical examination is notable for an irritable child with a temperature of 39°C. He has significant periorbital and tibial edema with abdominal fullness. Which of the following statements regarding the patient's likely condition, evaluation, or management are correct?
   A. This patient is predisposed to bleeding.
   B. This patient's urinalysis is likely to include red blood cell (RBC) casts.
   C. This patient is likely to have been infected with a toxin-producing bacteria.
   D. Blood cultures should be obtained, and the patient should be started on antibiotics, given an increased risk of developing spontaneous bacterial peritonitis.
   E. This patient is at increased risk of developing hearing loss.
8. A 2-year-old male child is brought in by his parents for itchy, scabbed papules on the ventral wrists and around the waistline. On further questioning, you determine that the mother and father both have itchy bumps on their skin too. What would be the next best step?
   A. No treatment is needed as this condition will resolve.
   B. Prescribe a topical steroid for everyone in the home.
   C. Prescribe permethrin 5% cream to be applied overnight to the skin (for all family members) and repeat the treatment in 1 week.
   D. Recommend that they take diphenhydramine to control itching.
   E. Treat the papules with cantharidin.
9. A 30-month-old girl was recently diagnosed with autism spectrum disorder. She is presently receiving speech and occupational therapy once a week. The diagnostic team recommended that she receive additional intensive, evidence-based intervention. Of the following, which is the intervention with the strongest evidence to support its use in this case?
   A. Applied behavior analysis
   B. Auditory integration therapy
   C. Developmental play therapy
   D. Sensory integration therapy
   E. Iron chelation
10. An 18-month-old girl presents with an erythematous papular rash that affects the elbows, knees, and cheeks and was preceded by a mild upper respiratory infection. Her mother is

concerned because this has been ongoing for over 2 weeks. What is the most likely diagnosis in this case?

A. Roseola
B. Pityriasis rosea
C. Gianotti–Crosti syndrome
D. Varicella
E. Fifth disease (erythema infectiosum)

11. An otherwise healthy sexually active 17-year-old girl comes in to your office for her annual health maintenance examination. She has had two male lifetime partners, occasionally uses condoms, and is not interested in birth control because she just broke up with her boyfriend. Her last menstrual period was 1 month ago. She currently denies abdominal pain, dysuria, and vaginal discharge. Which of the following screening tests should be performed?

A. Vaginal swab for *Trichomonas vaginalis*
B. Vaginal swab for bacterial vaginosis
C. Urethral swab for herpes simplex virus
D. Urine nucleic acid amplification test for gonorrhea and chlamydia
E. Cervical cytology for human papilloma virus

12. A 6-week-old female infant presents with increased tearing noted from her right eye. There is no color to the eye discharge, and conjunctival erythema and swelling are absent. The infant is without fever and, on examination, has a normal red reflex in each eye and normal extraocular movements. What is your next step in evaluation and management of this infant?

A. Begin topical erythromycin ointment.
B. Begin oral erythromycin for suspected *Chlamydia trachomatis* infection.
C. Refer to ophthalmology for probing of the nasolacrimal duct.
D. Inform parents that this condition is unlikely to resolve without treatment.
E. Observation only

	WBC	Glucose	Protein	Gram Stain
CSF Profile A	10,000	15	120	Gram-positive diplococci
CSF Profile B	6	50	35	Negative
CSF Profile C	240	55	45	Negative
CSF Profile D	145	55	180	Negative
CSF Profile E	5600	20	120	Negative

CSF = cerebrospinal fluid; *WBC* = white blood cell.

The response options for statements 142 and 143 are the same. You will be required to select one answer for each statement in the following set.

A. Quantitative measurement of serum immunoglobulins
B. Dihydrorhodamine (DHR) flow cytometry test
C. Complete blood count with differential
D. Total hemolytic complement (CH^{50})
E. T-cell subsets

For each patient, select the best initial screening test that may help lead to a diagnosis.

1. A 4-year-old girl with a history of recurrent skin abscesses, osteomyelitis, and pneumonia due to *Aspergillus*.
2. A 6-year-old boy with disseminated infection due to *Neisseria meningitides*.
3. A 6-year-old boy has hives, lip swelling, vomiting, and shortness of breath after being stung by an insect that his mother identifies as a honeybee. What is the next best step in management of this child once he recovers from this reaction?

A. Prescribe oral diphenhydramine and develop an emergency plan for any future

reactions.

B. Prescribe oral corticosteroids and advise the parents to have him avoid wearing bright clothing and scented lotion in the future.
C. Prescribe intramuscular epinephrine, review an emergency plan, and refer him to an allergist for possible venom immunotherapy.
D. Teach him how to appropriately remove an insect stinger and provide reassurance that this is likely not an allergic reaction.
E. Discuss management of local reactions to insect stings, including cool compresses and topical steroids.

4. During the evaluation of a 17-year-old boy for a preparticipation sports physical for football, you note asymmetry of his testes. His sexual maturity rating is 5 for both pubic hair and genital development. His left scrotum is nontender, appears larger when he is standing, and diminishes in size when supine. On palpation, the superior portion of the left testicle feels like a "bag of worms." The right testicle is uniformly soft and smooth to palpation. He denies sexual activity. Which of the following statements is correct?
   A. The adolescent should be referred to a urologist for surgical intervention.
   B. The adolescent should be reassured that no intervention is needed at this time.
   C. A urine nucleic acid amplification test should be sent for *Chlamydia trachomatis* and *Neisseria gonorrhoeae.*
   D. Transillumination of the scrotum will reveal a cystic mass.
   E. An additional physical examination finding for this condition includes painless inguinal swelling.
5. You are meeting with the family of a 4-year-old boy who has attention deficit/hyperactivity disorder, combined type, to discuss treatment options. His parents are interested in treatment and would like to know which options are available. Of the following treatments, which would you first recommend to the parents?
   A. Trial of nonstimulant medication
   B. Organizational skills training
   C. Behavioral management training with parents
   D. Play therapy
   E. Trial of stimulant medication
6. A 7-year-old girl is brought in by her parents for a 3–4 month history of thickened, yellow fourth and fifth toenails with pink scaling skin between the toes. Which would be the best treatment for this problem?
   A. Oral terbenafine
   B. High-potency topical steroids
   C. Topical clotrimazole
   D. Surgical removal of the affected nails
   E. Topical vitamin D analogues
7. A 16-year-old boy is brought to your office by his mother because she is concerned he may be depressed. The adolescent seems to have become more withdrawn over the previous 3 weeks and is sleeping more than usual. This is affecting his ability to attend school. Of the following, what additional symptoms would you expect the boy to display for a diagnosis of major depression?
   A. Cough from the initiation of tobacco use
   B. Decrease in his appetite
   C. Increase in extracurricular activities
   D. Epigastric abdominal pain
   E. Headache with visual aura
8. A 2-year-old boy is brought into the emergency department by paramedics. He was found

hiding in a closet within his apartment during a fire in his building. You notice that he appears quiet but with increased work of breathing. He has soot around his nares and singed nasal hairs, and it appears that his lips are cherry red. What is the next step in management of this child?

A. Intubate with rapid sequence induction.
B. Obtain a stat chest x-ray.
C. Obtain an arterial blood gas.
D. Arrange for transfer to a center that provides hyperbaric oxygen.
E. Determine body surface area (BSA) burned.

9. You are asked to counsel new parents of a male infant who are very anxious because they lost their first child to sudden infant death syndrome (SIDS). Your recommendation to the parents would include which of the following?

A. Recommend that the infant sleep in bed with parents.
B. Avoid any tobacco smoke in the home.
C. Prescribe a cardiorespiratory monitor to prevent SIDS.
D. Put the infant to sleep in the prone position.
E. Ensure the room is very warm to encourage rest and sleep.

Answers and Explanations

1. **The answer is A** [, section X.E.4, Figures 4-3 and 4-4]. The differential diagnosis of direct (conjugated) hyperbilirubinemia includes obstructive jaundice secondary to a choledochal cyst, obstructive jaundice secondary to biliary atresia, neonatal hepatitis, cystic fibrosis, and inborn errors of metabolism. Hepatic ultrasound is able to diagnose choledochal cyst and is also useful in the evaluation of biliary atresia. Sepsis (diagnosed with a blood culture) should be considered in the differential diagnosis of both direct and indirect hyperbilirubinemia; however, it is very unlikely in an otherwise well-appearing infant who is alert and feeding well. ABO incompatibility (diagnosed with Coombs testing), hypothyroidism (diagnosed with thyroid hormone studies), and hemolytic disorders such as hereditary spherocytosis (diagnosed with an osmotic fragility test) all are causes of indirect (unconjugated) hyperbilirubinemia.
2. **The answer is E** [, section III.E]. There are three major contraindications to administering the diphtheria, tetanus, and pertussis (DTaP) vaccine. These contraindications include a severe allergic reaction (i.e., anaphylaxis) after a previous vaccine dose or to a vaccine component, encephalopathy within 7 days of administration of a previous dose of DTaP, and a progressive neurologic disorder, which includes progressive encephalopathy and uncontrolled epilepsy. A mild respiratory illness with a low-grade fever is not a contraindication to administering the DTaP vaccine, nor is a history of moderate swelling at the injection site after a previous dose. Administration of intravenous immune globulin within the preceding 3–11 months is a precaution to immunization with live virus vaccines, such as measles, mumps, and rubella (MMR) and varicella. Immunocompromised status or the presence of an immunocompromised sibling in the household is not a contraindication to administration of DTaP.
3. **The answer is A** [, section V.D]. This child's presentation is most consistent with dermatomyositis. Characteristic cutaneous manifestations include a periorbital heliotrope rash that may cross the nasal bridge and an erythematous and hypertrophic rash over the metacarpal and proximal interphalangeal joints (Gottron papules). Characteristic laboratory and diagnostic studies include abnormal electromyography findings, abnormal muscle biopsy findings, and increased muscle enzymes, including creatine kinase. A positive antinuclear antibody is not specific and would be more suggestive of systemic lupus erythematosus (SLE) or juvenile idiopathic arthritis (JIA), although this patient fails to meet 4 of the 11 diagnostic criteria required for the diagnosis of SLE and has no arthritis, which is characteristic of JIA. Although both Epstein–Barr virus infection and cytomegalovirus infection may present with chronic fatigue, neither infection would present with the characteristic rashes described in this patient.
4. **The answer is B** [, Table 20-1]. The Glasgow coma score (GCS) is used to assess a patient's level of neurologic impairment. It is based on the physical examination and includes assessment for motor response, verbal response, and eye opening. In a young child, a modified scoring system can be used, which has been adapted for the nonverbal patient. The patient described has a GCS score of 5 because he does not open his eyes to pain or to voice (scored 1), has decerebrate posturing (scored 2), and moans with stimulation with incomprehensible words (scored 2). Because his GCS is <8, he has likely suffered severe head injury.
5. **The answer is B** [, section II.A]. The most common presenting symptoms of acute lymphocytic leukemia (ALL) are fever and bone or joint pain, as in this boy. The peak incidence of ALL is between 2 and 6 years of age, and ALL is more common in males. Pallor, hepatosplenomegaly, and lymphadenopathy are among the most common presenting findings on physical

examination. The white blood cell count varies on presentation and is elevated in only one-third of patients.

6. **The answer is A** [, section IV.B.2]. Hemophilia A, a deficiency of factor VIII, is an X-linked inherited disorder that occurs only in males. Typical features include deep soft-tissue bleeding and hemarthroses. Laboratory findings include a prolonged aPTT (activated partial thromboplastin time) in all but very mild cases, but prothrombin time and bleeding time are normal. Management includes replacement of factor VIII, which is not a vitamin K–dependent coagulation factor.
7. **The answer is C** [, section VI]. This patient's presentation is consistent with nephrotic syndrome, which is characterized by heavy proteinuria, hypoalbuminemia, hypercholesterolemia, and edema. Most children present with edema, which can range from mild periorbital edema to scrotal or labial edema and to widespread edema; this edema often follows an upper respiratory infection. Patients with nephrotic syndrome are at an increased risk for infection with encapsulated organisms, such as *Streptococcus pneumoniae.* Because of this risk, if a patient with active nephrotic syndrome becomes febrile, evaluation should include a blood culture, urine culture, and chest radiograph, and broad-spectrum empiric intravenous antibiotics should be initiated immediately. Patients with nephrotic syndrome are predisposed to thrombosis (stroke, renal vein thrombosis, deep vein thrombosis, and sagittal sinus thrombosis) secondary to hypercoagulability. Renal biopsy is rarely indicated in a child with nephrotic syndrome, unless the creatinine clearance is impaired or initial management with corticosteroids is ineffective. Most patients with nephrotic syndrome respond to corticosteroid therapy.
8. **The answer is C** [, section VII.B.1.b]. Bacterial vaginosis is the most common cause of vaginitis in adolescents. It results from a change in the patient's normal vaginal flora secondary to a reduction in lactobacilli. It presents with gray-white, malodorous discharge, a fishy odor, and little vaginal or vulvar inflammation. Wet-mount saline preparation demonstrates the presence of "clue cells." Bacterial vaginosis is not thought to be transmitted sexually, so partners do not need treatment. Neither antibiotics nor antiyeast medications are indicated.
9. **The answer is D** [, section V.C and Table 8-6]. This clinical presentation is consistent with bacterial endocarditis. Ophthalmologic examination is warranted to evaluate for Roth spots and retinal hemorrhages, which can help confirm the diagnosis. Diagnosis is often made on confirmation of vegetations by echocardiography. Transesophageal echocardiography is more sensitive than transthoracic echocardiography in detecting vegetations. Rheumatoid factor and other acute-phase reactants, as well as the white blood cell count and the erythrocyte sedimentation rate, are often elevated. Gram-positive cocci, including *Streptococcus* and *Staphylococcus* species, are the most common infecting organisms. Gram-negative organisms are uncommon causes of endocarditis. Management includes appropriate intravenous antibiotics, but antibiotics can be safely withheld until at least three blood cultures are obtained in an attempt to identify the infecting organism and to use appropriate antibiotic therapy.
10. **The answer is C** [, section X.E]. Myasthenia gravis is an immune-mediated condition caused by antibodies that form against the acetylcholine receptor at neuromuscular junctions. Most patients first come to medical attention with eye problems, especially bilateral ptosis. One of the hallmarks of patients with myasthenia gravis is that their weakness progresses as the day progresses. Fasciculations (i.e., spontaneous, small twitches of muscle fibers caused by denervation) are commonly seen in Guillain–Barré syndrome but not in myasthenia gravis. Botulism is associated with honey ingestion and would more likely present acutely with constipation followed by weakness. Deep tendon reflexes are normal in myasthenia gravis. The Tensilon test is a useful test that can confirm the diagnosis of myasthenia gravis. It is performed by intravenously injecting edrophonium chloride, a rapidly acting cholinesterase

inhibitor, which produces transient improvement of ptosis.

11. **The answer is E** [, Table 7-2, sections III.B, and III.C]. The majority of children with fever of unknown origin (FUO), defined as unexplained fever lasting longer than 8 days to 3 weeks, have a common infection with an unusual presentation. Infectious diseases are the most common causes of FUO, whereas rheumatologic causes (e.g., Kawasaki disease, systemic juvenile idiopathic arthritis) are the second most common cause of FUO. Hospitalization is often indicated to facilitate the evaluation and to document the fever and identify any coexisting signs and symptoms. A cause is identified in approximately 75% of patients after an extensive workup; no cause is identified in 25% of children, despite a thorough evaluation.
12. **The answer is C** [, section VI.C.1]. The most frequent cause of respiratory distress in preterm infants is respiratory distress syndrome (RDS) (also known as hyaline membrane disease or surfactant deficiency syndrome), which occurs in as many as 50% of newborns born before 30 weeks' gestation (0.5% of all neonates). Meconium aspiration syndrome, neonatal sepsis, and intraventricular hemorrhage may all present with respiratory distress, but these conditions occur less frequently than RDS. Bronchopulmonary dysplasia is a chronic complication of RDS and does not occur in the immediate newborn period.
13. **The answer is B** [, section II.D.6]. The patient's disorder, short bowel syndrome, occurs after surgical resection of small bowel or damage to the small intestine from Crohn disease or from radiation. The loss of small bowel reduces the absorptive capacity of the gut, leading to malabsorption and electrolyte abnormalities. Total parenteral nutrition (TPN) is commonly used to maintain adequate nutrition; however, TPN causes cholestatic liver disease and, in many patients, gallstones. Other complications of this disorder include bacterial overgrowth within the remaining intestine, nutritional deficiencies, poor bone mineralization, renal stones, and secretory diarrhea. Patients on TPN or those with short bowel syndrome generally do not have gastrointestinal bleeding, constipation, pancreatic insufficiency, or inflammatory bowel disease.
14. **The answer is D** [, section V.A.4.b, Table 17-6, and Figure 17-5]. A physeal fracture that extends through the physis and into both the epiphysis and metaphysis is a grade IV Salter–Harris fracture. A grade I fracture is within the physis. A grade II fracture is within the physis and extends into the metaphysis. A grade III fracture is in the physis and extends into the epiphysis. A grade V fracture describes a crush injury of the physis.
15. **The answer is D** [, section II.B.2.d.(2)]. The patient described has craniosynostosis, a premature closure of a cranial suture. Eighty to ninety percent of cases of craniosynostosis are sporadic in occurrence with an unknown cause. Ten to twenty percent of cases are familial or are a component of a genetic syndrome (e.g., Apert syndrome, Crouzon syndrome). Sleeping on the back and congenital muscular torticollis may cause plagiocephaly, which is skull asymmetry without premature suture closure. Perinatal asphyxia causes microcephaly as a result of inadequate brain growth, rather than premature suture closure.
16. **The answers are B and C, respectively** [, section I.K]. Sturge–Weber syndrome is a neurocutaneous syndrome characterized by a nevus flammeus ("port wine stain") in the area innervated by the ophthalmic branch of the trigeminal nerve (V-I). It is associated with seizures, intracranial and intraspinal malformations, and intracranial calcifications (question 16). Erythema toxicum neonatorum is a benign rash of infancy characterized by erythematous macules, papules, and pustules on the trunk and extremities. The lesions are filled with eosinophils, and no treatment is required (question 17).
17. **The answer is D** [, section VI.A]. Patients with homocystinuria are hypercoagulable due to increased homocysteine levels. The tendency toward thromboembolism leads to significant morbidity, including deep vein thrombosis, myocardial infarction, and stroke. Betaine reduces homocysteine levels and greatly decreases the risk of thromboembolic events. Propranolol, a β-blocker, is useful for patients at risk for aortic dissection, such as patients with Marfan

syndrome. Vitamin C may be useful in transient tyrosinemia of the newborn as it can assist in tyrosine elimination. d-Penicillamine increases the clearance of copper and is useful in Wilson disease. Zinc is useful for children who have problems with healing, such as patients with acrodermatitis enteropathica. Propranolol, vitamin C, d-penicillamine, and zinc do not play useful roles in the management of patients with homocystinuria.

18. **The answers are E, C, and B, respectively** [, sections II.B.2.d.(3).(c).1 and II.C.3.f; , sections IV.E.2 and IV.C.1]. McCune–Albright syndrome (question 19) is characterized by endocrine dysfunction (peripheral precocious precocity, hyperthyroidism), irregularly bordered hyperpigmented macules ("coast of Maine" spots), and fibrous dysplasia of the bones that may lead to fractures. Kallmann syndrome (question 20), a form of hypogonadotropic hypogonadism, is associated with anosmia (absent sense of smell). Prader–Willi syndrome (question 21) is characterized by hypotonia, hypogonadism, and small hands and feet, with growth problems in the first year of life (secondary to feeding problems), followed by hyperphagia and obesity later in childhood. Turner syndrome is characterized by ovarian dysgenesis, short stature, webbing of the neck, and left-sided congenital heart disease, with an increased incidence of hypothyroidism. Laurence–Moon–Biedl syndrome is characterized by hypogonadism, retinitis pigmentosa, obesity, and polysyndactyly.
19. **The answer is B** [, section VI.B.2; , section V.G]. Findings consistent with child abuse include specific types of fractures, such as metaphyseal ("corner" or "bucket handle") fractures. These fractures occur as a result of torsional force placed on an extremity (i.e., pulling and twisting) or from violent shaking. Other fractures highly suggestive of abuse include posterior and first rib fractures; fractures of the sternum, scapula, and vertebral spinous processes; and fractures in different stages of healing. Bruises on exposed areas, such as the knees, shins, elbows, and forehead, are common during childhood and are typical of accidental injury. Burns that have an irregular splashlike configuration are generally accidental. Toddler's fracture (i.e., spiral fracture of the distal tibia) can occur with little trauma, such as a fall when running and alone are not suggestive of abuse. Supracondylar fractures are common during childhood and usually occur when a child falls on an outstretched arm and alone are not suggestive of abuse.
20. **The answer is B** [, section IV.A.7 and Table 9-5]. Asthma is the most likely diagnosis because of the symptoms of recurrent cough and wheezing. This patient likely has persistent asthma, given the frequency and persistence of symptoms. Because asthma is an inflammatory disorder, anti-inflammatory medications, such as cromolyn sodium or inhaled corticosteroids, are recommended for persistent asthma symptoms. In as many as 50% of patients with asthma, symptoms may develop during the first year of life. Smoking should not be allowed in any place that a child with asthma may visit, including the home and automobile. Passive smoke exposure is an airway irritant and a trigger of asthma. Although albuterol would be useful for the management of acute symptoms, it has no effective role in prevention, except for preventing symptoms of exercise-induced asthma. Foreign body aspiration is less likely in a child with both persistent and recurrent symptoms. In addition, inspiratory and expiratory films could not be obtained in an 11-month-old infant; in this case decubitus films would be indicated if foreign body aspiration was suspected.
21. **The answer is D** [, section I.A.1]. The most common cause of cardiac arrest in a child is a lack of oxygen supply to the heart. Respiratory problems that result in a lack of oxygen supply include choking, airway disease, lung disease, suffocation, and brain injury. The end result of any of these processes is decreased oxygen tension within the blood (hypoxia). Cardiac arrest can often be prevented if assisted breathing is administered rapidly. Heart disease is an uncommon cause of cardiac arrest during childhood. Seizures, poisonings, and trauma are also less common causes of cardiac arrest than is hypoxia.
22. **The answer is D** [, section VII.B]. Peripheral tissue resistance to insulin is seen in type 2 diabetes mellitus (DM). All of the other choices listed are more commonly associated with

type 1 DM. The evolution of type 1 DM is thought to have numerous causes. It begins with a genetic predisposition (human leukocyte antigen [HLA] haplotypes DR3/DR4), a viral infection acting as an environmental triggering event, and lastly an autoimmune process that ultimately results in β-cell destruction. Autoimmune antibodies, such as islet cell and insulin antibodies, may be found in type 1 DM.

23. **The answer is B** [, section II.C.2–3]. Patients with celiac disease may present with vomiting, bloating, foul-smelling stools, or failure to thrive. Infants also may be irritable. This infant developed his symptoms after the introduction of wheat cereal that contains gluten. Gluten is found in wheat, rye, barley, and oats (if the oats are harvested in fields that also grow wheat). Celiac disease is a gluten-sensitive enteropathy in which antibodies to gluten cross-react and damage the mucosa of the small intestine, which results in flat, atrophic villi. Lactase deficiency causes bloating and watery stools but not failure to gain weight. Crohn disease is uncommon during infancy. Gastroesophageal reflux disease may be associated with vomiting and irritability; however, stools are not foul-smelling. Cow's milk protein intolerance may be associated with diarrhea, irritability, and vomiting, but stool blood and mucus are often present, and symptoms often begin before 6 months of age.
24. **The answer is B** [, section IV.D.2]. The 100% oxygen test helps distinguish whether cyanosis is caused by cardiac or respiratory disease. Patients with cyanotic congenital heart disease associated with reduced pulmonary blood flow, such as tetralogy of Fallot, do not respond with any increase of significance in the PaO^2 level when given 100% oxygen. In contrast, infants with cyanotic congenital heart disease associated with normal or increased pulmonary blood flow, such as truncus arteriosus, may have some increase in the PaO^2 level, but not as much of an increase as seen in patients with primary pulmonary disease. Patients with primary lung disease, such as neonatal pneumonia, respiratory distress syndrome, or meconium aspiration syndrome, demonstrate a very significant increase in the PaO^2 levels when administered 100% oxygen.
25. **The answer is D** [, section II.G]. This patient presents with diagnostic criteria consistent with Kawasaki disease, and treatment includes high-dose intravenous immune globulin together with high-dose aspirin therapy. Oral penicillin is not an appropriate course of management in this patient because there is no evidence of the fine sandpaper-like rash consistent with scarlet fever, a sequela of group A β-hemolytic streptococcal infection. Oral dicloxacillin can be used for suspected acute bacterial cervical adenitis; however, the lack of improvement on amoxicillin–clavulanic acid and the other findings on physical examination make cervical adenitis alone less likely. Admission for an evaluation for invasive bacterial disease (rule-out sepsis workup) is not indicated because this patient is neither toxic-appearing nor has meningeal signs. The presentation is also not consistent with high fever without a source, which would require empiric broad-spectrum antibiotic coverage. Steroids are controversial and currently not routinely indicated for the initial treatment of Kawasaki disease.
26. **The answers are B and A, respectively** [, section V.F]. Cardiomyopathy may be categorized as dilated, hypertrophic, or restrictive. Hypertrophic cardiomyopathy (question 29) may be inherited in an autosomal dominant manner or may occur in infants of diabetic mothers. Infants of diabetic mothers have transient septal hypertrophy and have a systolic ejection murmur because of obstruction of left ventricular outflow. Causes of dilated cardiomyopathy (question 30) include viral myocarditis, carnitine deficiency, anomalous origin of the left coronary artery, and hypocalcemia. Anomalous origin of the left coronary artery from the pulmonary artery may present with evidence of myocardial infarction. As a result of infarction, cardiac function may be impaired, and an echocardiogram shows a dilated ventricle with poor ventricular function. Causes of restrictive cardiomyopathy include inherited infiltrative disorders (such as hemochromatosis and Gaucher disease) and amyloidosis.

27. **The answer is E** [, section X.C.2]. Melena, a term used to describe dark and tarry stools, is most often caused by upper gastrointestinal (GI) bleeding proximal to the ligament of Treitz. The most common causes of melena in a 3-year-old girl include gastritis, ulcers, swallowed blood from epistaxis, mechanical injury to the mucosa from vomiting (Mallory–Weiss tear) or a foreign body, and varices. To best evaluate the cause of upper GI bleeding, upper intestinal endoscopy is used to visualize the source of bleeding and, if indicated, to perform biopsies and treat active bleeding. Computed tomography of the abdomen is not useful in the diagnosis of upper GI bleeding. A Meckel scan and colonoscopy have more utility in the investigation of lower, rather than upper, GI bleeding. Plain film radiography is generally not useful in diagnosis unless a foreign body or intestinal perforation is suspected.
28. **The answer is B** [, section VII]. This patient's clinical presentation of a prodrome of bloody diarrhea followed by the onset of anemia, thrombocytopenia, and acute renal failure is most consistent with hemolytic uremic syndrome (HUS). The most common subtype of HUS seen in childhood is Shiga toxin–associated HUS resulting from an intestinal infection with a toxin-producing bacteria. The treatment of Shiga toxin–associated HUS is supportive, and antibiotics are not indicated. Vascular endothelial injury by the Shiga toxin is the key to the pathogenesis of injury in Shiga toxin–associated HUS. The toxin binds to endothelial cells, causing endothelial cell injury, especially in the renal vasculature, leading to platelet thrombi formation and renal ischemia. Although the patient's bloody diarrhea may have contributed to his anemia, patients with HUS have hemolytic anemia. The prognosis for children with Shiga toxin–associated HUS is usually favorable but depends on the severity of the initial episode. In North America, the most common pathogen associated with Shiga toxin–associated HUS is *Escherichia coli* O157:H7.
29. **The answer is D** [, section I.D.2.d.(2)]. Although iron-deficiency anemia is the most common cause of anemia during childhood, other causes of anemia should be considered in patients who do not respond to iron therapy for suspected iron-deficiency anemia. In this case, this patient may have β-thalassemia minor (trait), a heterozygous condition that causes mild asymptomatic anemia. Because she did not respond to iron, she should undergo further testing, including an hemoglobin (Hgb) electrophoresis, blood smear, lead level, and an iron level (which is normal or elevated in β-thalassemia minor). Continuing to treat her with iron may not be beneficial at this point. Red blood cell transfusion is not indicated for this Hgb level. Folic acid is not helpful or indicated; folic acid deficiency causes a macrocytic anemia.
30. **The answer is A** [, section III.D]. This patient is presenting with symptoms of physiologic gastroesophageal reflux, a finding found in up to 60% of infants. Gastroesophageal reflux does not need workup, change in the diet, or medical treatment. The spitting up is benign and resolves with time. Given her normal weight gain and the absence of pain, she does not have gastroesophageal reflux disease (GERD). GERD in some cases merits further evaluation with a barium upper gastrointestinal study to evaluate the anatomy of the stomach, esophagus, and duodenum and a pH probe to confirm the presence of reflux.
31. **The answer is E** [, section VI.E]. Avulsed primary teeth do not require reimplantation. In the case of an avulsed secondary (permanent) tooth, extraoral time is the most important prognostic factor for successful reimplantation. A tooth that has been stored dry, even after only 30 minutes, has a very poor prognosis. Management of an avulsed secondary tooth includes gentle rinsing with saline or water, placement of the avulsed tooth into the tooth socket or into a liquid such as milk, and emergent referral to a dentist.
32. **The answer is E** [, section I.C]. The constellation of a nonthrombocytopenic petechial eruption on the thighs and a limp (arthritis) in a toddler, along with upper respiratory symptoms, is most consistent with the diagnosis of Henoch–Schönlein purpura (HSP). The renal manifestations of HSP are variable, ranging from mild hematuria or proteinuria to end-stage renal disease in 1% of patients. Classically, the renal manifestations of HSP may not become

clinically apparent for up to several months after the patient's initial presentation. HSP is a multiorgan system vasculitis associated with increased serum IgA levels. Recurrences of HSP are quite common, occurring in approximately 50% of patients. Steroids are the mainstay of therapy for severe abdominal pain. The rash of HSP characteristically appears on the lower extremities and buttocks, not the palms and soles.

33. **The answer is A** [, section IX.B]. The most important initial treatment for any bite is local wound care, which includes copious and prompt wound irrigation. Dog bites may become infected, especially bites to the hand, wrist, and foot and bites that are small puncture wounds, as in this patient. Large wounds, wounds to the face, and wounds less than 12 hours old should all be sutured. However, wounds greater than 12 hours old should be allowed to close on their own (except facial wounds, which may still be safely closed up to 24 hours later as a result of the high vascularity of the face). Aerobic and anaerobic organisms, including *Staphylococcus aureus* and *Pasteurella multocida,* are the usual pathogens causing infection. *Bartonella henselae* is not a usual pathogen in dog bites but rather is a cause of cat scratch disease. Antibiotics should be started empirically, without waiting for clinical signs of infection, because of the high risk of infection. Tetanus prophylaxis is necessary for unimmunized or underimmunized patients who sustain dog bites.
34. **The answers are E, C, A, and D, respectively** [, Table 18-2 and section III.B.3]. Diagnosis of a red eye can often be made on the basis of history and physical examination. Conjunctivitis that occurs between days 4–10 of life is most likely caused by *Chlamydia trachomatis* and is best treated with oral erythromycin (question 38). Oral therapy is used to kill *Chlamydia* organisms in both the conjunctiva and nasopharynx simultaneously. If *Chlamydia* organisms within the nasopharynx are not killed, pneumonia may develop between 1 and 3 months of age. Burning, crusting, and scales at the eyelash margin suggest blepharitis, a condition treated with baby shampoo scrubs of the eyelashes (question 39). Purulent conjunctivitis in a young child is typically bacterial in origin and would prompt administration of topical antibiotics, such as tobramycin (question 40). Itching is a hallmark of allergy and suggests allergic conjunctivitis. Allergic disease of the eyes is best treated with topical antihistamines or topical mast cell stabilizers (question 41).
35. **The answer is C** [, section V.D.2–3]. Because the clinical features of viral pharyngitis and group A β-hemolytic streptococcal (GABHS) pharyngitis overlap, children presenting with pharyngitis should undergo laboratory testing to confirm GABHS infection before the institution of antibiotic therapy. Such testings may include rapid antigen testing or a throat culture (the gold standard). Although infectious mononucleosis should be considered in patients with pharyngitis, this patient's acute presentation is unlikely to be caused by infectious mononucleosis, and therefore, a monospot test is not indicated. Supportive care with analgesics and lozenges is helpful for pharyngitis, but it is not the most important initial management step. A lateral neck radiograph is not indicated given the absence of clinical features consistent with upper airway obstruction.
36. **The answer is C** [, section II.B–C]. Communicating hydrocephalus is caused by decreased absorption of cerebrospinal fluid (CSF) or, less commonly, by increased CSF production. Meningitis causes inflammation and scarring of the arachnoid membrane, which prevents the normal absorption of CSF and results in communicating hydrocephalus. Brain atrophy does not cause hydrocephalus but rather a condition called *hydrocephalus ex vacuo*, in which the ventricles are enlarged because of loss of surrounding brain tissue. Chiari type II malformation produces a noncommunicating hydrocephalus caused by blockage of flow in the ventricular system. Aqueductal stenosis may cause noncommunicating hydrocephalus for the same reason. A Dandy–Walker malformation is characterized by an absent or hypoplastic cerebellar vermis and cystic enlargement of the fourth ventricle, which blocks the flow of CSF, thereby causing noncommunicating hydrocephalus.

37. **The answers are E and A, respectively** [, Table 10-1]. Scurvy (question 44) is caused by vitamin C deficiency and causes symptoms that include hematologic abnormalities, edema, poor wound healing as a result of impaired synthesis of collagen, and a characteristic spongy swelling of the gums. Vitamin A deficiency (question 45) presents with xerophthalmia (dry conjunctiva and cornea) and night blindness.
38. **The answer is B** [, section VII.B.4]. This patient's presentation with dysuria and increased urinary frequency are consistent with urethritis. A urinary tract infection is possible, but it is less likely in a male. Because of his sexual activity and the intermittent nature of his condom use, a sexually transmitted disease is most likely. Urethritis may be the result of *Neisseria gonorrhoeae* or nongonococcal causes, such as *Chlamydia trachomatis.* Diagnosis may be made presumptively by finding greater than five white blood cells per high-power field on a Gram stain of the patient's urethral secretions or by finding evidence of pyuria on first morning-voided urine. Urethritis is more common in males than in females. Unlike this patient, many patients have asymptomatic infection. Definitive diagnosis can be made either by culture of the urethral secretions (via a urethral swab) or by nonculture tests on urine or on discharge (direct fluorescent antibody staining, polymerase chain reaction, ligase chain reaction, enzyme-linked immunoassay, or nucleic acid hybridization).
39. **The answer is A** [, section VIII.B]. On the basis of this patient's clinical features, parotitis is the most likely diagnosis. Unilateral parotitis is generally caused by an infection with *Staphylococcus aureus, Streptococcus pyogenes,* or *Mycobacterium tuberculosis.* Testing for tuberculosis should be considered for patients with unilateral parotid infection. Mumps, Epstein–Barr virus, and cytomegalovirus generally result in bilateral parotitis. Management of bacterial parotitis rarely requires surgical drainage unless there is an abscess.
40. **The answer is B** [, section IV.B]. The clinical presentation is consistent with tetralogy of Fallot. Children with tetralogy of Fallot may be cyanotic or pink at rest. The degree of cyanosis depends on the amount of resistance to flow through the obstructed pulmonary outflow tract and on the systemic vascular resistance, both of which affect the degree of right-to-left shunting across the ventricular septal defect (VSD). Crying can be a cause of hypercyanotic, or "tet" spells in a child with tetralogy of Fallot. Crying increases the child's heart rate. The elevated heart rate increases right ventricular outflow tract resistance, which increases right-to-left shunting, causing increasing cyanosis. Patients with transposition of the great arteries, tricuspid atresia without a VSD, and total anomalous pulmonary venous connection are expected to be cyanotic at all times (including at rest). Patients with truncus arteriosus may not only be mildly cyanotic but also commonly manifest signs and symptoms of congestive heart failure, with poor weight gain because of excessive pulmonary blood flow.
41. **The answers are C, A, F, E, and D, respectively** [, sections V.A.2.1, III.C.3, III.E.3, III.F.2, and III.D.3]. Tinea corporis (ringworm) is a fungal infection characterized by oval or circular patches with central clearing (question 49). Seborrheic dermatitis in an adolescent may present with greasy scales and crusts in the nasolabial folds, beard areas, chest, and scalp (question 50). Psoriasis is characterized by scaling papules and plaques, and lesions may demonstrate the Koebner phenomenon, in which new lesions appear at the site of skin trauma (question 51). Miliaria rubra, or heat rash, occurs in association with heat and occlusive clothing. The sweat irritates the skin, causing pruritic papules, often on the neck, chest, inguinal area, or axilla (question 52). Pityriasis rosea is characterized by a large single scaly erythematous lesion ("herald patch") that is followed by oval erythematous macules and papules that follow skin lines in a "Christmas tree" distribution (question 53).
42. **The answer is D** [, section VI.C.1]. Latex allergy is seen in health care workers and in patients with myelomeningocele more frequently than in the general population because of more frequent exposure to latex (patients with myelomeningocele often require intermittent bladder catheterization, which exposes them to latex repeatedly). Latex exposure can cause acute

urticaria and anaphylaxis in patients with latex allergy. Patients with neural tube defects do not have increased risks of developing allergies to penicillin, cow's milk protein, dust mites, or wool.

43. **The answer is B** [, section XIII.D.4.c]. This infant most likely has congenital rubella syndrome. Cataracts, congenital heart disease (most often patent ductus arteriosus), and sensorineural hearing loss are the hallmarks of this syndrome. Presenting features may also include thrombocytopenia and extramedullary hematopoiesis manifesting as a "blueberry muffin" appearance to the skin. Congenital toxoplasmosis presents with hydrocephalus, intracranial calcifications, and chorioretinitis. Congenital varicella is uncommon but may present with a dermatomal rash or scarring. Perinatally acquired herpes simplex virus infection presents with a vesicular rash or encephalitis but not with structural defects. Congenital cytomegalovirus infection typically presents with microcephaly, hepatosplenomegaly, and cerebral calcifications and usually not with cataracts or congenital heart disease.
44. **The answer is B** [, Tables 2-1, 2-3 and 2-4]. A 6-month-old infant should be able to sit with support and may be able to sit independently. Language development in a normal 6-month-old includes babbling, which is placing consonants and vowels together. Another 6- to 7-month milestone is transferring objects from hand to hand. At 4 months of age, infants are learning to bring their hands to midline and to mouth but would not be able to transfer objects. By 8 months of age, infants should be sitting without support. At 9 and 10 months of age, infants should be able to use jargon, which integrates babbling with the intonational patterns, and would have moved beyond sitting with support to crawling, creeping, and pulling up to stand.
45. **The answer is C** [, section IV.B.5–6]. This patient's presentation with chronic cough, recurrent pneumonia, and failure to thrive is most consistent with cystic fibrosis. Patients with cystic fibrosis may also present with chronic diarrhea as a result of steatorrhea, and may have a history of meconium ileus at birth. Diagnosis of cystic fibrosis may be confirmed by documenting an elevated sweat chloride level or by documenting mutations in the gene associated with cystic fibrosis. Although a chest radiograph may help identify pneumonia, chest radiographic findings are not specific for cystic fibrosis. Sputum culture is difficult to obtain in a young child, and even if it could be obtained, it would not diagnose her underlying disorder. Foreign body aspiration, diagnosed by decubitus radiographs, should be considered in patients with cough, choking, stridor, and hoarseness, but it would not typically cause failure to thrive. *Mycoplasma pneumoniae* infection, suggested by elevated cold agglutinins, would not cause failure to thrive, recurrent pneumonia, or cough for 4–5 months.
46. **The answers are B, C, and A, respectively** [, Table 7-3]. Bacterial meningitis (question 58) is characterized by high white blood cell (WBC) count on cerebrospinal fluid (CSF) analysis, with a polymorphonuclear leukocyte (PMN) predominance, low glucose, and high protein. Tuberculous meningitis (question 59) is characterized by very high protein, low glucose, and a WBC count generally <500 cells/mm^3 with a lymphocyte predominance. Viral meningitis (question 60) may also have an early PMN predominance, but the CSF WBC count is usually lower than in bacterial meningitis, and the glucose is normal.
47. **The answer is B** [, section III.F.4.c]. *Chlamydia trachomatis* is a common cause of afebrile pneumonia in an infant 1–3 months of age. It presents with a staccato cough, respiratory distress, and a history of conjunctivitis (50%). On examination, patients often have tachypnea and wheezing. Infection with *Mycoplasma pneumoniae* is more common in older children and adolescents, and it typically presents with a chronic nonproductive cough and headache. Respiratory syncytial virus is a common cause of pneumonia and bronchiolitis during the late fall and winter (November through April). It should be considered in any infant with wheezing; however, upper respiratory symptoms such as rhinorrhea and low-grade fever generally develop before cough and wheezing. Bacterial infection with *Streptococcus*

pneumoniae can occur in young infants, although they would be expected to have fever. Asthma is a chronic disorder characterized by repeated episodes of wheezing and therefore is not present in a patient of this young age.

48. **The answer is E** [, section IX.B.1]. This patient's presentation with sudden onset of scrotal pain, a tender and swollen testicle, and absent cremasteric reflex on the affected side is consistent with torsion of the spermatic cord, which is a urologic emergency. Emergent surgical consultation and intervention are necessary. Detorsion of the torsed spermatic cord must be performed within 6 hours to preserve testicular function, and at the time of the procedure, the opposite testicle is also fixed to the scrotum because it has an increased incidence of torsion in the future. The diagnosis of torsion of the spermatic cord is a clinical diagnosis. Although not always necessary, confirmation of the torsion can be made by finding decreased uptake on radionuclide imaging or absent pulsations on Doppler ultrasound. Elevation of the torsed testicle can relieve pain in some instances; however, this is not a reliable finding in testicular torsion. This patient's presentation is inconsistent with epididymitis because the entire testicle, not just the epididymis, is tender and swollen.
49. **The answer is C** [, section IV.B.5]. An abnormal anal wink reflex raises concern that there may be a neurologic reason for enuresis, and imaging studies of the spine and brain should therefore be considered. Family history is frequently positive in uncomplicated nocturnal enuresis. Psychosocial factors such as parental divorce or the birth of a sibling are frequently associated with uncomplicated secondary enuresis, which does not require imaging studies if the neurologic examination is normal. Constipation is a frequent comorbid factor that should be treated because it may cause impingement on the bladder. Children with small bladder capacities often present with a history of frequent small voids and can sometimes be cured through bladder stretching exercises.
50. **The answers are D, E, and B, respectively** [, Table 13-3]. Most patients with sickle cell disease have one or more crises during their lifetime. A hyperhemolytic crisis (question 64) is characterized by rapid hemolysis that leads to anemia. Patients present with fatigue, pallor, and jaundice. Laboratory evaluation reveals decreased hemoglobin (Hgb), elevated bilirubin, and an elevated reticulocyte count. An aplastic crisis (question 65) is characterized by cessation of red blood cell (RBC) production, most commonly as a result of infection with parvovirus B19. Patients present with pallor and fatigue. Laboratory evaluation reveals decreased Hgb and decreased reticulocyte count. Treatment is transfusion of RBCs. Sequestration crisis (question 66) is characterized by the acute accumulation of blood within the spleen or liver. Patients may present with pallor, fatigue, shortness of breath, and shock. Laboratory findings include a low Hgb and very elevated reticulocyte count. Urgent transfusion of RBCs is indicated.
51. **The answer is C** [, Table 2-1]. When 4-month-old infants lie on their stomach, they can push up onto their elbows and look around with their head held up. When 4-month-old infants are pulled from a supine to a sitting position, they should also be able to keep their head even with their body. Two-month-old infants have head lag when pulled from a supine to a sitting position and can pull the shoulders up slightly and move the head from side to side when placed in the prone position. Six-month-old infants can lead with their head when pulled from a supine to a sitting position. Some 4-month-old infants can roll from a supine to a sitting position but are not able to get into a sitting position at this age.
52. **The answer is B** [, section III.A]. This patient's physical examination is consistent with developmental hip dysplasia (DDH). Patients with DDH whose diagnosis is delayed may present with a limb length discrepancy. Examination may also reveal asymmetric thigh or buttock folds and diminished abduction of the affected hip. Transient synovitis, a postinfectious inflammatory response within the joint, also causes a limp, but a limb length discrepancy would not be present. Legg–Calvé–Perthes disease is idiopathic avascular

necrosis of the femoral head that occurs most commonly in children 4–9 years of age. Femoral anteversion is an inward angulation of the femur that results in intoeing, and it is not manifested by a limb length discrepancy or asymmetric skin folds. Slipped capital femoral epiphysis is slippage of the femoral head off the femoral neck and is most common in overweight adolescent males.

53. **The answers are B, A, and B, respectively** [, section V.A–B and Figure 14-1]. Both Wilms tumor and neuroblastoma commonly present with an abdominal mass in the first 5 years of life. Clinical features of neuroblastoma vary based on the tumor location. Two percent of patients with neuroblastoma have acute cerebellar atrophy with ataxia, opsoclonus, and myoclonus (so-called "dancing eyes and dancing feet"; question 69). Clinical features of Wilms tumor include hemihypertrophy, aniridia, and genitourinary malformations (question 70). The prognosis for neuroblastoma is very good for infants younger than 1 year, and spontaneous regression is possible, even with metastatic disease (stage IV-S disease; question 71).
54. **The answer is D** [, section X.D.1 and Table 10-5]. Age is an important factor in determining the cause of lower gastrointestinal (GI) bleeding. In neonates and infants, an allergy to protein antigens in their food source can cause intestinal inflammation with GI bleeding, which may be occult or frank. Mucus may also be present in the stool. Juvenile polyp is the most common cause of lower GI bleeding after the neonatal period. Meckel diverticulum and infectious enterocolitis are important causes of bleeding, especially after infancy. Inflammatory bowel disease typically occurs later in childhood.
55. **The answers are D and B, respectively** [, sections IV.C.1 and IV.H.2]. Turner syndrome is characterized by short stature, a webbed neck with a low posterior hairline, a shield chest, and ovarian dysgenesis that manifests as delayed puberty. Complications of Turner syndrome include scoliosis, left-sided cardiac lesions, and hypothyroidism. Therefore, screening for hypothyroidism is indicated (question 73). Osteogenesis imperfecta type I is characterized by blue sclerae, fragile bones that result in frequent fractures, and easy bruisability. Patients are at risk for skeletal deformities and for early conductive hearing loss. In addition, they may have dentinogenesis imperfecta which leads to increased breakage and loss of teeth (question 74).
56. **The answer is D** [, section IV.C.4]. Irregular respirations with no particular pattern are also termed ataxic respirations and result from severe brainstem injury. This respiratory pattern often suggests impending brain death. Cerebellar injury and cerebral strokes do not usually result in changes in the respiratory pattern. Acute drug overdose with narcotics or sedatives causes hypoventilation.
57. **The answer is E** [, section I.D.2.b]. Pathologic short stature (child's height is greater than 3 standard deviations below the mean with abnormal growth velocity) may be characterized as proportionate or disproportionate. Disproportionate short stature is defined as short stature in patients who are very short-legged with an increased upper-to-lower (U/L) body segment ratio, suggesting either a skeletal dysplasia or rickets (the latter would also be expected to present with bowing). In contrast, malnutrition, child neglect, growth hormone deficiency, and fetal alcohol syndrome are all causes of proportionate short stature, in which the patient has a normal U/L body segment ratio.
58. **The answer is B** [, section III.B.5]. Osteomyelitis is characterized clinically by fever, irritability, localized bone pain, and swelling and erythema of the infected site. Osteomyelitis during childhood is most commonly acquired by hematogenous seeding. Direct inoculation and contiguous spread are less common ways of acquiring this infection. A plain radiograph is not a good study to assess early osteomyelitis because it is usually normal early in the course of disease. The elevation of periosteum as a result of infection does not usually become evident on a plain radiograph until after 10–14 days. *Staphylococcus aureus* and *Streptococcus pyogenes* are the two most common causative pathogens. *Salmonella typhi* infection occurs most commonly in a child with underlying sickle cell disease. Blood culture is positive in only 50%

of patients with osteomyelitis. All children with osteomyelitis require initial management with intravenous antibiotics.

59. **The answer is C** [, section I.H.1]. The normal umbilical cord should contain two arteries and one vein. The presence of only one umbilical artery should prompt suspicion of an associated underlying congenital cardiac or renal anomaly. Neither an umbilical hernia nor diastasis recti (the separation of the rectus abdominis muscles at the midline of the abdomen) is associated with underlying structural problems. Patients with hypospadias, in which the urethral meatus is located on the ventral surface of the penis, are not likely to have associated urinary malformations. This is in contrast to epispadias (in which the urethral meatus is located on the dorsal surface of the penis), in which associated problems, such as bladder extrophy, may be present. A nevus simplex (or "salmon patch") is the most common vascular lesion of infancy and is also not associated with underlying pathology. This is in contrast to a nevus flammeus, or "port wine stain" in the distribution of the ophthalmic branch of the trigeminal nerve, which may be associated with Sturge–Weber syndrome.
60. **The answer is B** [, section II.C]. This patient's age and his presentation with splenomegaly are most consistent with adult-type chronic myelogenous leukemia (CML). Most patients with adult-type CML are older children and adolescents, and they may be diagnosed with splenomegaly picked up as an incidental finding during a routine health maintenance visit. Adult-type CML is characterized by the presence of the Philadelphia chromosome. Juvenile monomyelocytic leukemia (JMML), another type of CML, often presents with fever, a chronic eczematous-type facial rash (not found in adult-type CML), lymphadenopathy, petechiae, and purpura. JMML occurs in young children and infants. Radiation therapy is ineffective in adult-type CML; chemotherapy and bone marrow transplantation are more useful. Adult-type CML follows a biphasic course, characterized by easy control of elevated white blood cell (WBC) counts for several years followed by an acute deterioration resembling acute leukemia. Adult-type CML is characterized by extremely high WBC counts, often >100,000 cells/mm^3.
61. **The answer is B** [, section VII.F]. This patient's clinical presentation, including the geographic location in which she lives, is consistent with Lyme disease. The management of Lyme disease is aimed at eradicating *Borrelia burgdorferi*, the spirochete that causes the infection. This patient has early localized disease and should be treated with amoxicillin. Doxycycline should be avoided in children younger than 9 years because of concerns regarding permanent tooth discoloration. Patients with complications of carditis or meningitis require intravenous penicillin or intravenous ceftriaxone.
62. **The answer is A** [, sections III.B.4 and III.B.6]. This patient presents with signs and symptoms consistent with croup (laryngotracheobronchitis). Given the lack of stridor at rest and the absence of respiratory distress, supportive care alone is indicated. Patients with stridor may benefit from a single dose of corticosteroid treatment to reduce airway inflammation. Patients with both stridor at rest and respiratory distress also benefit from nebulized racemic epinephrine to vasoconstrict subglottic tissues. Albuterol can be useful if wheezing is present, but does not have efficacy on the edematous subglottic tissues. Ribavirin is not effective in croup.
63. **The answer is B** [, section XVI.B]. This patient's presentation is typical of neurocysticercosis, a helminth infection caused by the ingestion of the eggs of *Taenia solium*, a pork tapeworm. Treatment includes anticonvulsant medications; surgical excision is not indicated. Ova and parasite evaluation detects the eggs of the organism in only 25% of cases. Diagnosis is often made by findings on computed tomography (CT) or magnetic resonance imaging, which reveal cysts that may be calcified. Calcifications are evidence of old, quiescent infection.
64. **The answer is D** [, section IV.F.6]. The antinuclear antibody (ANA), although not specific, is almost universally elevated in children with systemic lupus erythematosus (SLE) (>99%). If a patient has a negative ANA, it is very unlikely that he or she has SLE. Erythrocyte

sedimentation rate and rheumatoid factor are often, but not always, elevated in SLE but are nonspecific. Anti–double-stranded DNA antibodies are relatively specific for SLE, and uniquely, their levels can be used to monitor progression of disease, especially renal disease. Antibodies to the Smith antigen are elevated in only 30% of patients with SLE, but they are strongly suggestive of SLE when present.

65. **The answers are C, H, B, F, and G, respectively** [, Table 20-3; sections VIII.D.1, VIII.D.3, and VIII.D.6]. Antidotes exist for a relatively small number of toxins. Iron is commonly found in prenatal vitamins (question 84). The antidote for iron is deferoxamine, an iron chelator. The blood level of acetaminophen in the 15-year-old girl (question 85) should be plotted on the Matthew–Rumack nomogram. If it is elevated, she should be treated with *N*-acetylcysteine, the antidote for acetaminophen poisoning. Symptoms and signs of carbon monoxide toxicity include headache, vomiting, auditory and visual changes, slurred speech, and mental status changes (question 86). Cherry-red skin is a characteristic, although uncommon, finding. The antidote is 100% oxygen, which displaces carbon monoxide from the hemoglobin molecule. Isoniazid can cause seizures (question 87), and the antidote is pyridoxine (vitamin B^6). Dystonia can occur from several types of medications, including phenothiazines (question 88), and antidotes for dystonia include diphenhydramine and benztropine.
66. **The answer is A** [, section VIII.D]. Bleeding that is prolonged and that occurs at irregular intervals, as found in this patient, is termed menometrorrhagia. The bleeding may be secondary to dysfunctional uterine bleeding (DUB), the most common cause of vaginal bleeding during adolescence, but the presence of painful bleeding is inconsistent with DUB. Because she is having painful bleeding and because her bleeding is heavy, both a pelvic examination and laboratory studies to evaluate for pregnancy, anemia, and blood dyscrasias are indicated. Bleeding secondary to DUB occurs because of unopposed estrogen production. Dilation and curettage may be required for bleeding that does not stop with hormonal therapy, but it is not the first-line treatment.
67. **The answer is B** [, section VII.D]. The patient's presentation is consistent with Guillain–Barré syndrome, an acute inflammatory demyelinating polyneuropathy and a well-described cause of symmetric ascending weakness in childhood. Albuminocytologic dissociation in the cerebrospinal fluid (CSF), usually present 1 week after the onset of symptoms, is an important hallmark of Guillain–Barré syndrome. Patients classically have increased CSF protein levels but normal cell counts. Demyelination results in slowing of the nerve conduction velocity. Magnetic resonance imaging of the spine would be expected to be normal. Guillain–Barré syndrome is associated with many infectious agents, most commonly a recent infection with *Campylobacter jejuni.*
68. **The answer is D** [, section III.B.2]. The patient's presentation is most consistent with transient synovitis, a postinfectious inflammatory response in the hip joint that is a common cause of limp in toddlers. Transient synovitis commonly follows an upper respiratory infection or diarrheal illness, and is characterized by limp, irritability, low-grade fever or absence of fever, and a normal or slightly elevated white blood cell (WBC) count and erythrocyte sedimentation rate (ESR). Examination may reveal hip flexion, external rotation, and abduction, similar to that seen in septic arthritis, although usually less pain is elicited on movement of the hip joint compared with septic arthritis, in which pain is very significant. Septic arthritis and osteomyelitis also have an elevated WBC count and ESR, and patients are usually more ill-appearing. Slipped capital femoral epiphysis is a slipping of the femoral head off the femoral neck and typically presents with a painful limp, although this is more common in adolescence. A toddler's fracture is a spiral fracture of the tibia, which may occur after only mild trauma. A patient with a toddler's fracture may suddenly refuse to walk or bear weight. However, examination of the hip would be normal, although mild erythema, swelling, and tenderness may be found over the tibial fracture site.

69. **The answer is C** [, section X.A]. IgA deficiency is the most common immune deficiency and is associated with an increased incidence of sinusitis, otitis media, bronchitis, and pneumonia. Low quantitative IgA levels confirm the diagnosis. A complete blood count is usually part of the workup for immune deficiency but would not confirm IgA deficiency. Anergy skin testing and the assessment of T-cell response to mitogens evaluate the competency of T cell–mediated immunity, and patients with cellular-mediated immunodeficiency are more likely to present with recurrent viral, fungal, or protozoan infections. A normal total hemolytic complement demonstrates that all components of the complement pathway are present and functional. Patients with terminal complement deficiency usually present with recurrent meningococcal and gonococcal infections.
70. **The answer is A** [, section IV.A.2.b]. Blount disease, a progressive angulation of the proximal tibia, should be suspected in any child with progressive bowing, unilateral bowing, or persistent bowing after 2 years of age. In this patient with progressive bowing that is more prominent in one leg, Blount disease would be a concern. Blount disease is diagnosed with a standing anterior–posterior radiograph of the lower extremities that reveals an exaggerated metaphyseal–diaphyseal angle. Physical therapy is not effective. Genu varum (bowed legs) is not likely because the bowing is more prominent in one extremity, and because it is still present after 2 years of age. Genu valgum (knock-knees) is characterized by knees angulated toward the midline. Orthotic shoes are not useful in Blount disease.
71. **The answer is C** [, section VIII.A]. Sydenham chorea is an autoimmune response of the central nervous system to group A β-hemolytic streptococcal infection. The major clinical features include chorea and emotional lability. The choreic movements of the arms and legs can interfere with daily activities such as eating, writing, and walking. Migraine does not present with motor difficulties. In complex partial epilepsy, motor, psychomotor, or sensory findings may occur, but consciousness is decreased during the seizure. Hydrocephalus with increased intracranial pressure most commonly presents with vomiting and early morning headache rather than with emotional lability, restlessness, and clumsiness. Tourette syndrome presents with motor or phonic tics.
72. **The answer is C** [, section XVII.A.2]. The patient's clinical features are consistent with Rocky Mountain spotted fever, which is caused by infection with *Rickettsia rickettsii*, a gram-negative bacteria transmitted by the bite of a tick. Clinical features include fever, a petechial rash that begins on the hands and feet, myalgias, hypotension, and hepatosplenomegaly. Thrombocytopenia and anemia also occur. Treatment should be started empirically on the basis of the clinical and epidemiologic features rather than waiting for confirmation by serologic testing. Prophylactic antibiotics to prevent infection are not indicated. The incidence is highest in school-aged children.
73. **The answer is C** [, section IX.A.6 and Table 7-5]. The patient's clinical presentation is most consistent with toxic shock syndrome (TSS). The most common organism associated with TSS is *Staphylococcus aureus,* although some cases may be associated with group A β-hemolytic streptococcus. This patient's signs and symptoms are inconsistent with Kawasaki disease, hemolytic uremic syndrome (caused by *Escherichia coli* O157:H7), or Lyme disease (caused by *Borrelia burgdorferi).*
74. **The answers are C, B, D, and E, respectively** [, sections XI.A.2, XI.B, IV.D.1, and Chapter 10, Table 10-1]. Patients with Wilson disease (question 97) have a high serum copper level that leads to copper deposition in the brain, eyes, and liver because of a copper excretion defect. These patients present with neurologic findings such as behavioral changes, seizures and ataxia, hepatic dysfunction, and Kayser–Fleisher rings in the peripheral cornea that represent copper deposition in Descemet membrane. Patients with Menkes kinky hair disease (question 98) present with myoclonic seizures, progressive neurologic degeneration, mental retardation, and pale kinky friable hair. Menkes kinky-hair disease is caused by a defect in copper

transport, and patients have a low serum copper level. Patients with acrodermatitis enteropathica (question 99) present with a symmetric dry vesiculobullous scaly rash, failure to thrive, and chronic diarrhea. Acrodermatitis enteropathica is caused by zinc deficiency, and low serum zinc is found on laboratory evaluation. Patients with DiGeorge syndrome (question 100) have hypocalcemia (caused by parathyroid hypoplasia), cellular-mediated immunodeficiency, which may result in recurrent fungal infections (caused by thymic hypoplasia), and cardiac findings that may include aortic arch abnormalities. DiGeorge syndrome is caused by a defect in the structures derived from the third and fourth pharyngeal pouches.

75. **The answer is D** [, section I.G.6]. Hydronephrosis is the most common cause of an abdominal mass in healthy newborns. Although the differential diagnosis includes Wilms tumor and neuroblastoma, both are less common than hydronephrosis as an explanation for abdominal masses in infancy. Wilms tumor rarely presents in the immediate newborn period. Ovarian cysts are more likely to present with an abdominal mass than ovarian torsion.
76. **The answer is E** [, section XII.A.2]. The infant likely has a tracheoesophageal fistula. The most common type, involving >90% of cases, is comprised of proximal esophageal atresia with a distal tracheoesophageal fistula. This is commonly associated with polyhydramnios due to the fetus' inability to swallow amniotic fluid. Feeding difficulty is observed immediately after birth. Infants with tracheoesophageal fistula should be examined carefully for anomalies associated with VACTERL (see Chapter 5 section IV.I.1.2.). Hepatomegaly is not typically associated with esophageal atresia. Meconium-stained fluid can cause meconium aspiration syndrome and is more likely to present with respiratory distress than feeding intolerance. Congenital diaphragmatic hernia would likely have been apparent on chest radiographs.
77. **The answers are D, E, and B, respectively** [, sections VI.B and VI.C]. Babies born to mothers with SLE are at risk for congenital third-degree atrioventricular (AV) block due likely to immune-mediated damage to the conducting system through maternally passed autoantibodies. Babies often present with bradycardia (question 103). Long QT syndrome is a disorder of myocardial repolarization. Long QT syndrome may be congenital or acquired from electrolyte abnormalities (hypokalemia, hypomagnesemia) or medication side effects. This syndrome places children at risk for a lethal ventricular arrythmia known as torsades de pointes (question 104). Type I second-degree AV block (also known as Wenckebach) is characterized by progressive prolongation of the PR interval leading to failed AV conduction (question 105). First-degree AV block is characterized by PR prolongation without failed AV conduction. Type II second- degree AV block is an abrupt failure of AV conduction without progressive prolongation of the PR interval.
78. **The answer is A** [, section I.E.2]. The patient's restrictive vegan diet places her at risk for vitamin B12 deficiency. Clinical findings of B12 deficiency include hyporeflexia, ataxia, and a smooth red tongue, in addition to the classic symptoms and signs associated with anemia (fatigue and pallor). Vitamin B12 deficiency leads to a macrocytic anemia with a mean corpuscular volume (MCV) >95. Diagnosis is confirmed with low serum vitamin B12 levels. Other causes of vitamin B12 deficiency include pernicious anemia, inflammatory bowel disease, and short gut sydrome. This patient would not be expected to have a low white blood cell count or prolonged international normalized ratio (INR) based on the described symptoms and signs. Hyponatremia can produce fatigue and neurologic symptoms; however, symptomatic hyponatremia usually presents more acutely than the several month history noted in this case.
79. **The answers are E, A, and D, respectively** [, Figure 14-1]. Females with Turner syndrome are at risk for developing gonadoblastomas, a neoplasm that occurs in dysgenetic gonads (question 107). Risks for other types of cancer in patients with Turner syndrome are likely similar to that of the general population. Patients with Down syndrome are at risk for both

transient myeloproliferative disorder, and subsequently for acute myelogenous leukemia (question 108). Ataxia telangiectasia is characterized by immunodeficiency which may cause recurrent sinopulmonary disease, leading to chronic lung disease with bronchiectasis and pulmonary fibrosis. Patients with ataxia telangiectasia will develop malignancy, the majority of which are lymphomas (question 109).

80. **The answer is B** [, section IV.A.1, Figure 17-3 and Table 17-5]. This child has benign intoeing due to tibial torsion. Tibial torsion is distinguished from the other common causes of intoeing —metatarsus adductus and femoral anteversion—based on age and the thigh–foot angle with decreased external rotation. Metatarsus adductus is typically identified in children younger than 1 year, and femoral anteversion is typically identified in children older than 3 years. Talipes equinovarus ("club foot") is present at birth and has a fixed inversion and equinus position of the foot with minimal flexibility. Genu varum presents with bowed legs rather than intoeing.
81. **The answer is C** [, section IX.B.4.a]. The correct answer is to recheck the thyroid-stimulating hormone (TSH) and thyroxine (T4) levels. These results should be available rapidly, and levothyroxine can be initiated when hypothyroidism is confirmed. No delay should occur in repeat testing, and it would not be appropriate to wait 1 week to contact the family. Referral to a pediatric endocrinologist for additional workup may well be indicated once hypothyroidism is confirmed. Thyroid imaging may be useful once the diagnosis is confirmed.
82. **The answer is E** [, section II.A.5]. Testicular enlargement is the first sign of puberty in boys. Puberty refers to the activation of hypothalamic–gonadal axis. Puberty generally begins after the age of 9 years and is not considered delayed until after the age of 14 years. Typically, patients develop more classical signs of puberty (voice change, growth spurt, and facial hair) at the later stages of puberty. It is important to realize that the growth spurt in boys occurs late in puberty as compared with girls in which the growth spurt occurs early in puberty. Apocrine odor is a sign of adrenarche. The timing of adrenarche is not linked to activation of the hypothalamic–gonadal axis. Therefore, the presence of apocrine odor does not indicate that a patient is in puberty.
83. **The answer is B** [, section XIV.E-F]. This infant has a febrile urinary tract infection (UTI) consistent with pyelonephritis. Bagged urine cultures, especially in uncircumcised infants, are unreliable. This infant is also at risk for having significant vesicoureteral reflux because of the positive family history of kidney failure from reflux nephropathy and because of his history of prenatal hydronephrosis. Infants with suspected pyelonephritis should be admitted to the hospital for intravenous antibiotics for 2–3 days, pending the results of the catheterized urine culture and sensitivities, and then complete a 14-day course of antibiotics as an outpatient. Uncircumcised male infants under six months of age are at a greater risk for UTI than circumcised infants. An imaging evaluation is important in this infant because of both the pyelonephritis and the positive family history. It is useful to obtain the renal ultrasound in the first day or two in the hospital to assess for severe hydronephrosis that might require urgent urologic consultation. The voiding cystourethrogram (VCUG) should be postponed until the urine culture is subsequently shown to be negative. It will be important for the radiologist to assess the posterior urethra during the VCUG to rule out a posterior urethral valve. Although vesicoureteral reflux may not be as serious as previously thought, the highest risk group for renal parenchymal damage is the child younger than 2 years with vesicoureteral reflux and pyelonephritis.
84. **The answer is B** [, Table 8-1]. The murmur described in the vignette is a venous hum that results in a vibratory hum throughout the cardiac cycle as blood returns from the head through the internal jugular vein. The murmur disappears either when the child is supine or turns his or her head or when placing a finger over the internal jugular vein. Turbulence within the carotid artery would typically produce a bruit that would be a sign of obstruction

within the carotid artery, usually from plaques. A bruit would be unusual in a 7-year-old, but there are rare circumstances where a bruit may be appreciated. A patent ductus arteriosus (PDA) would be a continuous machinelike murmur, which should not be affected by position. Choice D refers to extra heart sounds, such as clicks transmitted to the aorta in aortic stenosis or bicuspid aortic valves. These murmurs are unaffected by the patient's position. Benign, functional cardiac murmurs that are "musical" in nature are typically systolic and are heard over the precordium.

85. **The answer is B** [, sections V.F.3.d and VI.C.3]. This vignette describes a very worrisome episode of syncope that occurred when the patient was exercising. The most concerning cardiac pathologies associated with this presentation include long QT syndrome and hypertrophic cardiomyopathy. Syncope with exercise is a "red flag" and should be fully investigated immediately by a pediatric cardiologist before any of the other interventions may be considered.
86. **The answer is B** [, section V.D.4]. The patient's history and findings, especially sharp pain that worsens when lying down, in the face of a pulsus paradoxicus, are classic for pericarditis with a pericardial effusion. The remainder of the physical findings would not be characteristic of pericarditis. Other common findings of pericarditis include a pericardial rub and muffled heart sounds. Bounding pulses are typically seen when there is significant reversal of blood flow, such as a large patent ductus arteriosus (PDA) or severe aortic regurgitation. An apical click is associated with a bicuspid aortic valve.
87. **The answer is C** [, Table 8-1]. The examination describes a healthy child with a benign family history. Her murmur as described is typical for a benign Still's (left ventricular outflow tract) murmur.
88. **The answer is C** [, section V.D.2]. This presentation is consistent with hand–foot–mouth disease, a contagious viral infection caused by coxsackievirus (an enterovirus). Painful blisters typically develop on palms, on soles, and in the mouth. This is typically a self-limited illness and does not required specific treatment. Amoxicillin is not recommended given that this is a viral infection. Acyclovir, an antiviral that has activity against herpes viruses, is not indicated for enteroviral infection.
89. **The answer is C** [Chapter 16, section II]. The constellation of findings is consistent with Kawasaki disease. She meets criteria with at least 5 days of fever, conjunctivitis, mucous membrane changes, rash, and a unilateral lymph node. This is an inflammatory condition, not infectious, and so antibiotic therapy is not indicated. While patients with Kawasaki disease may develop aseptic meningitis, the next best step in management is to treat with intravenous immune globulin (IVIG) and high-dose aspirin to prevent cardiac sequelae. Although steroids have been used in treatment of refractory Kawasaki disease, they have no role in primary therapy. Her risk of developing coronary artery aneurysms if left untreated is approximately 20%.
90. **The answer is A** [, section XVI.B]. This child's presentation and computed tomography (CT) findings (a parenchymal cyst that may be enhancing) are consistent with neurocystercercosis. New-onset seizures in a child from a developing country should include evaluation for parasite infection and neuroimaging. Anticonvulsant therapy may be indicated, but discontinuation of antiepileptic medication after 2 years of being seizure free can be considered. Patients usually acquire neurocystercercosis from ingestion of *Taenia* eggs, not from ingesting raw pork, but via the fecal oral route after contact with someone infected with the adult tapeworm, excreting eggs in their stool. Patients with neurocysticercosis have *Taenia* eggs or adult tapeworm identified in their stools only 25% of the time. Surgical intervention, and placement of a ventriculoperitoneal shunt, is only required if there is concomitant obstructive hydrocephalus, which is not present in this case.
91. **The answer is C** [, section VIII.B.1 and Chapter 1, section III.C.6]. Mumps virus is the most

common cause of viral parotitis, but other viruses can be implicated. Mumps is a vaccine-preventable disease, and the vaccine is recommended for administration at 12 months of age and again at kindergarten entry, but can be given any time with at least 4 weeks following the first vaccine. Diagnosis of mumps is made by culturing the virus from urine or by serologies, but not from parotid gland aspiration. Congenital infection with mumps has not been described. There is no recommendation to vaccinate with a measles, mumps, and rubella (MMR) vaccine before college entry, unless an individual has not yet received two vaccines.

92. **The answer is C** [, section IV.I]. Although universal tuberculosis screening was required for school entry in the past, targeted screening based on risk factors is now recommended. Indications for tuberculosis testing include birth in a high-risk area outside of the United States, travel for >1 week (cumulative) in a high-risk area outside of the United States, history of exposure to someone with active tuberculosis, or close contact with anyone with a positive skin test for tuberculosis (TB).
93. **The answer is C** [, section XIV.C]. The patient in this scenario is immunosuppressed and is taking an anti–tumor necrosis factor (TNF) drug, which will impair her T-cell immunity. She is therefore at risk for severe and disseminated disease. Other patients at high risk include young infants, pregnant women, and the elderly. Most infections are asymptomatic, although severe pulmonary infections can occur in healthy persons. Complications of systemic disease include meningitis, osteomyelitis, and lymphadenitis. Coccidioidomycosis is endemic in the Southwestern United States, northern Mexico, and areas of Central and South America. Histoplasmosis, another endemic fungal infection, is endemic in other parts of the country, including the Mississippi River Valley. Coccidioidomycosis is treated with antifungal medications (fluconazole).
94. **The answer is E** [, section XVII.A.2]. This boy likely has Rocky Mountain spotted fever (RMSF). He has fever, headache, and a typical rash and has just returned from an endemic area. Given that he is ill-appearing and has a petechial rash, sepsis with typical bacterial pathogens should also be considered. Empiric coverage of both rickettsial and typical bacterial pathogens includes doxycycline and a third generation cephalosporin. RMSF is a life-threatening infection and empiric treatment should be given rather than only supportive care.
95. **The answer is B** [, section XIII.A.3.b]. Children with perinatally acquired human immunodeficiency virus (HIV) infection are frequently asymptomatic in the first year of life but then develop recurrent common bacterial infections, including otitis media and pneumonia. Failure to thrive is a common presenting symptom as well. Other findings include difficult to treat thrush, *Pneumocystis jirovecii* pneumonia (PCP), and loss of developmental milestones. These symptoms may overlap with an adult presentation of HIV infection, but it would be very unusual for a young child with HIV infection to present in the first few years of life with cytomegalovirus (CMV) retinitis, shingles, or central nervous system (CNS) lymphoma, all which are acquired immunodeficiency syndrome (AIDS)–defining illnesses in adults with HIV infection. Children with perinatally acquired HIV infection do not develop Kaposi sarcoma in childhood, which may be a presenting sign in adults with a new diagnosis of HIV infection.
96. **The answer is C** [, section XI.C.2 and Table 7-6]. This child may have enterohemorrhagic *E. coli* (EHEC) and hemolytic uremic syndrome (HUS), given her decreased urine output and pallor. In this case, further examination should be done to confirm HUS. A complete blood count (CBC) should be obtained to examine for thrombocytopenia, as well as a peripheral smear to look for microangiopathic hemolytic anemia. She should not be given antibiotics, as this may increase the risk of HUS. Rehydration solutions should not contain KCl until her urine function is evaluated. Given that she has bloody diarrhea, she is not likely to have *Giardia lamblia.* Although *Clostridium difficile* can be a cause of bloody diarrhea in children, empiric treatment with antibiotics is not indicated in this child.

97. **The answer is B** [, section III.C.11]. Human papilloma virus (HPV) is one of the most common sexually transmitted disease in the United States. The vaccine is ideally administered before the onset of sexual activity to develop protective immunity but may be administered to males through age 21 years and to females through age 26 years. Vaccination is recommended for both males and females to decrease the contagious risk and to lower the risk of complications, including cervical, anal, oropharyngeal and penile cancers. Along with hepatitis B vaccine, HPV vaccine is one of the few cancer-preventive immunizations.
98. **The answer is E** [, Table 1-5]. Vitamin D supplementation is essential for bone health in the pediatric population, especially to prevent conditions such as rickets in infants and toddlers. Vitamin D facilitates the dietary absorption of calcium from the gastrointestinal (GI) tract. During the first year of life, the recommended daily dose is 400 IUs. To meet the daily recommended dose, formula-fed infants would need to ingest 1 L of formula/day. Most infants will not ingest this volume until 4 months of age or older. Maternal supplementation with vitamin D will not prevent vitamin D deficiency in infants, as breast milk contains low levels of vitamin D. Introduction of cow's milk before 12 months of age has been associated with iron-deficiency anemia and is therefore not recommended.
99. **The answer is C** [, Tables 1-1 and 1-3]. This 12-month-old patient is demonstrating inadequate weight gain. While this patient's current weight is approximately twice her birth weight, on average, infants triple their birth weight by 12 months of age. The clinician should take a detailed history about possible causes of failure to thrive, focusing in particular on caloric intake. Other aspects of her health screening are normal, including her head circumference, language and ambulation skills, as well as her hemoglobin and lead levels.
100. **The answers are C, B, D, E, and A, respectively** [, section IV and Table 7-3]. Enteroviral meningitis is characterized by low-level pleocytosis, with normal chemistries and a negative Gram stain. A normal cerebrospinal fluid (CSF) profile usually has less than 10 white blood cells (WBCs). Note that this can be higher in neonates but is typically <10 in healthy infants and children, with protein and glucose in the normal range. Tuberculous meningitis is characterized by moderate pleocytosis, with slightly low glucose, but markedly elevated protein, and a negative Gram stain. The CSF in partially treated bacterial meningitis typically shows an elevated WBC count with low glucose and high protein (similar to untreated bacterial meningitis), but negative Gram stain owing to antibiotic administration. The CSF profile in pneumococcal meningitis typically has a very elevated WBC count, depressed glucose, elevated protein, and a positive Gram stain (in this case gram-positive diplococci suggest pneumococcal meningitis, and gram-negative diplococci would be suggestive of *Neisseria meningitidis*).
101. **The answer is A** [, sections III.D-E]. Although most vaccines cause local pain and redness in the immediate period, some live attenuated vaccines such as measles, mumps, and rubella (MMR) and varicella zoster virus (VZV) vaccines can cause a fever and rash 1–2 weeks after administration. Mild febrile illness (e.g., upper respiratory infection) is not a contraindication for immunizations. No reputable studies have shown a link between vaccines and autism or developmental disabilities. Thimerosal has also not been linked with developmental disability, but as a precautionary measure to reassure the public, thimerosal has been removed from almost all pediatric immunizations.
102. **The answer is D** [, section VI.E.4]. A history of upper respiratory infection preceding periorbital and peripheral edema suggests the possible diagnosis of nephrotic syndrome, the most common form of which is minimal change disease. Diagnostic criteria include heavy proteinuria, hypoalbuminemia, hypercholesterolemia, and edema. Patients with nephrotic syndrome are at increased risk for infection with encapsulated organisms such as *Streptococcus pneumoniae*, and may therefore present with spontaneous bacterial peritonitis, pneumonia, or overwhelming sepsis. In this case, given the fever on presentation, after a blood culture is

drawn, the patient should be started on empiric broad-spectrum antibiotic coverage. Patients with nephrotic syndrome also have a predisposition to thrombosis and not bleeding. The presence of red blood cell (RBC) casts would suggest a diagnosis of glomerulonephritis and not nephrosis. Infection with a toxin-producing bacteria may predispose to hemolytic uremic syndrome. Hearing loss is associated with Alport syndrome, most commonly inherited in an X-linked dominant fashion, and characterized by hypertension, hematuria, progressive hearing loss that starts in childhood, and ocular abnormalities in a subset of patients.

103. **The answer is C** [, section V.D.2]. This child's presentation is most consistent with scabies infestation's given the location of the papules on the wrists and along the waistline, as well as the presence of similar symptoms in the parents. The most appropriate treatment is overnight application of permethrin 5% cream for the whole family, with a repeat treatment in 1 week to catch the newly hatched mites. Topical corticosteroids and oral diphenhydramine could be used to help treat the pruritus associated with scabies infestation, but they are not effective as primary treatments. Cantharidin is indicated for the treatment of molluscum contagiosum, not for scabies infestation.
104. **The answer is A** [, section II.C.5]. Applied behavior analysis (ABA) has the most evidence to support its use in the treatment of young children with autism spectrum disorder. Developmental play–based interventions such as floor time, sensory integration therapy, and auditory integration therapy are frequently used but have not yet been shown to be as effective for the core symptoms in children with autism spectrum disorder. Iron chelation is a highly controversial biomedical treatment that carries a significant risk for physical harm to the child.
105. **The answer is C** [, section V.C.5]. This toddler's presentation with a papular rash affecting the extremities and cheeks that has lasted >2 weeks is most consistent with Gianotti–Crosti syndrome (GCS). Also known as papular acrodermatitis, GCS most often occurs in children between the ages of 6 months and 12 years and is associated with hepatitis B, Epstein–Barr virus, enterovirus, and echovirus infections. Roseola presents as a pink papular rash that lasts only a few days and is preceded by a high fever, and varicella is associated with vesicular and crusted skin lesions as well as fever. The rash of fifth disease is a "slapped cheek" rash followed by a lacy reticulate rash on the extremities. Although the rash of pitryiasis rosea can also last several weeks, it is more common in older children presenting with oval pink scaling plaques on the trunk and extremities.
106. **The answer is D** [, section II.E.6]. Annual screening tests for a sexually active girl who is not consistently using a barrier method with each sexual encounter should include nucleic acid amplification tests (NAATs) of urine or a vaginal swab for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, serologic test for syphilis, and human immunodeficiency virus (HIV) testing. Routine screening of adolescents who are asymptomatic for *Trichomonas vaginalis*, bacterial vaginosis, herpes simplex, and human pailloma virus (HPV) is generally not recommended.
107. **The answer is E** [, section IV.A and Table 18-2]. This infant is presenting with nasolacrimal duct (NLD) obstruction. NLD obstruction is characterized by watery eye with increased tear lake, matted eyelashes, and often mucous in the medial canthal area. It resolves spontaneously without treatment in over 80% of cases by age 9–12 months, and so observation only would be the most appropriate management at this time. NLD probing by ophthalmology may be needed in older infants if the obstruction does not resolve. Because conjunctivitis is not present, topical antibiotics would not be indicated. *Chlamydia trachomatis* infection presents at 4–10 days of life, often with purulent or serous discharge.
108. **The answers are B and D, respectively** [, sections XI.A.4 and XII.D]. Chronic granulomatous disease (CGD) is characterized by defective neutrophil oxidative metabolism that results in impaired intracellular killing of catalase-positive bacteria and some fungal pathogens. Presentation classically includes abscess formation, and history of infection of the bones, skin,

liver, spleen and lungs. *Aspergillus* species is one of the major pathogens associated with CGD. Diagnosis is made by performance of the dihydrorhodamine (DHR) flow cytometry test (question 142). Deficiency of the late components of the classic pathway of complement (C5, C6, and C8) is associated with susceptibility to meningococcal infection. Testing for total serum hemolytic complement (CH^{50}) will evaluate for normal functioning of the classic complement pathway (question 143).

109. **The answer is C** [, sections I and V.D]. The child in the description has suffered anaphylaxis, a severe, potentially life-threatening, systemic reaction. Any child who has had a severe systemic reaction to insect venom should be prescribed intramuscular epinephrine, and an emergency plan should be developed, providing instruction on what to do in the event of a future reaction. As allergy immunotherapy can significantly reduce the rate of reactions in those sensitive to insect venoms, all patients should be referred to an allergist for consideration of venom immunotherapy. Although diphenhydramine and corticosteroids may be useful in severe allergic reactions, epinephrine is the principal treatment. Instruction on management of local reactions and removal of a stinger may be helpful but are not as important as prescribing epinephrine.
110. **The answer is B** [, section IX.C.4]. The physical examination of this adolescent boy, in which the left testicle feels like a "bag of worms" that diminishes in size when the patient is supine, is consistent with a diagnosis of a left varicocele. In most cases, no surgical intervention is needed for the treatment of a varicocele and reassurance only may be given. An emergent urology referral is indicated if the examination was consistent with a diagnosis of testicular torsion. If the patient were sexually active, a nucleic acid amplification test (NAAT) for gonorrhea and chlamydia would be indicated. A cystic mass on transillumination of the scrotum is consistent with the diagnosis of a hydrocele and painless inguinal swelling with a diagnosis of inguinal hernia.
111. **The answer is C** [, section II.D.6]. The current recommendations for the treatment of attention deficit/hyperactivity disorder (ADHD) vary based on the age of the patient. For preschool children, first-line treatment is parent- and school-based behavior management. If behavioral strategies are ineffective and moderate to severe impairments are seen in the child's functioning at home and preschool/child care and with peer interaction, then treatment with a stimulant medication is suggested. Organizational skills training and play therapy have not been shown to be effective as a first-line treatment at this age. A trial of nonstimulant medication is also not a first-line treatment.
112. **The answer is A** [, section V.A.3]. This patient's clinical presentation with nail dystrophy and skin changes between the toes is most consistent with tinea unguium (onychomycosis) and tinea pedis. Topical agents (clotrimazole) are not very effective for nail infection, but rather, systemic therapy (terbenafine) is indicated. Topical corticosteroids and topical vitamin D analogues are not appropriate for this condition but might be tried for psoriasis of the nails. Surgical removal of the nails is a last resort for chronic nail infection over many years.
113. **The answer is B** [, section III.B.2].The signs and symptoms of depression in an adolescent include behavioral, psychological, and physical manifestations that impair the teen's ability to function normally. A decrease in appetite, which eventually could lead to significant weight loss, fulfills one of the criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* to make a diagnosis of depression. Diminished interest in activities, fatigue, and energy loss are other general symptoms. A patient must fulfill five or more of nine specific criteria almost every day for at least 2 weeks to make a definitive diagnosis of major depressive disorder. Other symptoms such as cough, abdominal pain, and headache with visual aura are not part of the *DSM-5* criteria, although abdominal pain and headache may be present in a depressed teen. In addition, teens who are depressed usually diminish their extracurricular activities, not increase them.

114. **The answer is A** [, sections IV.C.1.a and VIII.D.6]. This patient has suffered a major burn injury with inhalation of hot gases. Management of any trauma victim begins with management of the airway. Any evidence of burns to the lips, nose, or tongue, such as singed nasal hairs or presence of soot in the nasal/oral airways, indicates a risk for progressive airway compromise. Management would therefore include immediate endotracheal intubation. Delay in securing the airway emergently could potentially lead to airway obstruction secondary to edema and inflammation. The finding of cherry-red lips is a late manifestation of carbon monoxide poisoning. Although obtaining a chest x-ray and arterial blood gas and determining body surface area burned are important management steps, they are not as important initially as airway management.
115. **The answer is B** [, sections IV.E.2.b and IV.E.6.c]. Tobacco smoke exposure is a known risk factor for sudden infant death syndrome (SIDS). Other risk factors include sleeping in the prone position and overheating. Infants should sleep in their own crib with a firm mattress and no pillow or excessive blankets. Cardiorespiratory monitors have not been shown to prevent SIDS.

Index

Note: Page numbers followed by “f” indicate figures and “t” indicate tables.

A

Abdominal wall defects, 90

Abnormal vaginal bleeding, 63–65

Absence epilepsy, of childhood, 308

Absence seizures, 305, 305f

Abstract thinking, 27

Acetaminophen toxicity, 471–472, 471t

Achondroplasia, 107

  macrocephaly due to, 4

Acne, 452

Acne vulgaris

  clinical features, 452–453

  management, 453

  pathophysiology, 452

Acquired adrenal insufficiency, 136

Acquired aplastic anemia, 332

Acquired heart disease, 201–206

  acute rheumatic fever, 201

  cardiomyopathy, 204–206

  infective endocarditis, 201–202, 202t

  Kawasaki disease, 201

  myocarditis, 204

  pericarditis, 203–204, 203f

Acquired microcephaly, 3, 4t

Acquired torticollis, 404

Acuity assessment, 427

Acute abdominal pain

  causes, 245–247

  definition, 244

  etiology, 245f

  evaluation, 244

Acute cerebellar ataxia, of childhood, 312

Acute kidney injury (AKI), 283–284

Acute lymphocytic leukemia (ALL), 348–350

  causes, 348

  classification, 348

  clinical features, 348

  diagnosis, 348–349

    prognostic factors at time of, 349, 349t

  epidemiology, 348

  etiology, 348

management
bone marrow transplant, 349
complications, 349–350
consolidation stage, 349
delayed intensification, 349
induction stage, 349
maintenance therapy, 349
prognosis, 350
Acute myelogenous leukemia (AML)
Auer rods, 350
causes, 350
classification, 350
clinical features, 350
diagnosis, 350
disorders associated with, 350
epidemiology, 350
etiology, 350
management, 350
prognosis, 350
Acute otitis media (AOM), 160–161
Acute pancreatitis, 246–247
Acute rheumatic fever, 201
Acyanotic congenital heart disease, 188–195, 189f, 189t, 190f, 190t, 191f, 193f, 194f
aortic stenosis, 195
atrial septal defect, 188–191, 189f, 189t, 190t
clinical and diagnostic features, 188
coarctation of the aorta, 194–195, 194f
patent ductus arteriosus, 193–194, 194f
pulmonary stenosis, 195
ventricular septal defect, 191, 191f, 194
Adaptive responses, 373
Additional disorders, 108
Adenosine deaminase deficiency, 375
ADHD *Attention deficit/hyperactivity disorder (ADHD)*
Adolescent
growth and development, 45–46, 46t
health screening, 46–51, 47f–49f, 50t
Adrenal gland disorders, 134–137
acquired adrenal insufficiency, 136
CAH, 135–136
classification, 134–135
general principles, 134
glucocorticoid excess, 136–137
β-Adrenergic agonists, for anaphylaxis, 367
Adrenocorticotropic hormone (ACTH), for infantile spasms, 308
Afebrile seizures, 305, 305f
α-Fetoprotein (AFP), 102
Alagille syndrome, 257–258

Alanine aminotransferase (ALT), 255
Alcoholism, 53
Allergen skin testing, 368
Allergic colitis, 254
Allergic conjunctivitis, 430, 431
Allergic contact dermatitis, 443
Allergic rhinitis, 367–369, 368f
  clinical features, 368
  defined, 367
  diagnosis, 368
  epidemiology, 367
  etiology, 367
  management
    allergen avoidance, 368–369
    immunotherapy, 369
    patient education, 369
    pharmacotherapy, 369
  pathophysiology, 368
  perennial, 367
  seasonal, 367
Allergy
  allergic rhinitis, 367–369, 368f
  atopic dermatitis, 369–370, 370t
  drug, 372
  food, 370–371
  insect venom, 371
  latex, 371
  urticaria, 371, 372t
Alloimmune hemolytic anemia, 324f, 329
Alopecia areata
  clinical features, 451–452
  epidemiology, 450
  etiology, 450
  management, 452
α-fetoprotein (AFP), in spina bifida detection, 302
Ambiguous genitalia
  differential diagnosis of, 133
  evaluation, 133–134, 134f
Amblyopia
  clinical features, 428
  defined, 428
  diagnosis, 428
  epidemiology, 428
  etiology, 428
  management, 428
Amebiasis, 174
Amenorrhea, 63, 64t
Amino acid metabolism defects, 110–114, 112t, 113t

homocystinuria, 111–113, 112t–113t
organic acidemias, 113–114
urea cycle disorders, 112t–113t, 113
Amniocentesis, 102
Amniotic band syndrome, 109
Amniotocele (dacryocele), 432
Anaphylactic shock, 460
Anaphylactoid, 372
Anaphylaxis
clinical features, 367
defined, 367
diagnosis, 367
etiology, 367
insect venom allergy, 371
management, 367
Anemia, 323–331
classification, 323, 324f
clinical features, 324t
concepts, 323
defined, 323
epidemiology, 323
fetal hemoglobin, 323
folic acid deficiency, 326–327
glucose-6-phospate dehydrogenase deficiency, 327–328, 328t
hemoglobin and age, 323
hemolytic, 327
alloimmune, 329
autoimmune, 328–329
microangiopathic, 329
hereditary elliptocytosis, 328
hereditary spherocytosis, 327
iron-deficiency, 324–325
lead poisoning, 326
macrocytic, 323, 326–327
microcytic, hypochromic, 323–326
normocytic, normochromic, 323, 327–331, 328t, 330t, 331t
RBC aplasias, 327, 331, 332t
RBC defects, 327–329
sickle cell, 330–331, 330t, 331t
sideroblastic, 326
thalassemias, 325–326
vitamin B_{12} deficiency, 327
Angelman syndrome, 106
Angulation of knee, 415
Ankylosing spondylitis, 395
Ann Arbor system, 352
Anorexia nervosa, 54–55, 55t

Anticipatory guidance, 16, 17t–18t
topics for, age-appropriate, 16, 17t–18t
Antidotes, 471t
Anti-double-stranded DNA (anti-dsDNA) antibodies, in SLE, 390
Antihistamines
for allergic rhinitis, 369
for anaphylaxis, 367
for Atopic dermatitis, 370
for urticaria (hives), 371
Antinuclear antibody (ANA), 387
Antiphospholipid antibodies, in SLE, 390
Anti-Smith (anti-Sm) antibodies, in SLE, 390
Antithrombin III deficiency, 339
Anxiety, 36–37
Aortic stenosis, 195
Apnea, apparent life-threatening event (ALTE), 229–230
Apnea of prematurity, 84–85
Appendicitis, 245–246
Arterial blood gas (ABG), 217
Arthralgias, 447
Arthritis, 392
inflammatory bowel disease associated, 395
psoriatic, 395
reactive, 395
rheumatic fever, 392
Aseptic meningitis, 158–159, 158t
Aspartate aminotransferase (AST), 255
Aspergillosis, 173
Aspiration pneumonia, juvenile dermatomyositis, 391
Asthma, 222–225, 223f, 225f, 372
Astrocytoma, 353
Astrocytomas, 354
Ataxia, 311
Ataxia telangiectasia, 376
Atlantoaxial instability, 404–405
Atopic dermatitis, 369–370, 370t, 444
acute *vs.* chronic manifestations, 369, 370t
clinical features, 369–370
defined, 369
diagnosis, 370
epidemiology, 369
management, 370
Atresias, 243
Atrial septal defect, 188–191, 189f, 189t, 190t
Attention deficit/hyperactivity disorder (ADHD)
assessment and diagnosis, 31
clinical features, 30
differential diagnosis, 31t

epidemiology and etiology, 30
management, 31
medications, 31–32, 32t
potential consequences, 31
Atypical hemolytic uremic syndrome (aHUS), 280
Autism spectrum disorder, 29–30
associated conditions, 30
clinical features, 30
epidemiology, 29
etiology, 29
management, 30
Autoimmune hemolytic anemia (AIHA), 324f, 328–329
Autoimmune hepatitis, 260–261
Autosomal dominant mode of inheritance, 100
Autosomal recessive mode of inheritance, 100

B

Back pain, 407–408, 407t
Bacterial infections, 163–165
Bacterial meningitis, 156–158, 157t
Bacterial pneumonia, 222
Bacterial tracheitis, 219
Bacterial vaginosis (BV), 58–59
BAER (brainstem auditory evoked response), in hearing screening, 11
Balanitis, 14
Becker muscular dystrophy (BMD), 314–315
clinical features, 315
defined, 314
diagnosis, 315
epidemiology, 315
etiology, 315
management, 315
pathology, 315
pathophysiology, 315
prognosis, 315
Beckwith-Wiedemann syndrome, 356
Beckwith–Wiedemann syndrome, 106
Behavioral concerns, 33–38
anxiety, 36–37
breath-holding spells, 37
colic, 33–34
discipline issues, 38
encopresis, 35
enuresis, 34–35
selective eating, 36
sibling rivalry, 37
sleep problems, 35–36
temper tantrums, 37

toilet training, 38
Benign epilepsy with centrotemporal spikes (BECTS), 308
Benign rolandic epilepsy *Benign epilepsy with centrotemporal spikes (BECTS)*
Berger disease, 277
Bernard-Soulier syndrome, 338
Bilateral conjunctivitis, 384
Biliary atresia, 257
Biliary enzymes, 255
Bilirubin, 86, 255
Binge drinking, 54
Binocular vision, 428
Biologic poisonings
black widow spider, 475–476
brown recluse spider, 476
coral snakes, 477
pit viper snakes, 476
Black widow spider, 475–476
Bleeding, gastrointestinal
definitions, 253
laboratory confirmation, 253
lower, 254
UGI bleeding, 253–254
Blepharitis, 432
Blood vessel, disorders of, 337
Blount disease, 415
Body mass index, 1
Body surface area (BSA), 464
Bone and joint infections, 166
Bone marrow transplant
for acute lymphocytic leukemia, 349
for acute myelogenous leukemia, 350
Bone marrow transplantation, chronic granulomatous disease, 377
Bone mineral disorders, 142–144
Bone tumors, 357–359
Ewing sarcoma, 358–359
osteogenic sarcoma, 357–358
Borrelia burgdorferi, Lyme disease, 394
Brachycephaly, 4
Bracing prevents progression, 405
Brain tumors, 353–354
classification, 353
clinical features, 353
diagnosis, 354
epidemiology, 353
grade, 353
histology, 353
location, 353
management, 354

prognosis, 354
signs and symptoms, 353–354
Brainstem auditory evoked response (BAER), in hearing screening, 11
Brainstem gliomas, 354
Breath-holding spells, 37
Bronchiolitis, 220–221
Bronchopulmonary dysplasia, 227–228
Brown recluse spider, 476
Bruton tyrosine kinase *(BTK)* gene, 377
Buccal cellulitis, 164
Bulimia nervosa, 54–55, 55t
Burkitt lymphoma, 352
Burns, 464–465
body surface area, 464
classification, 464
epidemiology, 464
first-degree, 464
management, 464–465
second-degree, 464
third-degree burns, 464

C

CAGE questionnaire, 54
Calcaneal apophysitis, 416
Calcium, for juvenile dermatomyositis, 391
Caloric irrigation, in comatose patients, 304
Campylobacter jejuni, Guillain-Barré syndrome, 312
Cancer
bone pain, 347
bone tumors, 357–359
brain tumors, 353–354
bruising, 347
causes, 347
early morning headache with vomiting, 347
environmental factors and, 347
etiology, 347
fever, 347
genetic disorders, 347, 348t
germ cell tumors, 359–360
hypertension, 348
immunodeficiency diseases and, 347
infectious diseases and, 347
Langerhans cell histiocytosis, 360–361
leukemias, 348–351
leukocoria, 348
liver tumors, 359
lymphomas, 351–353, 351t
neuroblastoma, 354–356

pallor, 347
palpable mass, 347
petechiae, 347
presenting features, 347
renal tumors, 354–357, 355t
retinoblastoma, 359
soft tissue tumors, 357
supraclavicular lymphadenopathy, 347
suprarenal tumors, 354–357, 355t
Wilms tumor, 356–357
Wiskott-Aldrich syndrome, 347
X-linked lymphoproliferative disease, 347
Candidal vulvovaginitis, 59
Candidiasis, 173
CAP (chronic abdominal pain)
clinical features, 248
definitions, 247–248
evaluation, 248
management, 249
prognosis, 249
risk factors, 248
Caput succedaneum, 3
Carbohydrate metabolism defects, 114–115
Carbohydrates, 15
Carbon monoxide, 474
Cardiac chest pain, 208–209, 209f
Cardiogenic shock, 460
Cardiology
acquired heart disease, 201–206
acyanotic congenital heart disease, 188–195, 189f, 189t, 190f, 190t, 191f, 193f, 194f
chest pain, 208, 209f
congestive heart failure, 187–188
cyanotic congenital heart disease, 196–201, 196t, 197f, 198t, 199f, 200f, 201f
dysrhythmias, 206–208, 206t, 207f
innocent cardiac murmurs, 188
Cardiomyopathy, 204–206
Cardiovascular system
systemic lupus erythematosus, 389
Caries, nursing, 15–16
Cartilage-hair hypoplasia syndrome, 340
Cat bites, 475
Cat scratch disease, 178–179
Celiac disease, 238–239
Cellulitis, 163–164
Cellulitis, important variants of, 164
Central hypotonia, 296
Central nervous system (CNS), systemic lupus erythematosus, 389
Central precocious puberty (CPP), 150

Central (or isosexual) precocious puberty (CPP), 129
Cephalohematoma(s), 3
Cerebral palsy, 27–28, 28t
Cervical adenopathy, 384
Cervical hydrosyringomyelia, and myelomeningocele, 301
Cervical lymphadenitis, 162
Cervical spine disorders, 404–405
Cervicitis, 59
Cervicitis trachomatis, 59–60
CHARGE Syndrome, 108
Chédiak-Higashi syndrome, 340, 378
Chemotherapy
  for brain tumors, 354
  for neuroblastoma, 356
Chest pain, 208, 209f
Chiari type II malformation, 300
Child abuse, 466–468
  concepts, 466
  physical, 466–467
  sexual, 467–468
Child cardiopulmonary resuscitation (CPR), 459–460
  airway, 459
  breathing, 459
  circulation, 459
  concepts, 459
  cycles, 460
  sequence, 459
Child with possible infection, 151
Chlamydia trachomatis infection, 33
Cholecystitis, 247
Cholestatic diseases of infancy, 256–258
Cholestatic jaundice, 255
Chorionic villus sampling (CVS), 102
Chromosomal (micro) deletion syndromes, 104–105
Chronic abdominal pain (CAP)
  clinical features, 248
  definitions, 247–248
  evaluation, 248
  management, 249
  prognosis, 249
  risk factors, 248
Chronic benign neutropenia (CBN), of childhood, 339
Chronic granulomatous disease (CGD), 377
Chronic kidney disease (CKD)
  clinical features, 284
  etiology, 284
  evaluation, 284
  management, 285

Chronic myelogenous leukemia (CML), 350–351
adult-type, 350, 351
classification, 350
clinical features, 351
epidemiology, 350
juvenile, 350, 351
management, 351
prognosis, 351
Circumcision, 13–14
CKD (chronic kidney disease)
clinical features, 284
etiology, 284
evaluation, 284
management, 285
Clavicular fractures, 417–419
Cluster headaches, 311
Coarctation of the aorta, 194–195, 194f
Cobb angle, 405, 406f
Coccidioidomycosis, 173–174
Cognitive deficits, 28–29, 29t
Cognitive development, 26–27
Cognitive-behavioral therapy (CBT), 37
Colic, 33–34
Collagen synthesis, inherited disorders of, 337
Coma
assessment, 302–304
causes, 302, 303t
in childhood and adolescence, 303t
defined, 302
etiology, 302
evaluation, 304
Comatose patient, 302–303, 303t *Coma*
assessment, 302–304
evaluation, 304
Common acute lymphocytic leukemia antigen (CALLA), 348
Common variable immunodeficiency
clinical features, 375
defined, 374
diagnosis, 375
epidemiology, 374
etiology, 375
management, 375
Compensated shock, 460
Complement, decreased, in SLE, 390
Complement system, disorders of, 378
Concrete thinking, 27
Congenital aplastic anemia, 332
Congenital aqueductal stenosis, 300

Congenital cataract, 435
Congenital diaphragmatic hernia, 89–90
Congenital glaucoma, 429, 434
  clinical features, 434
  defined, 434
  etiology, 434
  management, 434
  prognosis, 434
Congenital heart block, systemic lupus erythematosus, 389
Congenital microcephaly, 3, 4t
Congenital muscular torticollis, 6, 404
Congenital myasthenia, 316
Congenital myotonic dystrophy, 299
Congestive heart failure (CHF), 187–188
Conjunctivitis
  allergic, 430, 431
  bacterial, 430
  causes, 430
  chemical, 429
  with contact lens use, 430
  hemorrhagic, 431
  neonatal
    clinical features, 429, 429t, 430t
    defined, 429
    differential diagnosis, 429
    etiology, 429
  unilateral, 430
  viral, 431
Connective tissue disorders, 107
Constipation
  definitions, 249
  epidemiology, 249
  etiology, 249–250
  evaluation, 250
  management, 250
  normal stool patterns, 249
Contact dermatitis
  allergic, 443
  defined, 443
  primary irritant, 443
Contraception
  abstinence, 56
  barrier methods, 56
  etonogestrel implant, 56–57
  injections, 57
  intrauterine devices, 56
  methods, 57t
  oral, 57

vaginal ring, 57
Coral snakes, 477
Corneal abrasion, 433
Cornelia de Lange syndrome, 108
Coronary artery aneurysms
Coronary artery aneurysms, Kawasaki disease and, 385
Corticosteroids
for anaphylaxis, 367
for juvenile dermatomyositis, 391
malnutrition and, 337
for myasthenia gravis, 316
for rheumatic fever, 393
CRAFFT screening tool, 54
Cranial irradiation, 349
Craniopharyngioma, 354
Craniopharyngiomas, 353
Craniosynostosis, 4–6
clinical features of, 4–5
defined, 4
definition, 4
diagnosis of, 5
etiology, 4
management of, 6
CREST syndrome, 396
Cri du chat syndrome, 105
Crohn disease, 252
Crotalidae polyvalent antivenin, 476
Croup syndromes, 218–219, 218t
Cryptococcal infection, 174
Cryptorchidism, 66
Cyanosis
clinical significance, 80
definition, 80
etiology, 80
evaluation, 81
management, 81
Cyanotic breath-holding spells, 37
Cyanotic congenital heart disease, 196–201, 196t, 197f, 198t, 199f, 200f, 201f
general concepts, 196, 196t
TAPVR, 200–201, 201f
tetralogy of fallot, 197–198, 197f, 197t
TGA, 198
tricuspid atresia, 198–199, 199f
truncus arteriosus, 199–200, 199f
Cyclic neutropenia, 340
Cyclophosphamide, systemic lupus erythematosus, 390
Cystic fibrosis (CF), 225–227, 226t, 227f
Cysticercosis, 177

Cysts, 441

D

Dacryocystitis, 429
Dandy-Walker malformation, 300
Decompensated shock, 460
Decongestants, for allergic rhinitis, 369
Dehydration, 268–269
Delayed dental eruption, defined, 14
Delayed puberty, 130–131
Dental care, 14–16
  dental abnormalities, 15–16
  dental hygiene, 14–15
  dental trauma, 16
  tooth eruption, 14
Dental eruption
  delayed, defined, 14
  early, defined, 14
Dental floss, 15
Dental hygiene, 14–15
Dental trauma, 16
Depression, clinical features of, 52
Dermatology
  acne vulgaris, 452–453
  concepts, 441–443
  hair disorders, 450–452
  hypersensitivity disorders, 445, 445t
  inflammatory disorders, 443–445
  newborn skin diseases, 443
  pigmentary disorders, 450, 451t
  skin infections, 446–450, 448t
  vascular skin lesions, 453
Desmopressin acetate (DDAVP), 35
Development
  disorders
    attention deficit/hyperactivity disorder, 30–32, 31t, 32t
    autism spectrum disorder, 29–30
    cerebral palsy, 27–28, 28t
    cognitive deficits, 28–29, 29t
    intellectual disability, 28–29, 29t
    learning disabilities, 29
    motor deficits, 27–28, 28t
  normal
    assessment, 23–24
    cognitive development, 26–27
    domains, 24–27, 24t, 25t, 26t
    general principles, 23
    language skills, 25–26, 26t

milestones, 23–27, 24t, 25t, 26t
motor development, 24–25, 24t
social–emotional skills, 27
Developmental dysplasia of hip (DDH), 408–409
Developmental quotients (DQs), 24
Developmental screening, 16
Diabetes insipidus, 144–145
Diabetes mellitus, 137
Diabetic embryopathy, 109
Diabetic ketoacidosis (DKA), 139–140
Diarrhea, 166–168, 167t–168t
etiology, 166
evaluation, 166–167, 167t–168t
management, 167
Dietary counseling, for iron deficiency anemia, 325
DiGeorge, 104–105
DiGeorge syndrome, 376
Dihydrorhodamine (DHR), 377
Diphtheria
tetanus, and acellular pertussis (DTaP) vaccine, 7
Diplopia, 436
Discipline, basic premise of, 38
Discitis, 408
Disorders of adrenal gland, 134–137
Disorders of metal metabolism, 116–117
Disorders of puberty, 127–131
delayed, 130–131
normal, 127–128
precocious, 128–130
Disorders of sexual differentiation (DSD), 131–134
differential diagnosis, 132–133, 132f, 133f
female sexual differentiation, 132
male sexual differentiation, 131–132
normal sexual differentiation, 131, 131f
Disseminated intravascular coagulation (DIC), acquired clotting factor disorders, 337
Distributive shock, 460
Diurnal enuresis, management of, 35
Dog bites, 475
Doll's eyes, in comatose patients, 304
Dominant inheritance, 100
Double-blind placebo-controlled food challenge, in food allergy, 371
Down syndrome, 102, 103f, 103t
DQs (developmental quotients), 24
Drowning, 465–466
clinical features, 465–466
defined, 465
epidemiology, 465
management, 466

pathophysiology, 465
prognosis, 466
Drug allergy, 372
Duchenne muscular dystrophy (DMD), 314–315
clinical features, 315
defined, 314
diagnosis, 315
epidemiology, 315
etiology, 315
management, 315
pathology, 315
pathophysiology, 315
prognosis, 315
Duodenal hematoma, 464
Dysmenorrhea, 63
Dysrhythmias, 206–208, 206t, 207f
heart block, 207–208
long QT syndrome, 208
SVT, 206–207, 206t, 207f
Dysthymic disorder, 52
Dystrophin, 315

E

Early adolescence, 46
Early dental eruption, defined, 14
Ectoparasites, 449
Eczema *Atopic dermatitis*
Edema, scalp, 3
Edwards syndrome, 104
Ehlers–Danlos syndrome, classic type, 107
Electronic cigarettes (e-cigs), 53–54
Elemental iron, for iron deficiency anemia, 325
Emergency medicine
biologic poisonings, 475–477
burns, 464–465
child abuse, 466–468
child cardiopulmonary resuscitation, 459–460
drowning, 465–466
infant, 459–460
mammalian bites, 474–475
poisonings, 468–474, 470f, 471t, 473t
shock, 460–461
sudden infant death syndrome, 468
trauma, 461–464
Encopresis, 35
Endocrinology
bone mineral disorders, 142–144
diabetes insipidus, 144–145

diabetes mellitus, 137
diabetic ketoacidosis, 139–140
disorders of adrenal gland, 134–137
disorders of puberty, 127–131
disorders of sexual differentiation, 131–134
hypoglycemia, 145–146
short stature, 124–127
thyroid disorders, 140–142
type 1 diabetes mellitus, 137–138
type 2 diabetes mellitus, 138–139
Endophthalmitis, 429
Enteral therapy, 252
Enuresis, 34–35
classification, 34
definition, 34
epidemiology, 34
etiology, 34
evaluation, 34
management, 35
Ependymomas, 353
Epidemic keratoconjunctivitis, 431
Epidural hematoma, 462–463
Epiglottitis, 217–218
Epilepsy, 304
classification of, 305
diagnosis, 306
evaluation, 306
management, 306–307
prognosis, 307
Epileptic syndromes
absence epilepsy, 308
benign epilepsy with centrotemporal spikes, 308
classification, 307
clinical features, 308
defined, 307
infantile spasms, 307–308
management, 308
Epinephrine
for anaphylaxis, 367
for food allergy, 371
Erysipelas, 163
Erythema infectiosum, 447
Erythema multiforme (EM), 445, 445t
Esophageal atresia with tracheoesophageal fistula (EA/TEF), 88–89, 89f
Esotropia, 436
Etonogestrel implant, 56–57
Ewing sarcoma, 358–359
causes, 358

clinical features, 358, 358t
diagnosis, 358
epidemiology, 358
etiology, 358
management, 358
prognosis, 359
Exanthem subitum *Roseola infantum*
Exome sequencing, 101
Exotropia, 436
Extended oligoarthritis, 387
Eye alignment, 427
Eye misalignment, 428

F

Failure to thrive (FTT), 2–3, 3f
classification, 3
defined, 2
differential diagnosis of, 3f
evaluation of, 3
Fatty acid oxidation disorders, 115
Febrile seizures, 305, 307
classification, 307
defined, 307
diagnosis, 307
epidemiology, 307
etiology, 307
management, 307
prognosis, 307
risk factors, 307
Female
puberty, 45, 128
reproductive health issues
contraception, 56–57
pregnancy, 55–56
Female breast development, for sexual maturity ratings, 48f
Femoral anteversion, 415
Femur fractures, 420
Ferritin, 325
Fetal alcohol syndrome (FAS), 109
Fetal exposure to drugs of abuse, 88
Fetal hydantoin syndrome, 109–110
Fetus, genetic evaluation of, 102
Fever in child, 152–154, 152t
Fever of unknown origin (FUO), 154–155, 155t
Fluorescence in situ hybridization (FISH), 101
Fluoride, 14
Focal seizures, 305, 305f
Folic acid deficiency, 326–327

Food allergy, 370–371
clinical features, 370
defined, 370
diagnosis, 370–371
etiology, 370
management, 371
Forearm fractures, 420
Foreign body aspiration, 228–229
Fractures
clavicular, 417–419
femur, 420
forearm, 420
juvenile dermatomyositis, 391
supracondylar, 419–420
toddler, 420
types, 417
typical of child abuse, 420
Fragile X syndrome, 106
FTT (Failure to thrive), 2–3, 3f
classification, 3
defined, 2
differential diagnosis of, 3f
evaluation of, 3
Fungal infections, 173–174
aspergillosis, 173
candidiasis, 173
coccidioidomycosis, 173–174
cryptococcal infection, 174
FUO (fever of unknown origin), 154–155, 155t

G

Galactosemia, 114Galeazzi sign, 409
Gallbladder, hydrops of, Kawasaki disease and, 385
Gastroenterology
acute abdominal pain, 244–247, 245t
chronic abdominal pain, 247–249, 248t
constipation, 249–250, 250t
diarrhea, 250
gastroesophageal reflux, 240–241
gastrointestinal bleeding, 253–254, 254t
hepatitis, 255–261, 259f, 260f
inflammatory bowel disease, 251–252, 251t
intestinal anatomic obstructions, 241–244
liver abnormalities, 255–261, 259f, 260f
malabsorption, 237–239
nutrition, 236, 237t
Gastroesophageal reflux (GER)
clinical features, 240–241

definitions, 240
diagnosis, 241
management, 241
pathophysiology, 240
physiology, 240
Gastrointestinal bleeding
definitions, 253
laboratory confirmation, 253
lower, 254
UGI bleeding, 253–254
Gastrointestinal tract, Henoch-Schönlein effects on, 383
Gaucher disease type I, 116
Gene sequencing, 101
Generalized seizures, 305, 305f
Genetic disorders, 29
additional disorders, 108–109, 109t
amino acid metabolism defects, 110–114, 112t, 113t
carbohydrate metabolism defects, 114–115
chromosomal (micro) deletion syndromes, 104–105
connective tissue disorders, 107
fatty acid oxidation disorders, 115
fetal evaluation, 102
genetic tests, 101
imprinting disorders, 105–106
inheritance patterns, 100–101, 101f
lysosomal storage diseases, 115–116
mitochondrial disorders, 116
prenatal diagnosis, 102
sex chromosome syndromes, 104
skeletal disorders, 107
syndromes caused by teratogens, 109–110
terminology, 102
triplet repeat expansion disorders, 106
trisomy syndromes, 102–104, 103f, 103t
Genital ulcers, 61, 61t
Genital warts, 61
Genomic imprinting, 105
Genu valgum, 416
Germ cell tumors, 359–360
classification, 359
ovarian tumors, 360
teratomas, 359–360
testicular tumors, 360
Germinomas *Germ cell tumors*
Gianotti-Crosti syndrome, 447
Giardiasis, 174–175
Glanzmann thrombasthenia, 338
Glasgow coma scale, 302

Glasgow Coma Scale (GCS), 462, 462t
Glial cell tumors, 353
Glomerulonephritis
  classification, 276
  clinical features, 276
  definition, 275
  etiology, 275
  evaluation, 276
  types, 276–278
Glucocorticoid excess, 136–137
Glucocorticoids, systemic lupus erythematosus, 390
Glucose-6-phospate dehydrogenase deficiency, 327–328, 328t
Glycogen storage diseases (GSDs), 114
Gowers sign
  juvenile dermatomyositis, 391–392
Granulocytes, disorders of
  Chédiak-Higashi syndrome, 378
  chronic granulomatous disease, 377
  lymphocyte adhesion defects, 378
  neutropenia, 378
  Shwachman-Diamond syndrome, 378
Granulomatosis, with polyangiitis, 396
Gross motor development, 24–25, 24t
Growing pains, 417
Growth
  abnormalities of, 1–6, 2t, 3f, 4t, 5f, 6f
    defined, 2
    failure to thrive, 2–3, 3f
    head growth—related, 2t, 3–6, 4f
  head, abnormalities in, 2t, 3–6, 4f
  health supervision related to, 1–6, 2t, 3f, 4t, 5f, 6f
  normal, 1–6, 2t, 3f, 4t, 5f, 6f
Growth abnormalities, neonatology, 79–80, 80t
Guillain-Barré syndrome, 312–313
  clinical features, 312
  defined, 312
  diagnosis, 313
  etiology, 312
  management, 313
  pathophysiology, 312
  prognosis, 313
Gynecomastia, 65

H

Haemophilus influenzae type b (HIB), 217
  vaccine for, 7
Hair, disorders, 450–452
Hair loss, 451

Hand-foot-mouth disease, 449
Happy spitters, 240
Head growth, abnormalities in, 2t, 3–6, 4f
  clinical features, 4
  craniosynostosis, 4–6, 5f
  general concepts of, 3
  macrocephaly, 4
  microcephaly, 3
  plagiocephaly, 6, 6f
Headaches, 309–311, 309f
  causes, 309, 309f
  clinical information, 309
  cluster, 311
  duration, 309
  etiology, 309
  location and radiation, 309
  migraine, 310
  quality of pain, 309
  red flags, 309
  tension, 310–311
  time of onset, 309
HEADDSSS assessment, 50t
Health supervision, 1–22
  anticipatory guidance in, 16, 17t–18t
  circumcision, 13–14
  dental care in, 14–16
  developmental screening in, 16
  growth-related, 1–6, 2t, 3f, 4t, 5f, 6f
  immunizations in, 6–11
  well child care in, 1
  well child screening in, 11–13
  well child visit in, 1
Hearing impairment, 32–33
  hearing screening for, 11
Hearing loss
  medical evaluation, 33
  prognostic factors, 32–33
  types, 32
Hearing loss, medical evaluation for, 33
Hearing screening for, 11
Helminth infections, 176–177, 176t–177t
  cysticercosis, 177
  general concepts, 176
Hemangiomas, 338
Hemarthroses, in hemophilia A, 335
Hematology
  anemia, 323–331
  hemostasis disorders, 333–339, 334f, 334t, 335f

neutropenia, 339–340
pancytopenia, 331–332
polycythemias, 333
Hematuria, 269–270, 270f
clinical significance, 269, 270f
definition, 269
differential diagnosis, 271f
epidemiology, 269
evaluation, 270
Hemochromatosis, 326
Hemoglobin (Hgb), 323
Hemoglobinopathies, sickle cell, 324f, 330–331, 330t, 331t
Hemolytic anemia, 327
alloimmune, 324f, 329
autoimmune, 324f, 328–329
microangiopathic, 324f, 329
Hemolytic uremic syndrome (HUS), 329
atypical, 280
definition, 279
pneumococcal, 280
Shiga-like toxin–associated, 280
subtypes, 279
Hemophilia A, 334
clinical features, 335
inheritance, 335
laboratory findings, 335
management, 335
Hemorrhagic conjunctivitis, 431
Hemostasis, disorders of, 333–339, 334f, 334t, 335f
acquired clotting factor, 336–337
blood vessels, 337
clotting cascade, 333, 334f
concepts, 333, 334f
congenital clotting factor, 334
hypercoagulability, 339
platelet abnormalities, 337–339
Henoch-Schönlein purpura, 337
Henoch-Schönlein purpura (HSP), 383–384
clinical features, 383
defined, 383–384
diagnosis, 383–384
epidemiology, 383
management, 384
prognosis, 384
Henoch–Schönlein purpura (HSP) nephritis, 277
Hepatitis, 173
A, vaccine for, 9
assessment, 255

autoimmune hepatitis, 260–261
B, vaccine for, 7
cholestatic diseases of infancy, 256–258
general concepts, 255
infant jaundice, 255–256
viral hepatitis, 258–260, 259f, 260f
Wilson disease, 258
Hepatitis A infection, 258–259, 259f
Hepatitis A vaccine, 51
Hepatitis B infection, 259–260, 260f
Hepatitis B vaccine (HBV), 7
Hepatitis C infection, 260
Hepatitis D infection, 260
Hepatitis E infection, 260
Hepatoblastoma, 359
Hepatocellular carcinoma, 359
Hepatocellular enzymes, 255
Hereditary elliptocytosis, 328
Hereditary fructose intolerance, 115
Hereditary hemorrhagic telangiectasia, 337
Hereditary renal diseases
alport syndrome, 281
autosomal recessive polycystic kidney disease, 281
general concepts, 281
medullary sponge kidney, 281
multicystic renal dysplasia, 281
nephronophthisis, 282
Hereditary spherocytosis, 327
Herpes simplex virus infection, 448
Heterosexual gonadotropin-independent puberty, 129–130
Hip
developmental dysplasia of hip, 408–409
limp, 409–413, 410t, 411t
Hirschsprung disease, 244, 254
Hodgkin disease, 351–352, 351t
clinical features, 351, 351t
diagnosis, 351
epidemiology, 351
management, 352
prognosis, 352
Reed-Sternberg cell in, 351
staging, 352
Homocystinuria, 111–113, 112t–113t
Human bites, 475
Human immunodeficiency virus (HIV), 168–170
Human leukocyte antigen (HLA), for ataxia telangiectasia, 377
Human papilloma virus (HPV) vaccines, 10, 51
Hunter syndrome (MPS type II), 115

Hurler syndrome (MPS type I), 115
HUS (hemolytic uremic syndrome)
  atypical, 280
  definition, 279
  pneumococcal, 280
  Shiga-like toxin–associated, 280
  subtypes, 279
Hydroceles, 67
Hydrocephalus, 300–301
  clinical features, 300
  communicating, 300
  defined, 300
  etiology, 300
  evaluation, 300
  ex vacuo, 300
  macrocephaly due to, 9
  management, 300
  and myelomeningocele, 301
  noncommunicating, 300
  prognosis, 300–301
  types, 300
Hydrocephalus ex vacuo, 300
Hydroxychloroquine
  systemic lupus erythematosus, 390
Hygiene, dental, 14–15
Hypercoagulability, 339
Hyperkeratosis, 442
Hypertension
  classification, 272–273
  clinical features, 274–275
  definitions, 272
  etiology, 274, 274t
  evaluation, 275
  management, 275
  measurement, 273–274
Hyperthyroidism, 141–142
Hypertrophic pyloric stenosis, 241–242
Hyphema, 433
Hypocalcemia, 142–143
Hypogammaglobulinemia, 374
Hypoglycemia, 92, 145–146, 146
Hypopigmentation
  oculocutaneous albinism, 450
  pityriasis alba, 450
  postinflammatory, 450
  vitiligo, 450
Hypothyroidism, 140–141
Hypotonia, 296–299, 297f

classification, 296
clinical features, 296
defined, 296
differential diagnosis, 296–297, 297f
disorders, 298–299 *specific disorders*
evaluation, 297–298
Hypotonic disorders, peripheral
congenital myotonic dystrophy, 299
infantile botulism, 298–299
spinal muscular atrophy, 298
Hypovolemic shock, 460
Hypsarrhythmia, 308

I

IBD (inflammatory bowel disease)
clinical features, 251–252
definition, 251
epidemiology, 251
evaluation, 252
management, 252
IDMS (infants of diabetic mothers), 92
IgA deficiency, 374
IgA nephropathy, 277
Immune system, components of, 373
Immune thrombocytopenic purpura (ITP), 338
Immune-mediated thrombocytopenias, 338
Immunization(s), 6–11
active, 7
adolescent health screening, 50–51
adverse effects of, 10
contraindications to, 10–11
passive, 7
precautions with, 11
specific, 7–10
types of, 7
Immunocompromised hosts, VZIG in, 7
Immunodeficiency states
categories, 373, 373t
primary, 373, 373t
Immunology, 373, 373t
Immunotherapy
for allergic rhinitis, 369
insect venom allergy, 371
Impetigo, 163
Imprinting disorders, 105–106
Inactivated influenza vaccine (IIV), 9–10
Inborn errors of metabolism (IEM), 110
Incisor(s), mandibular central, 15

Indirect inguinal hernia, 66–67
Infant jaundice, 255–256
Infantile botulism, 298–299
Infantile hemangiomas, 453
Infants of diabetic mothers (IDMS), 92
Infectious diseases
  bone and joint infections, 166
  Cat scratch disease, 178–179
  cervical lymphadenitis, 162
  child with fever, 152–154, 152t
  child with possible infection, 151
  diarrhea, 166–168, 167t–168t
  fever of unknown origin, 154–155, 155t
  fungal infections, 173–174
  helminth infections, 176–177, 176t–177t
  meningitis, 156–159, 157t, 158t
  middle and lower respiratory infections, 161
  parasitic infections, 174–176
  parotitis, 162–163
  Rickettsial infections, 178
  skin and soft tissue infections, 163–165
  tuberculosis, 179–180
  upper respiratory infections, 159–161
  urinary tract infections, 168
  viral infections, 168–173
Infectious disorders
  respiratory tract
    bacterial tracheitis, 219
    bronchiolitis, 220–221
    epiglottitis, 217–218
    laryngotracheobronchitis, 218–219, 218t
    pertussis, 219–220
    pneumonia, 221–222
Infectious enterocolitis, 254
Infectious mononucleosis, 170–171
Infective endocarditis, 201–202, 202t
Inflammatory bowel disease (IBD)
  clinical features, 251–252
  definition, 251
  epidemiology, 251
  evaluation, 252
  management, 252
Inheritance patterns, 100–101, 101f
Innate responses, 373
Innocent cardiac murmurs, 188
Insect venom allergy, 371
Intellectual disability, 28–29, 29t
Internal tibial torsion, 414, 414f

Intestinal anatomic obstructions, 241–244
atresias, 243
Hirschsprung disease, 244
hypertrophic pyloric stenosis, 241–242
intussusception, 244
malrotation and midgut volvulus, 242–243
Intestinal obstruction, 90–91, 91f
Intestinal perforation, juvenile dermatomyositis, 391
In-toeing, 413
Intracranial bleeding, 462–463
Intracranial pressure, 463, 463t
Intranasal cromolyn sodium, for allergic rhinitis, 369
Intranasal steroids, for allergic rhinitis, 369
Intraocular pressure, 434
Intrathecal methotrexate, 349
Intrauterine devices (IUDs), 56
Intravenous immune globulin (IVIG)
for Guillain-Barré syndrome, 313
Kawasaki disease, 386
for myasthenia gravis, 316
Intussusception, 244
Iron deficiency anemia
risk factors for, 12
screening for, 12
Iron toxicity, 472–473, 473t
Iron-deficiency anemia, 324–325
Isoimmune thrombocytopenia, 338

J

Jaundice, 85–88, 86f, 87f
classification, 85–86
complications, 87–88
definition, 85
differential diagnosis, 86
evaluation, 86–87, 87f
management, 87
Juvenile ankylosing spondylitis, 398, 401
Juvenile dermatomyositis (JDM), 391–392, 399, 401
clinical features, 391
complications, 391
defined, 391
diagnosis, 391
epidemiology, 391
management, 391
prognosis, 391
Juvenile idiopathic arthritis (JIA), 386–388, 387t
classification, 387
clinical features, 387–388, 387t

defined, 386
diagnosis, 386, 387t
epidemiology, 386
laboratory findings, 388
management, 388
oligoarticular, 387
extended, 387
persistent, 387
polyarticular, 388
prognosis, 388
systemic-onset, 388
Juvenile myasthenia, 316
Juvenile myelomonocytic leukemia (JMML), 350, 351
Juvenile polyps, 254

K

Karyotype analysis, 101
Kawasaki disease (KD), 201, 384–386, 384t, 385t
atypical, 386
clinical features, 385, 385t
defined, 384
diagnostic criteria, 384–385, 384t
epidemiology, 384
incomplete, 386
laboratory findings, 386
management, 386
prognosis, 386
time course of disease, 385
Keratoconjunctivitis, epidemic, 431
Ketogenic diet, 307
Ketotic hypoglycemia, 146, 150
Kidney
Henoch-Schönlein effects on, 383
systemic lupus erythematosus, 389
Klinefelter syndrome (XXY), 104
Klippel–Feil syndrome, 405
Knee angulation, 415
Knock-knees, 416
Koebner phenomenon, 444
Kostmann syndrome, 340
Kyphosis, 407

L

Lactate dehydrogenase (LDH), 255
Langerhans cell histiocytosis, 360–361
clinical features, 360–361
defined, 360
diagnosis, 361

etiology, 360
management, 361
prognosis, 361
Langerhans cell histiocytosis (LCH), 360–361
Language, 25
Language skills, 25–27, 26t
Lap belt injuries, 464
Large cell lymphoma, 352
Laryngeal tumors, 357
Laryngotracheobronchitis, 218–219, 218t
Late adolescence, 46
Latrodectus antivenin, 476
Lead, 473
Lead screening, 13
Learning disabilities, 29
Legg–Calvé–Perthes, 411–412
Leiden deficiency, 339
Leukemias, 348–351
acute lymphocytic leukemia, 348–350, 349t
acute myelogenous leukemia, 350
chronic myelogenous leukemia, 350–351
Leukocoria
congenital cataract, 435
retinoblastoma, 435–436
LGA infants, 79–80
Limp, 409–413, 410t, 411t
Lipid screening, 12
Live attenuated influenza vaccine (LAIV), 9
Liver disease, acquired clotting factor disorders, 337
Liver tumors, 359
Long QT syndrome, 208
Louse infestation, 449
Lower extremity
growing pains, 417
Osgood–Schlatter disease, 416
patellofemoral pain syndrome, 416
sever disease, 416
torsional abnormalities, 413–416, 413t, 414f
Lower gastrointestinal bleeding, 254
Lyme disease, 394–395
clinical features, 394
constitutional symptoms, 394
defined, 394
diagnosis, 394–395
epidemiology, 394
erythema migrans, 394
etiology, 394
management, 395

prognosis, 395
Lymphoblastic lymphoma, 352
Lymphocyte adhesion defects (LAD), 378
Lymphocytes, disorders of, 374–377, 374f
ataxia telangiectasia, 376
DiGeorge syndrome, 376
IgA deficiency, 374–375
severe combined immunodeficiency disease, 375
Wiskott-Aldrich syndrome, 376–377
X-linked (Bruton) agammaglobulinemia, 377
Lymphomas, 351–353, 351t
Hodgkin disease, 351–352, 351t
Non-Hodgkin lymphoma, 351t, 352–353
Lysosomal storage diseases, 115–116

M

Macrocephaly, 8
Macrocytic anemia, 323, 326–327
Macules, 441
Magical thinking, 27
Malabsorption
celiac disease, 238–239
general concepts, 237–238
protein intolerance leading to, 238
short bowel syndrome, 239
Malaria, 175
Male
puberty, 45, 128
reproductive health issues
gynecomastia, 65
painful scrotal masses, 65–66
painless scrotal masses, 66–67
Male genitalia and pubic hair development, for sexual maturity ratings, 47f
Malnutrition, 236
and corticosteroids, 337
Malrotation and midgut volvulus, 242–243
Mammalian bites
cat, 475
dog, 475
epidemiology, 474
human, 475
Mandibular central incisors, 15
Mantoux skin test, 51
Marfan syndrome, 107
Marijuana, 54
MAS (meconium aspiration syndrome), 83–84
Maternal serum markers, 102
Maturity abnormalities, 78–79, 79t

Measles, 171–172, 447
mumps, and rubella (MMR) vaccine, 7
Measles, mumps, and rubella booster (MMR), 50
Meckel diverticulum, 254
Meconium, 83
Meconium aspiration syndrome (MAS), 83–84
Medulloblastoma, 353
Membranoproliferative glomerulonephritis (MPGN), 277–278
Membranous nephropathy (MN), 278
Mendelian inheritance, 100, 101f
Meningitis, 156–159, 157t, 158t
aseptic, 158–159, 158t
bacterial, 156–158, 157t
definition, 156
Meningocele, 301
Meningococcal vaccine, 51
Meningococcal vaccine (MCV), 10
Menkes disease, 117
Menstrual cycle, 62–63, 62f
Menstrual disorders, 62–65, 62f, 64t
abnormal vaginal bleeding, 63–65
amenorrhea, 63, 64t
dysmenorrhea, 63
normal menstrual cycle, 62–63, 62f
Metabolic disorders, 29
Metatarsus adductus, 413
Methylation studies, 101
Microangiopathic hemolytic anemia, 324f, 329
Microarray, 101
Microcephaly, 3–4
acquired, 3, 4t
causes of, 3, 4t
clinical features of, 4
congenital, 3, 4t
defined, 3
Microcytic, hypochromic anemia, 323–326, 324f
Micronutrients, 236
Middle adolescence, 46
Middle and lower respiratory infections, 161
Migraines, 310
with aura, 310
basilar artery, 310
classification, 310
clinical features, 310
defined, 310
diagnosis, 310
epidemiology, 310
etiology, 310

management, 310
ophthalmoplegic, 310
precipitating factors, 310
prognosis, 310
without aura, 310
Miliaria rubra (heat rash), 445
Miller Fisher syndrome, 312
Minimal residual disease (MRD), 349
Mitochondrial disorders, 116
Mitochondrial inheritance, 100
Mitral regurgitation, 392
Molluscum contagiosum, 449
Morbilliform, 447
Moro reflex, 25
Motility assessment, 427
Motor deficits, 27–28, 28t
Motor development, 24–25, 24t
differential diagnosis, 25
fine motor skills, 25, 25t
gross, 24–25, 24t
red flags in, 25
Movement disorders, 313–314
Mucopolysaccharidoses (MPSs), 115–116
Multifactorial inheritance, 100
Myasthenia gravis, 315–316
causes, 316
classification, 316
clinical features, 316
congenital, 316
defined, 315
diagnosis, 316
epidemiology, 316
etiology, 316
juvenile, 316
management, 316
neonatal, 316
prognosis, 316
Myelomeningocele
clinical features, 301–302
defined, 301
Myocarditis, 204, 392
rheumatic fever, 392
Myotonic dystrophy, 106

N

Naming period, of speech development, 26
Nasolacrimal duct (NLD) obstruction, 432
Nasopharyngeal tumors, 357

Natal teeth, defined, 15
Necrotizing enterocolitis (NEC), 91, 95, 98, 254
Necrotizing fasciitis, 164
Neonatal conjunctivitis
  clinical features, 429, 429t, 430t
  defined, 429
  differential diagnosis, 429
  etiology, 429
Neonatal hepatitis, 256–257
Neonatal hypoglycemia, 145–146
Neonatal metabolic (state) screening, 11–12
Neonatal myasthenia, 316
Neonatal teeth, defined, 15
Neonatology, 73–99
  apnea of prematurity, 84–85
  cyanosis, 80–81
  fetal exposure to drugs of abuse, 88
  growth abnormalities, 79–80, 80t
  hypoglycemia, 92
  infants of diabetic mothers, 92
  jaundice, 85–88, 86f, 87f
  maturity abnormalities, 78–79, 79t
  meconium aspiration syndrome, 83–84
  newborn evaluation, 73–78, 74t, 75f
  persistent pulmonary hypertension of newborn, 84
  polycythemia, 92–93
  respiratory distress syndrome, 81–83, 82f
  surgical conditions of newborn, 88–91, 89f, 91f
Nephroblastoma *Wilms tumor*
Nephrology
  acute kidney injury, 283–284
  chronic kidney disease
    clinical features, 284
    etiology, 284
    evaluation, 284
    management, 285
  dehydration, 268–269
  electrolytes, 268–269
  fluids, 268–269
  glomerulonephritis
    classification, 276
    clinical features, 276
    definition, 275
    etiology, 275
    evaluation, 276
    types, 276–278
  hematuria, 269–270, 270f
    clinical significance, 269, 270f

definition, 269
differential diagnosis, 271f
epidemiology, 269
evaluation, 270
hemolytic uremic syndrome
atypical, 280
definition, 279
pneumococcal, 280
Shiga-like toxin–associated, 280
subtypes, 279
hereditary renal diseases
alport syndrome, 281
autosomal recessive polycystic kidney disease, 281
general concepts, 281
medullary sponge kidney, 281
multicystic renal dysplasia, 281
nephronophthisis, 282
hypertension
classification, 272–273
clinical features, 274–275
definitions, 272
etiology, 274, 274t
evaluation, 275
management, 275
measurement, 273–274
nephrotic syndrome
classification, 278
clinical features, 278–279
definition, 278
diagnosis, 279
epidemiology, 278
management, 279
pathophysiology, 278
prognosis, 279
proteinuria, 270–272, 272f
classification, 272
detection, 271
epidemiology, 271
evaluation, 273f
renal tubular acidosis
clinical features, 282, 282t
definition, 282
etiology, 282, 282t
evaluation, 283
types, 282
structural and urologic abnormalities
acquired obstruction, 285
congenital obstructive abnormalities, 285

renal abnormalities, 285–286
vesicoureteral reflux, 286, 287f
urinary tract infection, 288–289
urolithiasis
clinical features, 288
diagnosis, 288
epidemiology, 287
etiology, 287–288
evaluation, 288
management, 288
Nephrotic syndrome
classification, 278
clinical features, 278–279
definition, 278
diagnosis, 279
epidemiology, 278
management, 279
pathophysiology, 278
prognosis, 279
Neural tube defect, 301
Neuroblastoma, 354–356
causes, 354
clinical features, 354, 355t
diagnosis, 354
epidemiology, 354
etiology, 354
incidence, 354
management, 356
prognosis, 356
staging, 354
Neurocutaneous syndromes, 451t
Neurofibromatosis, macrocephaly due to, 4
Neurofibromatosis type 1, 108–109
Neurogenic shock, 460
Neurology
Becker muscular dystrophy, 314–315
comatose patient, 302–303, 303t
Duchenne muscular dystrophy, 314–315
headaches, 309–311, 309f
hydrocephalus, 300–301
hypotonia, 296–299, 297f
movement disorders, 313–314
myasthenia gravis, 315–316
seizure disorders, 304–308, 305f, 305t, 306t
spina bifida, 301–302
unsteady gait, 311–313, 311t
Neutropenia, 339–340
autoimmune, 340

causes, 339–340
cyclic, 340
definition, 339
genetic syndromes and, 340
isoimmune, 340
mild, 339
moderate, 339
risk of infection, 339
severe, 339
Nevocellular nevi, 450
acquired, 450
congenital, 450
Nevus simplex/flammeus, 453
Newborn evaluation, 73–78, 74t, 75f
abdominal examination, 76
chest examination, 76
craniofacial examination, 74–75, 75f
extremity examination, 77
general appearance and initial assessment, 73, 74t
genitalia examination, 77
neck and clavicle examination, 75–76
neurologic examination, 74
pregnancy and maternal history, 73
skin examination, 77–78
spine examination, 77
Niemann–Pick disease types A and B, 116
Night terrors, 36
Nightmares, 35
Nikolsky sign, 445
Nitroblue tetrazolium (NBT) test, 377
Nodules, 441
Noncardiac chest pain, 209
Non-Hodgkin lymphoma, 351t, 352–353
classification, 352
clinical features, 351t, 352
diagnosis, 352
epidemiology, 352
management, 353
prognosis, 353
staging, 352
Noninfectious disorders, respiratory tract
apnea, apparent life-threatening event, 229–230
asthma, 222–225, 223f, 225f
bronchopulmonary dysplasia, 227–228
cystic fibrosis, 225–227, 226t, 227f
foreign body aspiration, 228–229
Noninvasive prenatal testing (NIPT), 102
Nonketotic hypoglycemia, 145

Nonstimulant medications, ADHD, 32
Noonan syndrome, 108
Normal puberty, 127–128
Normocytic, normochromic, 323, 324f, 327–331, 328t, 330t, 331t
Normocytic, normochromic anemia, 323, 324f, 327–331, 328t, 330t, 331t
Nursemaid's elbow, 403–404
Nutrition, 236, 237t

O

Obesity, 54
Object permanence, 27
Ocular trauma
  corneal abrasion, 433
  hyphema, 433
  orbital floor fracture, 433
  retinal hemorrhages, 432–433
Oculocephalic maneuver, in comatose patients, 304
Oculocutaneous albinism, 450
Ointments, 442
Omphalocele, 94, 97
Oncology
  bone tumors, 357–359, 358t
  brain tumors, 353–354
  germ cell tumors, 359–360
  Langerhans cell histiocytosis, 360–361
  leukemias, 348–351
  liver tumors, 359
  lymphomas, 351–353, 351t
  renal tumors, 354–357
  retinoblastoma, 359
  soft tissue tumors, 357
  suprarenal tumors, 354–357
Onychomycosis *Tinea unguium*
Ophthalmology
  abnormal tearing, 432
  amblyopia, 428
  congenital glaucoma, 434
  conjunctivitis, 429–432, 429t, 430t
  leukocoria, 435–436
  ocular examination, 427
  ocular trauma, 432–433
  red eye, 429–432, 430f
  retinopathy of prematurity, 434–435
  strabismus, 436
  vision screening, 427
  visual development, normal, 427–428
Optic glioma, 354
Oral and inactivated polio virus (OPV/IPV), vaccines for, 7–8

Oral contraceptives, 57
Oral rehydration therapy (ORT), 269
Orbital floor fracture, 433
Orbital tumors, 357
Organic acidemias, 113–114
Orthopedics
  fractures, 417–420, 418f, 419f, 419t
  hip, 408–413, 411t
  lower extremity, 413–417, 413t, 414f
  spine, 404–408, 406f, 407t
  upper extremity, 403–404
Osgood–Schlatter disease, 416
Osteogenesis imperfecta (OI), 107
Osteogenic sarcoma, 357–358
  causes, 358
  clinical features, 358, 358t
  diagnosis, 358
  epidemiology, 357
  etiology, 358
  management, 358
  prognosis, 358
Osteomyelitis, 412–413
Osteopenia, juvenile dermatomyositis, 391
Otitis externa, 161
Otoacoustic emission (OAE), in hearing screening, 11
Ovarian tumors, 360
Overgrowth syndrome, macrocephaly due to, 4

P

Painful scrotal masses, 65–66
Painless scrotal masses, 66–67
Pallid breath-holding spells, 37
Pancytopenia, 331–332
  acquired, 332
  congenital, 332
  defined, 331
Papular acrodermatitis *Gianotti-Crosti syndrome*
Papules, 441
Papulovesicular, 447
Parachute reaction, 25
Paraphimosis, 14
Parasitic infections, 174–176
  amebiasis, 174
  giardiasis, 174–175
  malaria, 175
  toxoplasmosis, 175–176
Parenteral rehydration, 269
Parotitis, 162–163

Passive autoimmune thrombocytopenia, 338
Patau syndrome, 104
Patellar chondromalacia, 416
Patellofemoral pain syndrome, 416
Patent ductus arteriosus (PDA), 193–194, 194f
Pavlik harness, 409
PCV13, 9
PDA (patent ductus arteriosus), 193–194, 194f
Penile abnormalities, anatomic, 14
Percutaneous umbilical blood sampling, 102
Perianal cellulitis, 164
Pericarditis, 203–204, 203f
Peripheral hypotonia, 296
Persistent neonatal hypoglycemia, 145
Persistent oligoarthritis, 387
Persistent pulmonary hypertension of newborn (PPHN), 84, 94, 97
Pertussis, 219–220
Pharmacologic anesthetics, during circumcision, 14
Pharyngitis, 159–160
Pharyngoconjunctival fever, 431
Phenylketonuria (PKU), 118, 121
Phimosis, 14
Phototherapy, 87
Physical abuse
  clinical features, 467
  diagnosis, 467
  epidemiology, 466–467
  management, 467
Picky eating, 36
Pierre Robin sequence, 109
Pigeon-toe, 413
Pit viper snakes, 476
Pityriasis alba, 450
Pityriasis rosea, 444
Plagiocephaly, 6, 6f
Plasmapheresis
  for Guillain-Barré syndrome, 313
  for myasthenia gravis, 316
Plumbism, 13
Pneumococcal hemolytic uremic syndrome, 280
Pneumococcal vaccine, 9
Pneumonia, 221–222
Poisonings
  acetaminophen toxicity, 471–472, 471t
  antidotes, 471t
  carbon monoxide, 474
  caustic agents, 473–474
  concepts, 468–469

evaluation, 469
iron toxicity, 472–473, 473t
lead, 473
management, 469
physical examination findings, 470f
salicylates, 472
Polyarteritis nodosa, 396
Polycythemia, 92–93
Polycythemias
appropriate, 333
complications, 333
defined, 333
inappropriate, 333
primary, 333
relative, 333
secondary, 333
Port wine stain, 95, 98
Port wine stains, 453
Positive Barlow maneuver, 408
Positive Ortolani maneuver, 409
Postinflammatory hypopigmentation, 450
Post-Streptococcal Glomerulonephritis (PSGN), 276–277
Postterm delivery, 79
Postural reactions, 24t, 25
Postural roundback, 407
Potter syndrome, 109
PPHN (persistent pulmonary hypertension of newborn), 84
PPSV23, 9
Prader–Willi syndrome, 105
Precocious puberty, 128–130
Pregnancy, 55–56
newborn evaluation, 73
Premature adrenarche, 128–129
Premature thelarche, 128
Prespeech period, of speech development, 26
Preterm delivery, 78–79, 79t
Primary irritant contact dermatitis, 443
Primary ocular herpes simplex virus, 431
Priming, 368
Primitive neuroectodermal tumors (PNETs), 353, 354
Primitive reflexes, 24t, 25
Problem drinking, 54
Protein C deficiency, 339
Protein S deficiency, 339
Proteinuria, 270–272, 272f
classification, 272
detection, 271
epidemiology, 271

evaluation, 273f
Pseudostrabismus, 436
Psoriasis, 444
Psoriatic arthritis, 395
Psychosocial development, 45–46
Puberty
females, 45
males, 45
Puberty disorders, 127–131
Pulmonary disease, 216–217
Pulmonary stenosis, 195
Pulmonology
pulmonary disease, 216–217
respiratory system, 216
infectious disorders, 217–222
noninfectious disorders, 222–230
Pustules, 441
Pyogenic granulomas, 453

Q

22q11.2 deletion syndrome, 104–105

R

Radiation therapy, for brain tumors, 354
Rapid eye movement (REM) sleep, 35
Rashes
periorbital violaceous heliotrope, 391
transient salmon-pink macular rash, 388
RAST tests, in food allergy, 371
Raynaud phenomenon, systemic lupus erythematosus, 389
Reactive arthritis, 395, 399, 401
Recessive inheritance, 100
Red blood cells (RBC)
aplasias, 327, 331, 332t
extrinsic defects, 324f, 328–329
intrinsic defects, 324f, 327
Red eye
causes, 430
differential diagnosis, 430f
etiology, 429
evaluation, 430
management, 431
Red reflex assessment, 427, 427t
Reed-Sternberg cell, in Hodgkin disease, 351
Reed-Sternberg cells, 362, 365
Renal tubular acidosis (RTA)
clinical features, 282, 282t
definition, 282

etiology, 282, 282t
evaluation, 283
types, 282
Renal tumors, 354–357, 355t
Reproductive health issues
in female
contraception, 56–57
pregnancy, 55–56
in males
gynecomastia, 65
painful scrotal masses, 65–66
painless scrotal masses, 66–67
Respiratory distress syndrome (RDS), 81–83, 82f, 95, 98
clinical features, 82
complications, 83
definition, 81
differential diagnosis, 82f
epidemiology, 82
evaluation, 82
management, 83
pathophysiology, 81–82
prognosis, 83
Respiratory system, 216
Respiratory tract
infectious disorders
bacterial tracheitis, 219
bronchiolitis, 220–221
epiglottitis, 217–218
laryngotracheobronchitis, 218–219, 218t
pertussis, 219–220
pneumonia, 221–222
noninfectious disorders
apnea, apparent life-threatening event, 229–230
asthma, 222–225, 223f, 225f
bronchopulmonary dysplasia, 227–228
cystic fibrosis, 225–227, 226t, 227f
foreign body aspiration, 228–229
Retinal hemorrhages, 432–433
Retinoblastoma, 359, 435–436
clinical features, 435
defined, 435
diagnosis, 435
epidemiology, 435
etiology, 435
management, 435–436
prognosis, 436
Retinopathy of prematurity (ROP)
complications, 434

defined, 434
etiology, 434
management, 434–435
screening and prevention, 435
Rhabdomyosarcoma, 364, 366
causes, 357
clinical features, 357
diagnosis, 357
epidemiology, 357
etiology, 357
management, 357
prognosis, 357
sites, 357
Rheumatic fever, 392–393, 393t, 399, 401
clinical features, 392
defined, 392
diagnosis, 393, 393t
epidemiology, 392
etiology, 392
Jones criteria for, 393, 393t
laboratory findings, 393
management, 393
prognosis, 393
Rheumatologic markers
juvenile idiopathic arthritis, 388
systemic lupus erythematosus effects on, 389
Rheumatology
Henoch-Schönlein purpura, 383–384
juvenile dermatomyositis, 391–392
juvenile idiopathic arthritis, 386–388, 387t
Kawasaki disease, 384–386, 384t, 385t
Lyme disease, 394–395
rheumatic fever, 392–393, 393t
systemic lupus erythematosus, 389–390, 389t
Rickets, 143–144
Rickettsial infections, 178
Roseola infantum, 447
RTA (renal tubular acidosis)
clinical features, 282, 282t
definition, 282
etiology, 282, 282t
evaluation, 283
types, 282
Rubella, 172–173, 447
Russell–Silver syndrome, 106

S

St. Vitus dance *Sydenham chorea*

Salicylates, 472
Salter–Harris Classification, 419f, 419t
Scabies, 450
Scalp edema, 3
Scarlet fever, 164–165
Scheuermann kyphosis, 407
Scleroderma, 396
Scoliosis, 405, 406f, 407t
Scurvy, 337
Seborrheic dermatitis, 444
Sebum, 452
Seizures
  absence, 305, 305f
  afebrile, 305, 305f
  causes, 304, 305t
  classification, 305, 305f
  defined, 304
  diagnosis, 306
  epidemiology, 304
  etiology, 304, 305t
  evaluation, 306
  febrile, 305, 307, 318, 321
  focal, 305, 305f
  generalized, 305, 305f
  management, 306–307
  prognosis, 307
  tonic-clonic, 305, 305f
Seizure disorders, 304–308, 305f, 305t, 306t, 318, 321
  causes, 304, 305t
  defined, 304
  diagnosis, 306
  differential diagnosis, 306, 306t
  epidemiology, 304
  etiology, 304
  evaluation, 306
  management, 306–307
  prognosis, 307
Selective eating, 36
Selective mutism, 36
Sensorimotor period, 26
Sensory impairments, 32–33
  hearing impairment, 32–33
  visual impairment, 33
Separation anxiety disorder, 36
Septic shock, 460
Serologic testing, Lyme disease, 395
Seronegative spondyloarthropathies, 395
Serum sicknesslike reaction, 445

Sever disease, 416
Severe combined immunodeficiency disease (SCID)
autosomal recessive, 375
clinical features, 375
defined, 375
diagnosis, 375
etiology, 375
management, 375
X-linked, 375
Severe congenital agranulocytosis, 340
Sex chromosome syndromes, 104
Sexual abuse
concepts, 467
diagnosis, 467–468
epidemiology, 467
history of, 467
laboratory studies, 468
management, 468
physical examination, 468
Sexual maturity, 1
Sexual maturity ratings
for female breast development, 48f
for female pubic hair development, 49f
for male genitalia and pubic hair development, 47f
Sexually transmitted infections (STIs)
cervicitis, 59–60
clinical features, 58–61
epidemiology, 58
genital ulcers, 61, 61t
genital warts, 61
PID, 60
risk factors, 58
urethritis, 60–61
vaginitis, 58–59
Shiga-like toxin–associated hemolytic uremic syndrome, 280
Shock, 460–461
cardiogenic, 460
classification, 460
compensated, 460
concepts, 460
decompensated, 460
diagnosis, 460–461
distributive, 460
hypovolemic, 460
management, 461
septic, 460
Short bowel syndrome, 239
Short stature

categorization, 125–126, 126f
definition, 124
endocrinopathies, 127
evaluation, 126–127, 127t
general concepts, 124
history, 124–125, 125f
physical examination, 125
Shwachman-Diamond syndrome, 340, 378, 380, 382
Sibling rivalry, 37
Sickle cell (SS) hemoglobinopathies, 324f, 330–331, 330t, 331t
Sideroblastic anemia, 326
Simple URIs, 159
Sinusitis, 159
Sjögren syndrome, 396
Skeletal disorders, 107
Skin
anti-infective agents, 442
anti-inflammatory agents, 442–443
creams, 442
destructive therapies, 442
examination, 441
Henoch-Schönlein effects on, 383
hydration, 442
lotions, 442
Lyme disease, 394
ointments, 442
rheumatic fever, 392
solutions, 442
systemic lupus erythematosus effects on, 389
thickened, 442
topical anti-inflammatory agents, 443
Skin and soft tissue infections, 163–165
Skin infections
bacterial, 447
ectoparasites, 449–450
fungal, 446
viral, 447–449
Skin tests, in food allergy, 371
Sleep problems, 35–36
abnormal patterns, 35
epidemiology, 35
night terrors, 36
nightmares, 35
normal patterns, 35
Slipped capital femoral epiphysis (SCFE), 412
Small-for-gestational-age (SGA) infants, 79, 80t
Social phobia, 36
Social skills, 27

Soft tissue tumors, 357 *Rhabdomyosarcoma*
Sotos syndrome, macrocephaly due, 4
Spectrin, 328
Speech, 25
Sphingolipidoses, 116
Spina bifida (SB)
  causes, 301
  clinical features, 301–302
  defined, 301
  diagnosis, 302
  epidemiology, 301
  etiology, 301
  management, 302
  occulta, 301
  prognosis, 302
  types, 301
Spinal muscular atrophy (SMA), 298, 317, 320
Spine
  back pain, 407–408, 407t
  cervical spine disorders, 404–405
  kyphosis, 407
  scoliosis, 405, 406f, 407t
Splenectomy, for ataxia telangiectasia, 376
Spondylolisthesis, 408
Spondylolysis, 408
Standardized growth curves, 2
Staphylococcal Scalded Skin Syndrome (SSSS), 164
Status epilepticus, 304
Stereopsis, 428
Steroids
  Henoch-Schönlein purpura, 384
  Kawasaki disease, 386
Stevens-Johnson syndrome (SJS), 445, 445t
Stimulant medications, ADHD, 31–32, 32t
STIs *Sexually transmitted infections (STIs)*
Stork bites, 453
Strabismus
  clinical features, 436
  defined, 436
  etiology, 436
  management, 436
  vertical, 436
Streptococcus mutans, nursing caries due, 20, 22
Streptococcus pneumoniae, 409
Streptococcus pyogenes, 409
Structural and urologic abnormalities
  acquired obstruction, 285
  congenital obstructive abnormalities, 285

renal abnormalities, 285–286
vesicoureteral reflux, 286, 287f
Subdural hematoma, 463
Substance abuse, 52–54
alcohol, 53
diagnosis, 52
epidemiology, 52
etiology, 52
marijuana, 54
risk factors, 53
tobacco, 53–54
Sudden infant death syndrome (SIDS), 468
Suicide, epidemiology, 51–52
Supracondylar fractures, 419–420
Supraglottitis *Epiglottitis*
Suprarenal tumors, 354–357, 355t
Surgical conditions of newborn, 88–91, 89f, 91f
abdominal wall defects, 90
congenital diaphragmatic hernia, 89–90
esophageal atresia with tracheoesophageal fistula, 88–89, 89f
intestinal obstruction, 90–91, 91f
necrotizing enterocolitis, 91
Survival motor neuron gene *(SMN1)*, 298
SVT, 206–207, 206t, 207f
Sydenham chorea, 313–314, 392
clinical features, 313
defined, 313
diagnosis, 313
differential diagnosis, 313
epidemiology, 313
management, 314
pathophysiology, 313
prognosis, 314
rheumatic fever, 392, 393
Syndromes caused by teratogens, 109–110
Systemic lupus erythematosus (SLE), 389–390, 389t, 399, 401
causes, 389
clinical features, 389
defined, 389
diagnostic criteria, 389, 389t
epidemiology, 389
etiology, 389
laboratory findings, 390
management, 390
prognosis, 390
Systemic scleroderma, 396
Systemic-onset juvenile idiopathic arthritis, 399, 401

T

Takayasu arteritis, 395

Talipes equinovarus (clubfoot), 414

Tantrums, temper, 37

TAPVR, 200–201, 201f

Tay–Sachs disease, 116, 118, 122

Tdap (Tetanus, diphtheria, and acellular pertussis booster), 50

Telogen effluvium, 452

Temper tantrums, 37

Tension headaches, 310–311

Teratomas, 359–360, 364, 366

Testicular neoplasms, 66

Testicular tumor, 363, 366

Testicular tumors, 360

Tetanus, diphtheria, and acellular pertussis booster (Tdap), 50

Tetralogy of fallot, 197–198, 197f, 197t

α-Thalassemia, 325–326

β-Thalassemia, 325–326

β-Thalassemia minor, 326

Thrombocytopenia, 337

  immune-mediated, 338

    neonatal, 338

  isoimmune, 338

  passive autoimmune, 338

Thrombocytopenia-absent radius (TAR) syndrome, 337

Thrombosis, disease states associated with, 339

Thymectomy, for myasthenia gravis, 316

Thyroid disorders, 140–142

Tinea capitis, 446, 452

Tinea corporis, 446

Tinea cruris, 446

Tinea faciei, 446

Tinea pedis, 446

Tinea unguium, 446

Tinea versicolor, 446

Tobacco, 54–55

Toddler fractures, 420

Toilet training, 38

Tonic-clonic seizures, 305, 305f

Tooth (teeth)

  natal, defined, 18

  neonatal, defined, 18

Tooth brushing, age for, 14

Tooth eruption, 14

Topical antihistamines, 431, 437, 439

Torsional abnormalities, 413–416, 413t, 414f

Torticollis, 404

Total body fluid requirement, 268

Tourette syndrome, 314
clinical features, 314
defined, 314
diagnosis, 314
differential diagnosis, 314
epidemiology, 314
etiology, 314
management, 314
prognosis, 314
tics in, 314
Toxic epidermal necrolysis, 445
Toxic shock syndrome (TSS), 165, 165t
Toxic synovitis, 410
Toxoplasmosis, 175–176
Traction alopecia, 452
Transient neonatal hypoglycemia, 145
Transient salmon-pink macular rash, 388
Transient synovitis, 410
Trauma, 461–464
abdominal, 464
chest, 464
concepts, 461
dental, 16
Glasgow Coma Scale, 462, 462t
head, 462–463
injuries, 462–464
primary survey, 462, 462t
adjuncts, 462
secondary survey, 462
spinal cord injury, 464
Trichotillomania, 452
Tricuspid atresia, 198–199, 199f
Tricyclic antidepressants, 35
Triggers, 36
Trigonocephaly, 5
Triple/quadruple markers, 102
Triplet repeat expansion disorders, 106
Trisomy 13, 104
Trisomy 18, 104
Trisomy 21, 102, 103f, 103t
Trisomy syndromes
trisomy 13, 104
trisomy 18, 104
trisomy 21, 102, 103f, 103t
Truncus arteriosus, 199–200, 199f
Tuberculosis (TB), 179–180
screening for, 12–13
Tumor lysis syndrome, 350, 362, 365

Tumor necrosis factor (TNF) inhibitors
Kawasaki disease, 386
Turner syndrome, 118, 121
Turner syndrome (XO), 104
Type 1 diabetes mellitus, 137–138
Type 2 diabetes mellitus, 138–139

U

UGI bleeding, 253–254
Ulcerative colitis, 251, 251t
Ultrasound, 102
Unilateral conjunctivitis, 430
Uniparental disomy (UPD), 105
Universal newborn hearing screening, 11
Unsteady gait, 311–313, 311t
vs. cerebellar dysfunction, 311
vs. Guillain-Barré syndrome, 311
defined, 311
differential diagnosis, 311–312, 311t
Upper extremity
anterior shoulder dislocation, 404
brachial plexus injury, 403
nursemaid's elbow, 403–404
Upper respiratory infections (URIs)
acute otitis media, 160–161
general concepts, 159
otitis externa, 161
pharyngitis, 159–160
simple, 159
sinusitis, 159
Urea cycle disorders (UCDs), 112t–113t, 113
Urethritis, 60–61
Urinalysis, 12
Urinary tract infection (UTI), 288–289
Urinary tract infections (UTIs)
in uncircumcised male infants, 13
URIs (upper respiratory infections)
acute otitis media, 160–161
general concepts, 159
otitis externa, 161
pharyngitis, 159–160
simple, 159
sinusitis, 159
Urolithiasis
clinical features, 288
diagnosis, 288
epidemiology, 287
etiology, 287–288

evaluation, 288
management, 288
Urology, 268–295
Urticaria, 445
Urticaria (hives), 371, 372t
acute, 371
causes, 371, 372t
chronic, 371
classification, 371
defined, 371
management, 371
UTI (urinary tract infection), 288–289

V

Vaccine(s)
DTaP, 7
HBV, 7
Hep A, 9
HIB virus, 8
human papilloma virus, 10
influenza, 9–10
live, 8
meningococcal, 10
MMR, 8
non-live, 8
OPV/IPV, 7–8
pneumococcal, 9
rotavirus, 8
varicella, 8
VACTERL (VATER) association, 108
Vagal nerve stimulator, 307
Vaginal ring, 57
Vaginitis, 58–59
Valvulitis, 392
rheumatic fever, 392
Varicella, 173
Varicella (chickenpox), 447, 448t
Varicella vaccine, 51
Varicella (chickenpox) virus
vaccine for, 8
Varicella zoster immune globulin (VZIG), for immunocompromised patients, 7
Varicoceles, 67
Vascular skin lesions, 453
Velocardiofacial syndrome, 104–105
Ventricular septal defect (VSD), 191, 191f, 194
Vertical strabismus, 436
Vesicles, 441
Vigabatrin

for infantile spasms, 308
Viral conjunctivitis, 431
Viral exanthem, 447
Viral hepatitis, 258–260, 259f, 260f
Viral infections
hepatitis, 173
human immunodeficiency virus, 168–170
infectious mononucleosis, 170–171
measles, 171–172
rubella, 172–173
varicella, 173
Viral pneumonia, 222
Vision screening, 11, 427
Visual acuity, development, 427–428
Visual impairment, 33
Vitamin D, for juvenile dermatomyositis, 391
Vitamin K deficiency, acquired clotting factor disorders, 336
Vitiligo, 450
von Willebrand disease, 334, 336, 342, 345
von Willebrand factor (vWf), 336
VSD (ventricular septal defect), 191, 191f, 194
VZIG (varicella zoster immune globulin), for immunocompromised patients, 7

W

Warts, 449
Well child care, general concepts of, 1
Well child screening, 11–13
cholesterol screening, 12
hearing screening, 11
iron-deficiency anemia screening, 12
lead screening, 13
lipid screening, 12
neonatal metabolic (state) screening, 11–12
tuberculosis screening, 12–13
urinalysis screening, 12
vision screening, 11
Werdnig-Hoffman disease, 298, 317, 320
West syndrome, 308
Wheals, 441
Williams syndrome, 105
Wilms tumor, 356–357
clinical features, 356
diagnosis, 356
epidemiology, 356
management, 356
prognosis, 356
staging, 356
Wilson disease, 116–117, 118, 121, 258

Wiskott-Aldrich syndrome, 337, 376–377, 380, 382
Word combination period, of speech development, 26

X

X-linked (Bruton) agammaglobulinemia, 377
X-linked dominant mode of inheritance, 100
X-linked–recessive mode of inheritance, 100

Y

Yoslk sac tumor, 360, 364, 366